Behavioral/Systems/Cognitive

Involvement of the Basal Ganglia and Cerebellar Motor Pathways in the Preparation of Self-Initiated and Externally Triggered Movements in Humans

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The subthalamic nucleus (STN) is part of the cortico-basal ganglia (BG)–thalamocortical circuit, whereas the ventral lateral nucleus of the thalamus (VL) is a relay nucleus in the cerebello-dentato-thalamocortical (CTC) pathway. Both pathways have been implicated in movement preparation. We compared the involvement of the STN and VL in movement preparation in humans by recording local field potentials (LFPs) from seven patients with Parkinson's disease with deep-brain stimulation (DBS) electrodes in the STN and five patients with tremor and electrodes in VL. LFPs were recorded from DBS electrodes and scalp electrodes simultaneously while the patients performed self-paced and externally cued (ready, go/no-go) movements. For the self-paced movement, a premovement-related potential was observed in all patients from scalp, STN (phase reversal, five of six patients), and VL (phase reversal, five of five patients) electrodes. The onset times of the potentials were similar in the cortex, STN, and VL, ranging from 1.5 to 2 s before electromyogram onset. For the externally cued movement, an expectancy potential was observed in all patients in cortical and STN electrodes (phase reversal, six of six patients). The expectancy potential was recorded from the thalamic electrodes in four of five patients. However, phase reversal occurred only in one case, and magnetic resonance imaging showed that this contact was outside the VL. The cortico-BG–thalamocortical circuit is involved in the preparation of both self-paced and externally cued movements. The CTC pathway is involved in the preparation of self-paced but not externally cued movements, although the pathway may still be involved in the execution of these movements.

Key words: **movement preparation; Parkinson's disease; essential tremor; deep-brain stimulation; cerebellothalmocortical pathway; subthalamic nucleus**

Introduction

Previous studies have examined the cortical structures involved in self-paced and externally cued movements in humans. Back-averaging of midline EEG reveals a slow, negative potential termed the Bereitschaftspotential (BP) that begins 1–3 s before the onset of self-paced movement (Kornhuber and Deecke, 1965; Barrett et al., 1986). Studies using subdural electrodes have shown that the supplementary motor area (SMA) (Ikeda and Shibasaki, 1992; Ikeda et al., 1992) and contralateral primary sensorimotor cortex (Ikeda et al., 1995) are involved in generating the BP. This was confirmed with functional magnetic resonance imaging (fMRI) studies (Thickbroom et al., 2000; Cunnington et al., 2003). Similar cortical areas were found to be active during the preparation of externally cued movements. A slow, negative potential, termed the contingent negative variation (CNV), can be observed in recordings from scalp electrodes between the warning signal (S1) and the imperative signal (S2) (Walter et al., 1964). A simultaneous EEG and fMRI study has shown activity in bilateral thalamus, anterior cingulate, and SMA during a CNV task (Nagai et al., 2004).

Slow cortical potentials such as BP and CNV are likely generated by thalamocortical projection to apical dendrites in the cortex (Birbaumer et al., 1990). The roles of the subcortical structures involved in movement preparation remain unclear. Two subcortical pathways that may affect motor cortical activity are the cortico-basal ganglia (BG)–thalamocortical circuit and the cerebello-dentato-thalamocortical (CTC) circuit. Stereotactic electrode implantation for deep-brain stimulation (DBS) has provided the opportunity to record single neuronal activity intraoperatively as well as local field potentials (LFPs) from the DBS electrodes postoperatively. Subthalamic nucleus (STN) DBS has been shown to alleviate levodopa-responsive motor symptoms (Krack et al., 2003) in Parkinson's disease (PD), whereas stimulation of the ventral lateral nucleus of the thalamus (VL) is used to treat several types of tremor (Schuurman et al., 2000). We used the nomenclature of Ilinsky and Kultas-Ilinsky (2002), in which VL corresponds to Vim (ventrointermediate), Vop (ventrooralis posterior), and Voi (ventralis oralis internus) of Hassler's no-

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Table 1. Demographic and clinical characteristics of patients with STN and VL DBS

Patient	Age (years)	Sex	Disease duration (years)	Diagnosis	Medications (mg/d)
1	49	M	4	PD	Pramipexole (0.25)
2	63	M	15	PD	Levodopa (800), bromocriptine (20)
3	63	F	9	PD	Levodopa (40)
4	52	F	12	PD	Levodopa (800), pramipexole (4.5), amantadine (300)
5	56	F	23	PD	Levodopa (250), ropinirole (12), trihexiphenidyl (2)
6	37	F	7	PD	Levodopa (700), amantadine (100)
7	42	F	12	PD	Levodopa (200), ropinirole (12)
8	70	M	15	Essential tremor	Primidone (500)
9	26	M	5	Multiple sclerosis	None
10	70	F	10	Essential tremor	None
11	63	M	46	Essential tremor	None
12	63	F	12	Essential tremor	Primidone (187.5)

Patients 1–7 had STN electrodes, and patients 8–12 had VL electrodes. Levodopa was administered with a peripheral Dopa-decarboxylase inhibitor. M, Male; F, female.

menclature (Hassler, 1959). VL receives input from the cerebellum (Ilinsky and Kultas-Ilinsky, 2002) and projects to the cortex. Movement-related potentials (MRPs) occurring before self-paced movement, analogous to the cortical BP, have been reported in the STN (Paradiso et al., 2003) and VL (Paradiso et al., 2004). In addition, MRPs were observed during a CNV task in the putamen, caudate nucleus, and pallidum (Bares and Rektor, 2001). Activity within VL during an externally cued movement paradigm has not been reported.

