Bereitschaftspotential augmentation by neuro-feedback training in Parkinson's disease

Tomoyuki Fumuro [a], Masao Matsuhashi [b], Takahiro Mitsueda [a], Morito Inouchi [a], Takefumi Hitomi [a], Tomokazu Nakagawa [a], Riki Matsumoto [a], Jun Kawamata [a], Haruhisa Inoue [a], Tatsuya Mima [b], Ryosuke Takahashi [a], Akio Ikeda [a,*]

[a] Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[b] Human Brain Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan

See Editorial, pages 1262–1263

ARTICLE INFO

HIGHLIGHTS

• This study showed that Parkinson's disease (PD) patients could restore decreased early component of Bereitschaftspotential (BP) by means of neuro-feedback (NFB) to control negative slow cortical potentials (SCPs).
• It is the first study to demonstrate that decreased pre-movement cortical activity can be restored by endogenous, subject's own effort, without externally driven modulatory stimuli or medication.
• Good NFB performance of negative SCPs shifts (negativation) most likely increases excitatory field potentials of pyramidal cells in the supplementary motor area.

ABSTRACT

Objective: Decreased early Bereitschaftspotential (BP) is one of the electrophysiological characteristics in patients with Parkinson's disease (PD). We examined whether PD patients could increase BP amplitude by means of neuro-feedback (NFB) training for their slow cortical potentials (SCPs).
Methods: We worked with 10 PD patients and 11 age-matched controls. BP was measured for self-paced button pressing by their right thumb. The subjects were instructed to make the introspective efforts to produce negative SCPs (negativation). The one-day session consisted of three trials, that is, the first BP, NFB training and the second BP, and each patient performed this routine for 2–4 days. Amplitudes of the first and second BPs were compared between the two groups that were divided depending on NFB performance.
Results: Good NFB performance had the tendency of larger early BP in the second BP recording than in the first one, whereas in the poor NFB performance the early BP was smaller in the second BP recording than in the first one in both patient and normal groups ($p < 0.001$).
Conclusions: Good NFB performance of negativation could increase excitatory field potentials of pyramidal cells for the generation of early BP.
Significance: Voluntary regulation of SCPs could enhance BP in PD patients and in aged controls.

1. Introduction

Parkinson's disease (PD) is a degenerative disorder of the dopaminergic neurons of the central nervous system that impairs motor skills, speech and other functions (Jankovic, 2008). It is characterised by muscle rigidity, tremor, a slowing of physical movements (bradykinesia) and even a loss of physical movements (akinesia) in an extreme situation. The primary motor symptoms are the results of decreased activities of the motor cortices through the basal ganglia–thalamo-cortical loop, caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain (Zaidel et al., 2009). Anatomical studies of the primate basal ganglia systems show that a major portion of

* Corresponding author. Address: Department of Neurology, Kyoto University Hospital, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Tel.: +81 75 751 3772; fax: +81 75 751 9416.
E-mail address: akio@kuhp.kyoto-u.ac.jp (A. Ikeda).

pallidal output is directed to the non-primary motor areas of the frontal cortex, in particular to the supplementary motor area (SMA) (Jurgens, 1984; Schell and Strick, 1984). In humans, it was reported that the SMA is crucial to the organisation of both initial as well as sequential movements (Roland et al., 1980, 1982) and an abnormality of sequencing hand and elbow movements has been demonstrated in patients with unilateral SMA damage (Dick et al., 1986). A similar disturbance of sequenced hand and elbow movements has been demonstrated in patients with PD (Benecke et al., 1987), suggesting impairment of SMA function.

Bereitschaftspotential (BP) is a negative slow electroencephalographic (EEG) potential preceding self-paced movement (Deecke and Kornhuber, 1978). BP consists of an early and a late component (Tamas and Shibasaki, 1985; Shibasaki and Hallett, 2006). The early component of BP could reflect the activity of SMA as its maximum amplitude at the vertex (overlying SMA) regardless of the body parts involved in the movements (i.e., eye, hand, arm or foot) (Deecke and Kornhuber, 1978). The late component is lateralised to the hemisphere contralateral to the side of the movements and is considered to represent activity mainly of the primary motor cortices (Shibasaki et al., 1978; Ikeda et al., 1992).

Dick et al. reported that the early component of BP was smaller in PD patients than in control subjects whereas its late component was not (Dick et al., 1989). Furthermore, the amplitude of the early component of BP was shown to be smaller in the off-phase of L-DOPA medication and returned to normal in the on-phase (Dick et al., 1987).

Scalp-recorded EEG is comprised of a very wide range of oscillatory activities from delta to gamma, and of even direct current (DC) potential shifts, which we call slow cortical potentials (SCPs) in this report. Negative and positive SCP shifts reportedly reflect increase and decrease of the excitability of underlying cortical networks (Birbaumer et al., 1990). In epilepsy patients, negative SCPs are recorded at the time of seizure onset as ictal EEG changes (Ikeda et al., 1996). In recent years, the neuro-feedback (NFB) training was launched as an attempt to reduce seizure frequency by regulating their SCPs presumably as positive as possible in polarity (positivation) (Kotchoubey et al., 1999). In their study the Cz electrode was used to record and control SCPs and the authors showed that cortical excitability could be modified through the effort to control one's own SCPs. Using the NFB system, once they were well trained and became capable of modifying SCPs between the negativity and the positivity shifts, the degree of seizure control became better in the well-trained group than in the poorly trained group (Kotchoubey et al., 2001). We previously reported that, after enough training to regulate their SCPs by means of NFB, young normal subjects produced a larger early component of BP while they were trying to produce negative SCP shifts (negativation), as compared with the BP obtained before NFB training (Fumuro et al., 2010). By contrast, no significant differences were observed in the late component of BP between the two conditions. These results suggested that the self-regulated negative SCPs (negativation) might activate the generators of the early component of BP.

The aim of this study was to clarify whether PD patients could restore their BP amplitude by means of NFB to control negative SCPs (negativation). We therefore, investigated the effects of self-regulation of SCPs on the BP amplitude from 10 PD patients and from 11 age-matched normal controls.

2. Methods

2.1. Subjects

We investigated 10 right-handed patients (two males and eight females) clinically diagnosed as PD aged 36–71 (average of 63) years.

Table 1
Patient profile.

Patient No.	Age (years)/gender	Diagnosis	H–Y grade[a]	LED[b] (mg/d)
1	71/W	PD	III	750
2	71/W	PD	IV	350
3	65/W	PD	III	500
4	69/W	PD	III	600
5	68/W	PD	II–III	325
6	54/M	PD	I–II	350
7	36/M	PD	IV	720
8	71/W	PD	IV	413
9	56/W	PD	I–II	125
10	71/W	PD	II	305

W: woman; M: man; PD: Parkinson's disease.
The actual study was done while the medication was one in each patient.
[a] H–Y grade = Hoehn and Yahr grade (Hoehn and Yahr, 1967).
[b] LED = levodopa equivalent dose calculated by Tomlinson et al. (2010).

Their clinical features are summarised in Table 1. Eleven right-handed normal adults (one male and 10 females) aged 60–69 (average of 65) years were also investigated as controls. The dominant hand was assessed by the Edinburgh Handedness Inventory. In patients with PD, this study was done while medication was continuing (Table 1). All subjects signed the written informed consent form about the study. This study was approved by the Ethics Committee of Kyoto University School of Medicine (No. E-308).

2.2. Recording condition

Five Ag/AgCl scalp electrodes placed at C3, C1, Cz, C2 and C4 according to the International 10–10 System were used for EEG recording. An electro-oculogram (EOG) was recorded for horizontal and vertical eye movements by placing the four skin electrodes on the bilateral outer canthi and on the upper and lower edges of the left orbital, respectively. An electromyogram (EMG) was recorded from the right abductor pollicis brevis muscle by a pair of skin electrode over the muscle.

EEGs, EOGs, EMGs and input signals made by pressing the button with the subject's right hand were recorded using a DC-EEG feedback system NEURO PRAX (neuroConn GmbH, Ilmenau, Germany) (Schellhorn et al., 2004).