The aim of this study was to determine the roles of the cortico-BG–thalamocortical circuit and CTC pathways in the preparation of self-paced and externally cued movements. Because reduced amplitude for both BP and CNV has been reported in PD patients, we hypothesized that the STN is involved in the preparation of both self-paced and externally triggered movements. Previous studies reported that humans (Ikeda et al., 1994) or animals (Sasaki et al., 1979, 1990; Ohishi et al., 2003) with lesions of cerebellum or the cerebellar output pathway had absent BP but normal CNV-like potentials. We therefore hypothesized that potentials similar to the BP but not expectancy potential analogous to the cortical CNV would be observed in the VL.

Materials and Methods

Patients

We studied seven PD patients (two men and five women; age, 51.9 ± 9.9 years; range, 37–63) and five patients with tremor (three men and two women; age, 58.4 ± 18.5 years; range, 26–70) who had surgically implanted DBS electrodes (Table 1). The electrodes were placed bilaterally in the STN for treatment of PD and unilaterally in the VL for treatment of tremor. The DBS electrodes were targeted to the STN or VL using magnetic resonance image-guided stereotaxy and intraoperative microelectrode recordings (Hutchison et al., 1998; Kumar et al., 2003). The studies were performed 2–5 d after implantation of the DBS electrodes when the electrode leads were externalized, before connection to the pulse generator. The patients were on their usual medications. All patients provided written informed consent, and the study was approved by the University Health Network Research Ethics Board.

Tasks

Self-paced movement. The experimental procedure for the self-paced movements has been described previously (Paradiso et al., 2003, 2004). The patients were seated in a comfortable armchair, looking at a fixation point placed 3 m in front of them. They were asked to make a brisk, self-paced, unilateral wrist extension followed by passive flexion, approximately once every 5–10 s. Two recording sessions lasting at least 10 min each were conducted for each patient. Only right-hand movements were studied in PD patients, whereas all tremor patients performed wrist extensions on the side contralateral to the DBS electrodes. A timeline of the self-paced movement task is shown in Figure 1*A*.

Externally cued movement. A choice reaction-time paradigm was used.

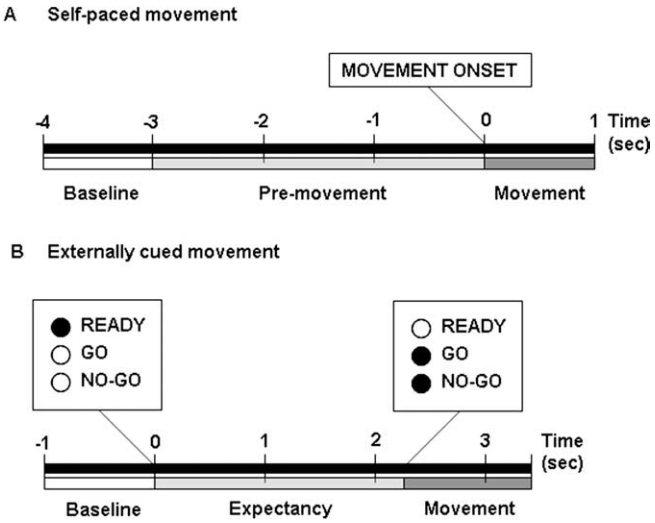

Figure 1. The experimental timeline for self-paced movement (***A***) and externally cued movement (***B***).

A light panel placed in front of the patients presented warning (S1) and imperative (S2) signals. The S1 (red light) was followed 2.25 s later by either an S2-go (light 1) or an S2-no-go (light 2) signal delivered in random order. The patients were instructed to extend their wrist as soon as they saw the S2-go, but not to move on seeing S2-no-go signal. S1 would then be illuminated again, marking the beginning of the next trial after of a delay of either 5 or 7 s from the last go or no-go signal. Each patient underwent at least two recording sessions with each lasting a least 10 min. The timeline for the externally cued movement trials is shown in Figure 1*B*.

Recording

LFPs were recorded from quadripolar DBS electrodes (model 3387; Medtronic, Minneapolis, MN) that contain four contacts numbered 0–3, with contact 0 being the closest to the tip of the electrode. These contacts are 1.3 mm in diameter, 1.5 mm in length, and spaced 1.5 mm apart. Scalp EEG was recorded with silver–silver chloride electrodes placed at Fp1, Fz, Cz, Pz, C3, and C4 according to the International 10–20 System. Eye movements were assessed with the frontal-polar electrodes. Linked ear electrodes were used as reference. The impedance was ≤5 kΩ for all electrodes. The electromyogram (EMG) of the active extensor carpi radialis muscle was recorded with surface electrodes. SynAmp amplifiers (NeuroScan Laboratories, El Paso, TX) were used for all recordings. The sampling rate was 2.5 kHz. Filters were set at 0.05–70 Hz for scalp and DBS electrodes and 30–500 Hz for EMG.