As the main concern of this study was to record SCPs or DC potentials reliably, we confirmed the following four conditions completely (Fumuro et al., 2010):

(1) NEURO PRAX contains a DC differential amplifier, which has a huge size of input impedance of >10 gigaohm. The huge size of the input impedance minimises the effect of electrode impedance and further enables us to record stable DC potentials without a high-pass filter (Cooper et al., 1980).

(2) Sintered Ag/AgCl electrodes were soaked in a Ten20 Conductive Paste (Weaver and Company, Aurora, CO, USA) for more than 30 min before measurement in order to stabilise the polarisation potential of the electrodes. These electrodes had lower polarisation potentials and were shown to provide stable recording condition (Tallgren et al., 2005).

(3) Before electrode attachment, the skin on which to place the surface electrodes was cleaned by both cleansing paste (Skin Pure; Nihon Kohden, Tokyo, Japan) and sanitary cotton moistened with ethanol and then electrodes as described above were firmly attached.

(4) Before actual recording sessions, we checked and confirmed that the offset voltages of all the electrodes were within ±20 mV range relative to the A1, and the standard deviation of the drifts were <1000 μV. We also visually confirmed that there was no noticeable, even very low, amplitude or very

Table 2
Analysis of NFB performance and BP (session-based and subject-based).

	PD patients (n = 10)	Healthy volunteers (n = 11)
(1) Session-based analysis		
The total number of one-day sessions	27	31
NFB performance analysis[a]	17	20
Good NFB performance	8 (47%)	12 (60%)
Poor NFB performance	9 (53%)	8 (40%)
BP analysis[b]	13	17
Good NFB performance	7	10
Poor NFB performance	6	7
(2) Subject-based analysis		
Total number of subjects	10	11
The number of subjects for BP analysis[c]	7	9
The number of good NFB group	4	5
The number of poor NFB group	3	4

[a] The first-day sessions (n = 10 and 11) were excluded for further analysis in PD and normals. It was because that in the initial training period subjects could not be familiar with or not good at this internal neuro-feedback process which could distort the finding erroneously.

[b] The first-day sessions (n = 10 and 11) and one-day sessions of poor BP reproducibility (n = 4 and 3) were excluded for further analysis in PD and normals.

[c] Subjects having only single one-day session (n = 1 and 1) and poor BP reproducibility (n = 2 and 1) were excluded from further analysis in PD and normals.

slow artefacts on the EEG waveforms before and throughout the measurement. Ordinary impedance check with 10 Hz alternating current used for conventional EEG, that is, AC potential, recording was not performed.

All signals were digitised at the sampling rate of 128 Hz and band-pass filter from DC to 30 Hz was applied. The subjects sat in a chair comfortably with their arms and hands on the armrests. A computer screen was placed in front of the subjects 130–150 cm from their faces. The eye movement-correction program built into the NEURO PRAX was used to diminish eye movement artefacts. EEG signals were referred to A2 during both NFB training and BP recording.

2.3. Task

2.3.1. Procedural overview

The subjects performed three kinds of tasks in 1 day in the following order: (1) the first BP recording, followed by a 5-min break; (2) NFB training to regulate SCPs (2–5 times of sub-sessions with 3-min breaks), followed by a 5-min break; and (3) the second BP recording while subjects made introspective efforts that produced the negative SCP shifts (negativation) (Fig. 1). The subjects repeated the set of procedures (1)–(3) (1-day session) as described above 2–4 times each on another day, with 1–6 days of interval in between. The BP recording and the NFB training on the first day for each subject were regarded as rehearsal sessions and thus
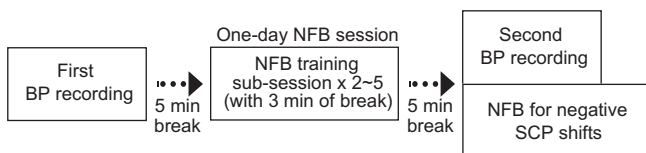