Data analysis

Off-line data processing was performed with Scan 4.3 software (NeuroScan Laboratories). Only recordings from DBS electrodes contralateral

to the hand movement were analyzed. DBS recordings were transformed into a bipolar montage between two consecutive contacts. The scalp electrodes remained referenced to linked ears. For self-paced movements, epochs starting 4 s before and ending 1 s after the EMG onset were created. For externally triggered movements, the epochs extended from 1 s before S1 to 1 s after S2. An outline of the epochs for both self-paced and externally cued movement can be seen in Figure 1. Epochs with eye movement or recording artifacts were rejected. For externally cued movements, epochs in which the subject performed the wrong action for a given prompt (e.g., wrist extension during a no-go trial) were also rejected. All remaining epochs were baseline corrected and averaged. Because we are interested in the premovement potentials and the subjects could not predict in the premovement period whether the trial would be a go or no-go trial, the go and no-go trials were averaged together. For analysis of self-paced movements, a baseline period was established between 4 and 3 s before onset of movement, whereas for cued movements, the baseline period 1 s before S1 was used.

MRP amplitude, onset, and significance were determined using custom algorithms, written with Matlab 7 (The Mathworks, Natick, MA). The BP was not split into subcomponents (such as the negative slope) because the individual components could not be reliably identified from subcortical recordings. Maximum amplitude of the MRP was calculated as the mean of a 50 ms time window centered on the largest voltage. A time window was used to prevent overestimation of the amplitude because of oscillatory components of the signal. The maximum MRP amplitude for self-paced movement was analyzed from the end of the baseline period to movement onset. For externally cued movement, the amplitude analysis period began from 1 s after S1 to the presentation of S2. The onset of the potential was determined by calculating the average of a 50 ms sliding window. The window moved backward in time from the maximum amplitude until the average voltage of the window became 0 or changed sign. To test the significance of a potential in each patient, a paired *t* test was used to compare the average amplitude of the baseline period to the average of the 50 ms maximum amplitude period for each sweep. Thus, every trial would have a value for baseline and maximum amplitude. These values where then compared with a *t* test provided with Matlab 7 (The Mathworks). Other methods to determine average waveform significance have plotted the average wave against a line representing either 3 SDs of the baseline or a 95% confidence interval to demonstrate significance. These methods ignore trial-to-trial differences that are eliminated by the averaging process. Our method allows trial-to-trial variation to be factor in significance, while using onset and maximum amplitude values that are not influenced by subjective interpretation or fluctuations in the average waveform.

Electrode localization

The positions of the contacts were identified using a high-resolution T2-weighted fast spin-echo sequence designed to reduce magnetic susceptibility artifacts and noise. This method has been described in detail (Saint-Cyr et al., 2002) and was used to determine the position of electrodes implanted in the STN (Paradiso et al., 2003) and VL (Paradiso et al., 2004) in previous studies. Briefly, the DBS electrodes were visualized in each of the three planes. The three-dimensional location of the electrode tip relative to the anterior and posterior commissure line, the midcommissural point, and the midline was first determined. Measurement data were normalized to an intercommissural distance of 23 mm, and the position of the electrodes was plotted onto sagittal and coronal planes of the STN and VL, according to the Schaltenbrand and Wahren (1977) atlas. Individual differences in the size and location of the thalamic nuclei and STN were corrected by correlating MRI measurements with intraoperative neurophysiological mapping data. Therefore, there are slight differences in individual boundaries for STN and VL. For illustrative purposes, only one boundary of the STN and VL is shown because the individual differences are small. The position of each contact was then calculated according to the known dimensions of the DBS electrode and the angle of implantation.

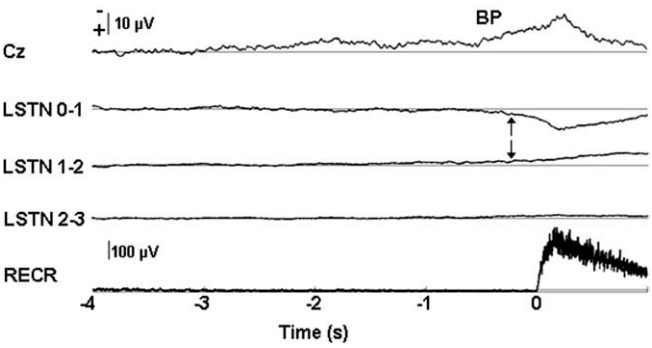

Figure 2. MRP in STN during self-paced movement in patient 2. Back-averaged recordings from Cz (central midline scalp electrode) and bipolar contacts in the STN are shown. The upward direction is negative. An EMG was recorded from the right extensor carpi radialis (RECR) muscle. There is a negative premovement in the Cz electrode (BP) and a negative MRP in contact 1 in the left STN (LSTN; arrows).