Fig. 1. Procedural overview. Subjects performed 3 kinds of tasks in one day in the following order: (1) the first BP recording, followed by 5 min of break, (2) NFB training to regulate SCPs (2–5 times of sub-sessions with 3 min of break), followed by 5 min of break, (3) the second BP recording while subjects made introspective efforts that produced the negative SCP shifts.
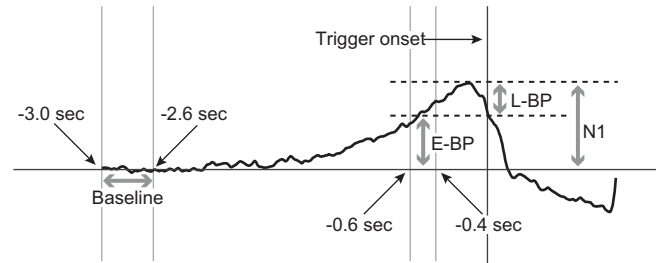

Fig. 2. Schema of BP components and its measurement. Baseline: mean amplitude of the movement-related cortical potentials (MRCPs) between 3.0 and 2.6 s before the trigger onset. Early BP (E-BP): mean amplitude of the MRCPs between 0.6 and 0.4 s before the trigger onset. Pre-movement negative peak (N1): the largest pre-movement negative potentials between −0.5 s and the trigger onset time measured from the baseline. Late-BP (L-BP): this steeper negativity was obtained by subtracting the E-BP from N1.

those were not included for the final analysis. This was not informed to the subjects before examination.

2.3.2. BP recording

The subjects were instructed to look at the blank screen in front of them but not to fixate on a certain point. They were told not to blink from 3 s before to 1 s after the button-press. They performed self-paced, brisk button-press by their right thumb about every 10 s. All subjects had approximately 100 trials of button-press, which was sufficient to obtain approximately 80 epochs of artefact-free trials. EEG signals were referred to as A2 during BP recording, and the reference was changed to linked reference of A1 and A2 for BP analysis.

Four seconds of analysis epochs from −3 to +1 s to the onset of button-press were cut out from the raw data in an off-line manner; EEG data during BP recording were first linearly detrended for each 4 s of the EEG segment. Applied detrend could work for a linear fit (in the least-squares sense) to EEG data and then remove the inappropriately occurring trend from it. The epochs containing artefacts exceeding 150 µV in amplitude (from negative peak to positive peak or vice versa) in the EEG channels were excluded. Artefact-free EEG epochs were precisely aligned to the trigger signal of button-press and averaged. EEG baseline was defined as the mean amplitude of the first 0.4 s of the epoch.

At least 50 artefact-free epochs were averaged. To confirm the reproducibility, the epochs were divided into two groups (odd and even numbers of epochs during BP recording) and were averaged to make two subensembles of waveforms. The sessions where two subensembles of BP were not reproducible were excluded from further analysis. We evaluated the following three measures (Fig. 2):

(1) Early BP (E-BP): Mean amplitude of the movement-related cortical potentials (MRCPs) between 0.6 and 0.4 s before the trigger onset. It corresponds to the E-BP (Shibasaki et al., 1980; Shibasaki and Hallett, 2006).

(2) Pre-movement negative peak (N1): The largest pre-movement negative potentials occurring between −0.5 s and the trigger onset measured from the baseline. As this study employed the button-press for the trigger onset instead of surface EMG onset, the pre-movement potentials often peaked immediately before the button-press trigger onset, and thus its amplitude could contain the whole BP and motor potential in Shibasaki and Hallett (2006). Therefore, we termed it the pre-movement negative peak.

(3) Late-BP (L-BP): This steeper negativity was obtained by subtracting the E-BP from N1 and arbitrarily referred to as L-BP. It mainly corresponds to NS′ (Shibasaki et al., 1980; Shibasaki and Hallett, 2006) although it may partly contain motor potential as explained just above.
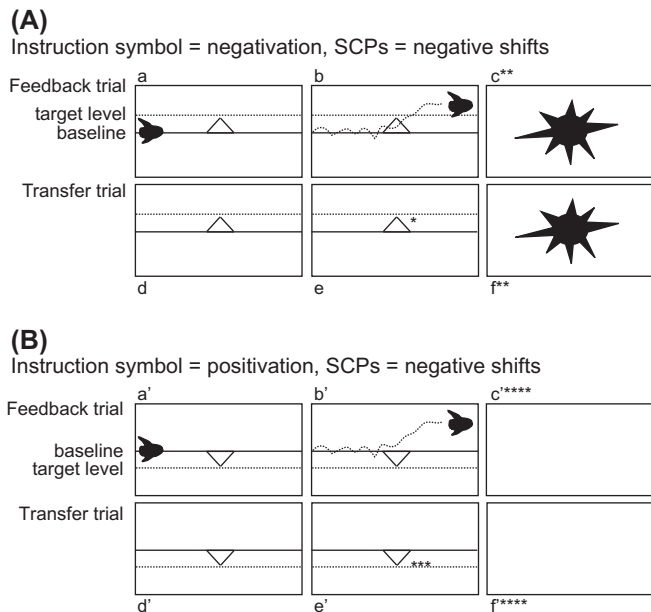
(A)
Instruction symbol = negativation, SCPs = negative shifts

(B)
Instruction symbol = positivation, SCPs = negative shifts

Fig. 3. The actual display during NFB trial. Depending on the task (negative shift or negativation vs. positive shift or positivation), a triangle or reversed triangle appears in the center of the display at the beginning (a, d, a′ and d′). During NFB, the actual state of SCPs is shown as a marker of the fish and it moves toward the right (b, b′). When the subjects successfully control SCPs upon the task, a reward-mark appears in the center at the end (c, f). The same procedures are also done without any appearance of SCP information (without a marker of fish), as shown in d, e, f, d′, e′ and f′. The details are described in the Section 2.3.3. *Instruction symbol to produce negative SCPs shifts (negativation). **The shining sun as the reward mark for successful trial. ***Instruction symbol to produce positive SCPs shifts (positivation). ****Since the SCPs shifts fail to exceed the defined target level, no reward mark appears (Cited and modified from Fumuro et al., 2010).

2.3.3. NFB: self-regulation of SCPs

NFB training to regulate SCPs was done after 5 min of break following the first BP recording. The procedure was the same as the previous study (Kotchoubey et al., 2001; Fumuro et al., 2010).

SCPs recorded from Cz were continuously shown on the front screen as a slowly moving sunfish from the left to the right by 8 s as an almost real-time demonstration (the feedback time delay was around 150 ms) (Fig. 3). The sunfish also shifted upward (negative shift or negativation) or downward (positive shift or positivation), according to the change of SCPs. Namely, the sunfish worked as a visual feedback of the subjects' own SCPs at Cz. Once the sunfish appeared at the left edge, the dichotic instruction symbols appeared in the centre of the screen: the upward or downward arrowhead at the same time (Fig. 3). The direction of the apex of the arrowhead, up or down, indicated the polarity to which the subjects should shift their SCPs.

The subjects were told to regulate the SCPs upon the instruction symbols, and by means of this real-time feedback of SCPs at Cz the subjects tried to learn how to control it by themselves. Therefore, any specific suggestions on how to regulate SCPs were not initially provided by the examiners; the subjects were advised to concentrate on the SCP shift and to find the most successful strategy to move the sunfish towards the required direction. The examiner gave them some examples of mental introspection to control SCPs, which were done and were found useful in the young subjects in our previous study (Fumuro et al., 2010), if they wanted to know.

Each trial lasted 10 s, which was from 2 s before to 8 s after the appearance of the instruction symbols on the centre of the screen. The next trial was separated from the previous trial by random intervals of 1–6 s. Negative- and positive-feedback trials were presented pseudo-randomly at equal probability. NFB training sub-sessions were conducted 2–5 times in 1 day, and each sub-session had 52 trials. The number of sessions was determined based on each subject's condition and fatiguability.

Since this training procedure was expected to be done finally without the apparatus, trials with and without feedback information (the moving sunfish) were intermixed pseudo-randomly in equal numbers, the latter called transfer trials (Fig. 3A and B: lower half).

The trial was judged successful for feedback control once the SCP amplitude exceeded a defined target level and remained at least for 2 s in the last 4 s of the trial. This target level was set by the examiner as follows: in the negative shift trials, the level was set to the range from the baseline to −30 to −50 μV, and in the positive shift trials it was from the baseline to +30 to +50 μV. The EEG baseline was obtained from the first 1 s of the trial. In the case of successful trial, another graphic symbol ('the shining sun') appeared as a reward mark (Fig. 3A: right). The reward marks were also presented in transfer trials when judged successful. The data in the transfer trials were employed for the judgement of performance as described later in the method. The effective visual field for each eye is described below: sunfish: 3 × 3 (degree in horizontal × vertical), arrowhead: 1–2 × 3, the shining sun: 6–8 × 5–7, width of display: 9–10 × 11–13.