Results

Self-paced movements and STN recordings

Figure 2 shows an example of the BP and STN MRPs recorded during self-paced movements from patient 2, and Table 2 depicts the main findings for self-paced movements in the seven patients with STN DBS electrodes. The scalp recording showed a significant premovement potential or BP preceding wrist extension in six of seven patients.

In the STN contacts, significant contralateral MRPs were recorded in all seven patients with phase reversal in five of six patients. Phase reversal indicates a change in polarity between two electrodes. The three most distal contacts (0–2) of the left STN electrode were fused in patient 1 because of a short circuit from electrode disruption, and phase reversal could not be determined. The onset times of the STN MRP and the cortical BP were not significantly different.

Self-paced movements and VL recordings

Figure 3 shows the scalp and VL MRPs in patient 11 preceding self-paced movements, and the values of all five patients are shown in Table 3. All patients, except patient 9, had significant cortical BP, and all five patients had significant contralateral premovement MRP with phase reversal in the VL. There was no significant difference in cortical BP amplitude or onset time between STN and VL patients. The incidence of phase reversal of the contralateral premovement potential for self-paced movements was not significantly different in STN and VL recordings (Fisher's exact test).

Externally cued movements and STN recordings

Figure 4 shows the averaged responses from patient 4, and Table 4 depicts the individual values. A CNV was observed before the externally cued movement from the scalp electrodes in all seven patients. The onset time of the CNV was not evaluated because it generally started shortly after the warning signal (S1). A significant premovement MRP was present in all seven patients in the contralateral STN with phase reversal in five of six patients (the three distal contacts were fused in patient 1). The incidence of phase reversal of the premovement potential in the STN for self-paced and externally triggered movements was not significantly different (Fisher's exact test). Except for patient 4, phase reversal for the premovement MRP preceding self-paced (Table 2) and externally triggered movements (Table 4) occurred at the same

STN contact, although the polarity of the potential may be different.

Table 2. Latency and amplitude of cortical BP and subthalamic MRP for self-paced movement

		Cortical BP		Contralateral STN		
Patient	Number of sweeps	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Contact
1	65	2507	18.0	1530	7.3	CF
2	55	3082	11.9	738	4.2	−1
3	60	1641	10.5	1233	1.6	−2
4	42	540	12.5	796	11.3	0/1
5	89		NS	3338	1.8	+1
6	33	3206	15.0	2967	2.7	−1
7	24	1306	7.3	3346	6.1	+2
Mean	53	2047	12.5	1993	5.0	
SD	22	1059	3.7	1182	3.5	

Right-hand movement was performed in all patients. The cortical BP was recorded from Cz scalp electrode. Latency is the time by which the onset of the potential preceded movement onset determined by EMG. Contact refers to the contact with phase reversal, and the polarity is indicated (+, positive polarity; −, negative polarity). If there was no phase reversal, the contact pair with the largest amplitude is indicated. CF indicates that some of the quadripolar electrode contacts have become fused. NS indicates the amplitude of the potential did not reach significance.

Externally cued movements and VL recordings

Figure 5 illustrates the scalp and VL recording of patient 11, and Table 5 displays the individual values. The scalp recording showed a CNV in all five patients. Significant potentials in the VL preceding the S2 were observed in four of five patients, but phase reversal was only observed in patient 2. For VL recordings, the incidence of phase reversal was significantly lower for externally cued than self-paced movements ($p = 0.048$, Fisher's exact test). For externally cued movement, the incidence of phase reversal was significantly lower for VL compared with STN electrodes ($p = 0.015$, Fisher's exact test). For all patients with VL electrodes, the contacts that showed phase reversal or maximum amplitude were different for self-paced (Table 3) and externally triggered movements (Table 5).

Contact localization

Localization of contacts with phase reversal or maximum MRP amplitude using postoperative MRI is shown in Figures 6–8. MRI of patient 1 was not analyzed because a short circuit between the three distal contacts made it impossible to localize the field potentials to a specific contact. Patient 2 did not have postoperative MRI. The contacts with phase reversal or maximum amplitude for both self-paced and externally cued movement were located within the STN in four of five patients (Fig. 6). In patient 3, the contact was located lateral to the STN. For the VL, the MRPs with phase reversal before self-paced movement were localized within the VL in four of five patients. The contact for patient 11 was located inferior to the VL. For externally cued movement in VL patients, only the premovement potentials from patient 9 had phase reversal, and the contact was located posterior to the VL. Of the remaining patients without phase reversal, the contacts with maximum-amplitude MRP were localized within the VL in three of four patients. The contact of largest amplitude in patient 11 was localized slightly inferior to the VL.

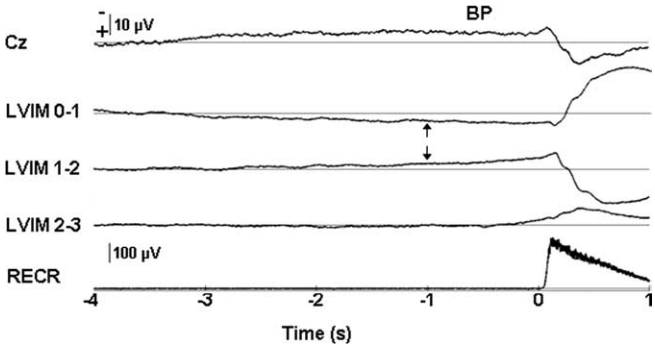

Figure 3. MRP in ventral lateral thalamus during self-paced movement in patient 11. Back-averaged recordings from Cz and bipolar contacts in the left VL thalamus (LVIM) are shown. EMG was recorded from the right extensor carpi radialis (RECR) muscle. There is a negative premovement in the Cz electrode (BP) and a negative premovement potential at contact 1 of the thalamic electrode (arrows).

Discussion

The finding for premovement MRP for self-paced movements confirms our previous studies in a different cohort of patients (Paradiso et al., 2003, 2004). Therefore, we will focus the discussion on the externally cued movement and the comparison between self-paced and externally cued tasks.

The functions and cortical generators of CNV

We used a CNV paradigm with a warning signal (S1) followed by a go/no-go signal (S2) at a fixed interval, similar to those used in previous studies (Ikeda et al., 1997; Gerschlager et al., 1999; Kuhn et al., 2004). The CNV is thought to reflect the cognitive process associated with planning or anticipation of the imperative stimulus and is considered an index of cortical arousal during orienting and attention (Tecce, 1972). It helps prepare the upcoming movement and shortens the reaction time. Subdural recordings suggest the early component of CNV arises from the prefrontal cortex, but other areas including the primary sensorimotor, temporal, and occipital cortices contribute to the later components (Hamano et al., 1997). A simultaneous EEG and fMRI study has shown activity in bilateral thalamus, anterior cingulate, and SMA during a CNV task (Nagai et al., 2004).

Involvement of the STN in the preparation of externally triggered movement

Monopolar contacts record both distant and local potentials. To reduce the effects of distant potentials and volume conduction, we subtracted the potentials recorded from the adjacent DBS contacts to produce bipolar recordings. Phase reversal, or a change in polarity between adjacent bipolar contacts, would indicate that the generator of the potential is located close to the contact where phase reversal occurs. For the externally cued movement, we observed a slow potential in the STN similar to the cortical CNV. Phase reversal between adjacent pairs of bipolar contacts was frequently observed indicating that the contacts are near the generator of the potential. In most patients, phase reversal of the premovement potentials for self-paced, and externally cued movements occurred at the same STN contact, suggesting that the generators for these potentials are close to each other.

Using a slightly different paradigm and different analysis technique, Kuhn et al. (2004) did not find a potential between the warning and imperative signals in LFP from the STN in PD patients. This may be because our PD patients were studied in the "on" medication state, whereas in the study by Kuhn et al. (2004), the results from patients in the on and "off" medications states were combined. It is known that CNV amplitude increases with dopaminergic medications in PD patients (Amabile et al., 1986; Jahanshahi et al., 1995; Oishi et al., 1995). In addition, the polar-

Table 3. Latencies and amplitudes of cortical BP and thalamic MRP for self-paced movement

			Cortical BP		Contralateral VL		
Patient	Hand side	Number of sweeps	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Contact
8	R	75	1554	8.2	979	5.7	−1
9	R	128	NS	NS	1510	3.6	+2
10	L	84	2757	3.1	1941	7.6	+2
11	R	263	3376	5.4	2792	5.1	−1
12	R	87	818	6.9	296	2.4	−1
Mean		112	2126	5.9	1504	4.9	
SD		72	1155	2.2	947	2.0	

The cortical BP was recorded from the Cz scalp electrode. Latency is the time by which the onset of the potential preceded movement onset determined by EMG. Contact refers to the contact with phase reversal, and the polarity is indicated (+, positive polarity; −, negative polarity). Hand side indicates whether wrist extension was performed on the left (L) or right (R). NS indicates the amplitude of the potential did not reach significance.

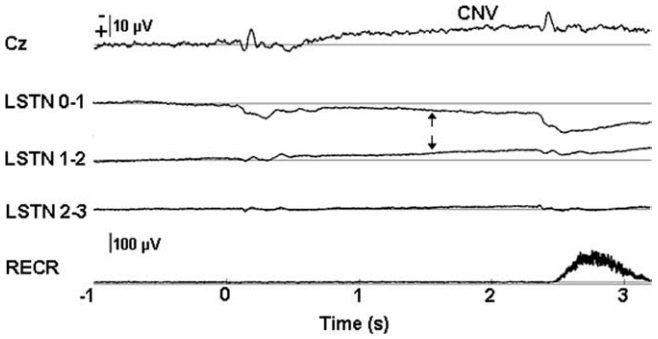

Figure 4. Expectancy potential in STN before externally cued movement in patient 11. Back-averaged recordings from Cz and bipolar contacts in the left STN (LSTN) are shown. EMG was recorded from the right extensor carpi radialis (RECR) muscle. There is a negative premovement potential at contact 1.