After each sub-session, the experimenter asked the subjects their introspective strategies and encouraged them to renew them if the result of the previous sub-session did not have many successful trials.

3. Analysis

3.1. Analysis of NFB (Table 2: upper half)

EEGs of the transfer trials in the latter half of the two to five sub-sessions out of 1-day training were processed by a high-frequency filter of 2 Hz, and then separately averaged for the negativity and positivity trials. (In the case of a total of three or five sub-sessions, the second or third sub-session was included in the average.) Trials containing artefacts exceeding 200 μV (peak to peak) in any of the EEG channels were excluded from the average.

A 1-day session was classified as a good NFB performance if the averaged waveforms of the negativity trials exceeded that of the positivity trials of at least three electrodes including Cz in the period of 2–6 s after the visual symbol appeared on the left (Fig. 4: left). Otherwise, it was classified as a poor NFB performance (Fig. 4: right).
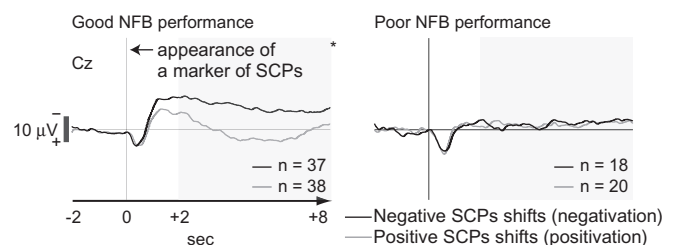

Fig. 4. Example of averaged waveform of the SCPs shift in the good NFB one-day session (left) and poor NFB one-day session (right) (a normal control). The thick line is the results of negative SCPs performance (negativation), and thin lines for the positive SCPs performance (positivation). *n* = the number of trials. *If averaged waveforms of the negativity trials exceed that of the positivity trials at least 3 electrodes including Cz during this time period, it was judged as good performance. Otherwise, judged as poor.

3.2. Analysis of BP (Table 2: lower half)

All statistical analyses were performed with SPSS (version 15.0, SPSS Inc., Chicago, IL, USA). Analysis was performed for three BP components (E-BP, N1 and L-BP) at Cz because that mean differences between the first and second BP amplitudes were the most prominent at Cz as compared with other electrodes and that the visual feedback of the subjects' own SCPs was recorded from Cz during NFB training. The Shapiro–Wilk test was used to assess for normality; if normality is accepted, analysis of variance (ANOVA) was used. Otherwise, the Mann–Whitney U test was used. In order to take the multiplicity of comparisons into account, p values were corrected with Holm's correction in all statistical analyses. In order to strengthen the findings, we have analysed all the data in the session-based and subject-based analyses as follows.

3.2.1. Session-based analysis (Figs. 5–7)

The first 1-day sessions in all the subjects and any 1-day sessions without reproducibility of subensembles of BP waveform were excluded, and then the mean difference between the first and second BP amplitudes was compared. In subjects who had both good and poor NFB performance, those 1-day sessions were
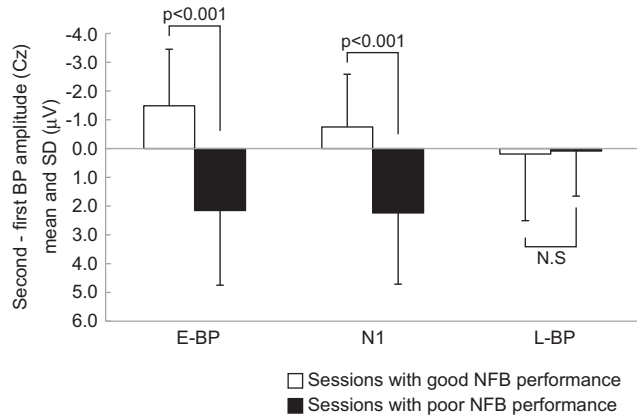