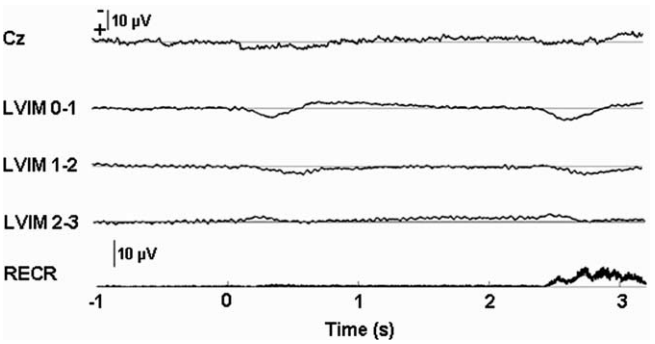

Figure 5. Expectancy potential in ventral lateral thalamic nucleus during externally cued movement in patient 8. Back-averaged recordings from Cz and the three bipolar electrodes implanted in the left VL (LVIM) are shown. EMG was measured from the right extensor carpi radialis (ECR). A small premovement potential was recorded with maximum amplitude at contact 0–1, but no phase reversal was observed.

Table 4. Amplitude of cortical CNV and subthalamic MRPs for externally cued movement

		Cortical CNV	Contralateral STN	
Patient	Number of sweeps	Amplitude (μV)	Amplitude (μV)	Contact
1	120	4.8	3.8	CF
2	89	8.6	4.6	−1
3	71	5.2	2.2	+2
4	173	5.1	1.6	−2
5	52	4.7	2.4	−1
6	112	16.1	2.7	−1
7	68	4.5	3.6	+2
Mean	98	7.0	3.2	
SD	41	4.3	1.0	

Right-hand movement was performed in all patients. The cortical CNV was recorded from the Cz scalp electrode. Contact polarity was determined by the direction of phase reversal (+, positive polarity; −, negative polarity). CF indicates that some of the quadripolar electrode contacts have become fused.

ity of the CNV-like potential in the STN may be positive or negative. Kuhn et al. (2004) used a grand average that may eliminate a slow potential because of phase cancellation. However, they found desynchronization of LFP activity in the β-frequency band with a similar time course as the CNV-like potential in our study.

Several fMRI studies examined BG activation during movement tasks. An event-related fMRI study found activation in the BG with self-paced but not with externally triggered movements (Cunnington et al., 2002). However, the externally triggered movements occurred at random without a warning signal. Therefore, a CNV-like movement preparation process was not engaged. Another study showed activation of the premotor cortex, putamen, and thalamus with externally triggered movements, although the signal intensity in the BG correlated with the movement rate for self-paced but not for externally triggered movements (Taniwaki et al., 2003). The premovement and postmovement periods were not separated in this study, and a complex hand sequence task with no warning signal was used. Therefore, differences in the experimental paradigms likely explain the differences between our study and these studies.

Our results are consistent with an event-related fMRI study that found BG activity before an externally triggered task increased with greater complexity of task preparation (Elsinger et al., 2006). The CNV amplitude is decreased in PD patients (Amabile et al., 1986; Praamstra et al., 1996; Ikeda et al., 1997). These findings are consistent with involvement of BG in the preparation of an externally triggered movement.

Role of CTC pathway in the preparation of externally triggered movement

Recordings from VL during externally cued movement produced premovement potentials with no phase reversal in most patients. One patient (patient 9) had phase reversal, but the contact was located outside the VL. The premovement potentials for self-paced and externally cued movements occurred at different contacts. Thus, the premovement potentials for externally cued movements likely originated from sources outside the VL nucleus. This suggests that the CTC circuit is involved in preparation for self-paced but not externally cued movement.

Our findings contrast several previous studies showing that the BG is more involved in internally generated movement, whereas the CTC pathway is more involved in externally triggered tasks. For example, some dentate neurons in the monkey (Mushiake and Strick, 1993) are preferentially involved in the movements based on visual cues. Similarly, cooling or electrolytic lesions of the dentate nucleus in the monkey increased reaction time (Tsujimoto et al., 1993), decreased movement accuracy (Beaubaton and Trouche, 1982), and reduced the cortical poten-

tial that immediately preceded movements made in response to visual stimuli (Tsujimoto et al., 1993). Neuronal recording (van Donkelaar et al., 1999) and inactivation (van Donkelaar et al., 2000) studies in the monkey thalamus also suggest that the BG receiving area is more involved in the internally generated movements, whereas the cerebellar receiving area is more involved in visually triggered tasks, but there was considerable overlap. However, these studies did not dissociate the preparation from the execution phase of movement, and they used visually guided movements whereas we used a simple ballistic movement. Similarly, an fMRI study found activation of the BG and the CTC pathway with an externally triggered task, but interactions in the CTC pathway were stronger for externally triggered than internally generated tasks (Taniwaki et al., 2006). However, the premovement and postmovement periods were not separated, and the externally triggered task involved complex hand sequences with no warning signal. Therefore, these studies suggest that the CTC pathway is involved in the execution of externally triggered tasks, but they cannot be directly compared with our study that focuses on movement planning.

Table 5. Amplitude of cortical CNV and thalamic MRPs for externally cued movement

			Cortical CNV	Contralateral VL	
Patient	Hand side	Sweeps	Amplitude (μV)	Amplitude (μV)	Contact
8	R	102	5.5	6.3	0/1
9	R	90	11.4	2.0	1+
10	L	58	4.0	NS	1/2
11	R	51	6.4	2.0	0/1
12	R	139	2.6	1.3	1/2
Mean		92	6.0	2.9	
SD		33	3.3	2.3	

The cortical CNV was recorded from the Cz scalp electrode. Hand side indicates whether wrist extension was performed on the left (L) or right (R). Contact refers to the contact with phase reversal, and the polarity is indicated (+, positive polarity; −, negative polarity). If there was no phase reversal, the contact pair with the largest amplitude is indicated.

Our findings are consistent with the results of cerebellar hemispherectomy in monkeys that markedly prolonged the reaction time for a simple visually initiated movement but had little effect on a warning–imperative visually triggered movement that was similar to our externally cued task (Sasaki et al., 1990). Moreover, cerebellar hemispherectomy had little effect on the CNV-like potential between warning and imperative stimuli in the frontal cortical areas in monkeys (Sasaki et al., 1990), whereas it markedly reduced the premovement potential for self-paced movement in rats (Ohishi et al., 2003) and monkeys (Sasaki et al., 1979). Similarly, a patient with an infarct of the cerebellar efferent pathway showed absent BP but normal CNV from scalp recordings (Ikeda et al., 1994).

A difference between the self-paced and externally triggered paradigm in our study is that the subject determined the timing of self-paced movement. Therefore, one possible interpretation of our results is that the cerebellum is involved in the timing of movement (Braitenberg, 1967; Keele and Ivry, 1990; Harrington et al., 2004; Xu et al., 2006). However, our movement tasks also differ in other aspects. For example, in the externally triggered task, the subjects were uncertain as to whether they had to perform or stop the movement with the go signal. Additional studies with different experimental designs are needed to confirm that the differences between self-paced and externally triggered movements we observed were attributable to differences in timing requirement.

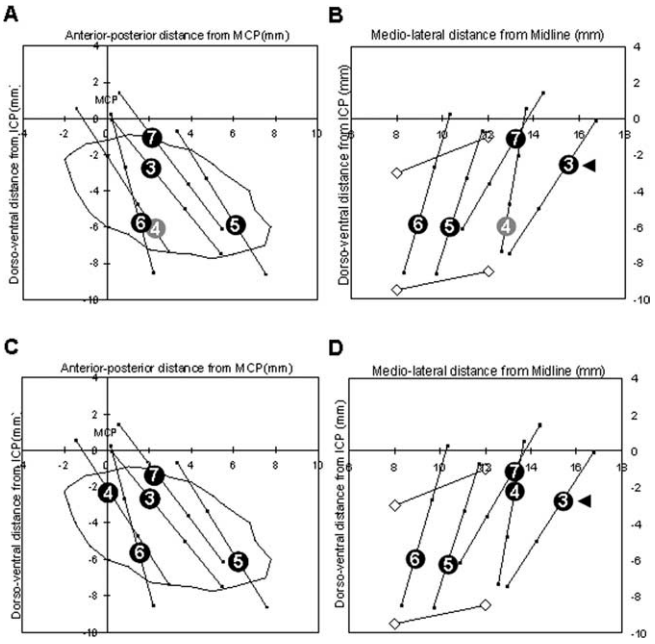

Figure 6. Location of contralateral STN contacts with phase reversal or maximum amplitude of premovement potential determined by MRI. ***A***, ***B***, Position of the contacts for self-paced movement are shown in the sagittal plot corresponding to the Schaltenbrand and Wahren (1977) atlas plate (***A***), 12 mm lateral to the midline, and in coronal planes (***B***). ***C***, ***D***, The relevant contacts during externally cued movement are shown in the sagittal (***C***) and coronal (***D***) planes. The outlines of the STN and coordinate axis are centered on the mid-commissural point (MCP). The electrode tracts are demonstrated by a line passing through the nucleus, with points indicating the site of the four contacts. The contacts where phase reversal occurred are indicated by black numbered circles. If no phase reversal was observed, a gray numbered circle between the contact pair that had the highest amplitude is shown. The number in each contact corresponds to the patient number shown in Table 1. The intercommisural plane (ICP) is perpendicular to the mid-commissural line at the MCP. In ***A*** and ***C***, anterior is to the left, and posterior is to the left. Arrows indicate that the contact is localized outside the STN.

Implications for PD

Several studies reported decreased early BP amplitude in PD (Dick et al., 1989; Jahanshahi et al., 1995), although some studies have found normal BP amplitude (Oishi et al., 1995; Ikeda et al., 1997). CNV amplitude (Amabile et al., 1986; Pulvermuller et al., 1996; Ikeda et al., 1997) is decreased in PD. Both BP and CNV amplitude have been reported to improve with dopaminergic medications (Amabile et al., 1986; Dick et al., 1987; Jahanshahi et al., 1995; Oishi et al., 1995). However, the CNV is more clearly affected in PD than the BP (Ikeda et al., 1997; Berardelli et al., 2001). An explanation is that PD patients fail to prepare for the upcoming movement during the warning–imperative interval and rely on the imperative signal as an external trigger. In self-paced movements, some degree of preparation must occur (Berardelli et al., 2001).

Our findings suggest the CNV may be more affected in PD because it requires BG activation, whereas both the BG and the CTC pathway are involved in generating the BP. A greater role of the BG in generating the CNV over the BP is consistent with the increase in CNV (Gerschlager et al., 1999) but not BP (Brown et al., 1999) amplitude with STN DBS. In the CNV paradigm, the warning signal provides a predictable timing cue for the imperative signal. Our findings may explain the observation that PD

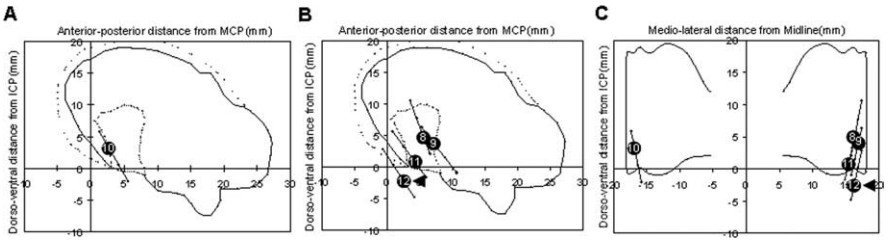

Figure 7. Location of contralateral VL contacts with phase reversal or maximum amplitude of premovement potential for self-paced movement determined by MRI. Sagittal plots corresponding to the Schaltenbrand and Wahren (1977) atlas plate, 14.5 mm lateral to the midline right sagittal (***A***), left sagittal (***B***), and coronal view of the VL (***C***). The outline of the VL and coordinate axis are centered on the mid-commissural point (MCP). The electrode tracts are demonstrated by a line passing through the nucleus, with points indicating the site of the four contacts. If phase reversal was observed between two adjacent bipolar electrodes, the contact where polarity shifted is marked by a black numbered circle. If no phase reversal was observed, then a gray numbered circle is shown between two participating contacts. The number in each contact corresponds to the patient number shown in Table 1. The intercommisural plane (ICP) is perpendicular to the mid-commissural line at the MCP. ***A***, ***B***, In the sagittal plane, anterior is to the left, and posterior is to the right. The contour line represents the limit of the nonreticular thalamus, and the dotted line represents the limit of the reticular thalamus. ***C***, In the coronal plane, the straight vertical line is the most lateral plate representing the VL, and there were no data points more laterally. The thick solid line delimits the VL. An arrow indicates that the contact is localized outside of the VL.

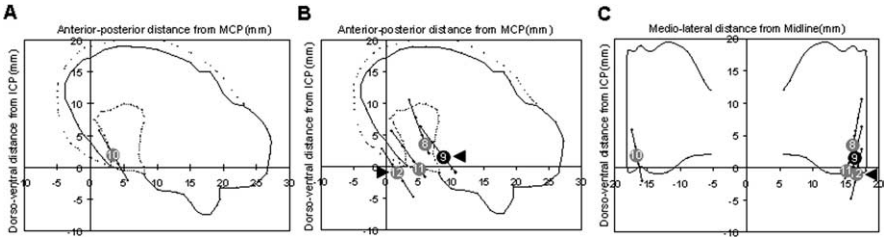

Figure 8. Location of contralateral VL contacts with phase reversal or maximum amplitude of premovement potential for externally cued movement determined by MRI. See the description for Figure 7.

patients often do not use predictive or timing cues to plan movement (Cunnington et al., 1995, 1999).

Limitations of the study

A relatively small number of patients were studied because we are limited by the number of patients who undergo DBS surgery. However, only a few centers are performing LFP studies in the BG in awake, cooperative human subjects. Postoperative drowsiness and fatigue probably contributed to experimental error and low number of trials in some subjects. At the thalamic level, the cerebellar terminations are more caudal than those arising from the BG, but there may be interdigitation and overlap. Therefore, a small contribution from the BG receiving area of the thalamus cannot be excluded.

Patients had different underlying diseases, and the surgical placement of electrodes in different locations may have impacted results. PD patients have decreased premovement MRP amplitude (Aotsuka et al., 1996; Ikeda et al., 1997), which may explain the low amplitude potentials in some patients. However, PD patients were medicated, which has been shown to normalize the scalp BP and CNV (Dick et al., 1987; Berardelli et al., 2001). The impact of essential tremor on premovement MRP has not been explored. It has been proposed that ET patients may have cerebellar abnormalities (Deuschl et al., 2000), although this may mainly involve abnormal input to the cerebellum from the inferior olive, whereas the cerebellar output pathway to the thalamus appears to be intact (Pinto et al., 2003). Moreover, almost all patients had significant scalp BP and CNV, indicating the neural processes underlying these potentials are active. The cortical BP and CNV in PD and tremor patients are comparable because they had similar onset latencies and amplitudes. Nevertheless, the possibility that the underlying diseases of our patients influenced our results cannot be excluded.

Conclusions

The cortico-BG–thalamocortical pathway is active during the preparatory phase of both externally cued and self-paced movement. In contrast, the CTC circuit shows reliable activation before self-paced movement but not before externally cued movement.

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