Fig. 5. Effects of NFB performance on BP for Cz. Each bar indicates the mean difference between the second and first BP amplitudes at Cz (the second BP amplitude was subtracted from the first BP amplitude). The second E-BP and N1 tended to be larger than the first ones in the good NFB one-day sessions, whereas in the poor NFB performance the second E-BP and N1 tended to be smaller than the first one. L-BP did not show any difference. In good NFB performance, the number of trials of BP was 82 ± 17 (mean ± SD) in the first BP, and 82 ± 16 in the second BP. Similarly, in poor NFB performance, the number was 97 ± 30 and 92 ± 23, respectively.
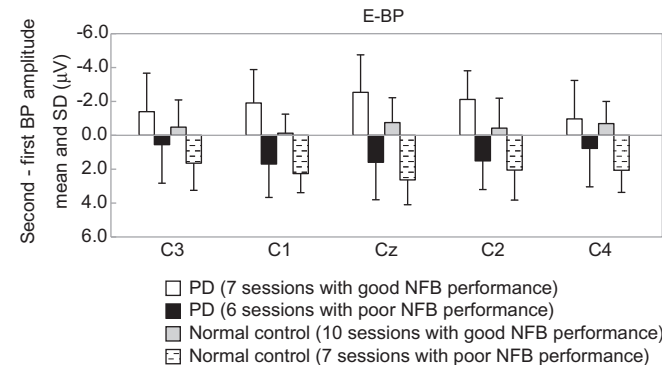

Fig. 6. Effects of NFB performance on early BP for scalp distribution. Each bar indicates the mean difference between the second and first BP amplitudes at each electrode (the second BP amplitude was subtracted from the first BP amplitude). Cz showed the maximum value with bilateral attenuation.
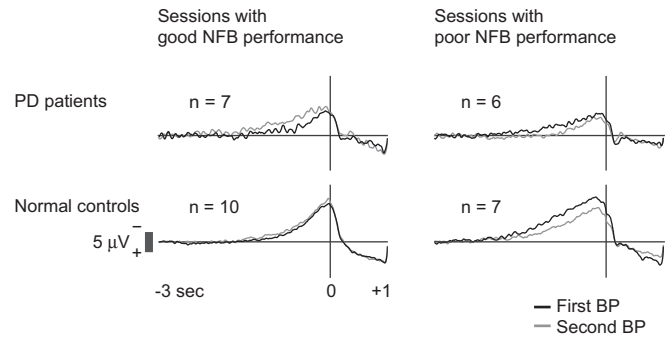

Fig. 7. Grand-averaged BP in PD patients and normal controls (Cz) by session-based analysis. The thick waveform shows the BP measured before the NFB training (first BP). The thin one was the BP (second BP) measured after the training while self-regulated negative SCPs (negativation) was performed. Good NFB performance had the tendency of larger early BP in the second BP than in the first one, whereas the early BP tended to be smaller in the second BP than in the first one in the poor NFB performance in both PD and normal control. n = the number of session.

separately enrolled in both good and poor NFB performance, respectively. Two-way ANOVA having two between-subject factors (1 – disease: PD patients and normal controls, 2 – NFB performance: good and poor NFB performance) was conducted to analyse the mean difference between the first and the second BP amplitudes at Cz.

3.2.2. Subject-based analysis

Similar to the session-based analysis, the first 1-day sessions in all the subjects and any 1-day sessions without reproducibility of subensembles of BP waveform were excluded and then the mean difference between the first and second BP amplitudes was compared in each subject. The last 1-day session was adopted for the analysis of the mean difference between the first and second BP amplitudes. All subjects were finally divided into two subject-analysis groups. Two-way ANOVA was conducted to analyse the mean difference between the first and the second BP amplitudes in the same manner as the session-based analysis.

3.2.3. Comparison of BP between PD patients and normal controls

A statistical analysis with the Mann–Whitney U test was performed to assess the difference of the first and second BP between PD patients and normal controls at Cz regardless of the degree of their NFB performance. This analysis adopted the data of the session-based BP analysis.

4. Results

4.1. Performance of NFB (Table 2: upper half)

In PD patients, out of a total of 27 sessions of 1-day duration, the first 1-day session in 10 patients was automatically excluded from further analysis. This was because, in the initial training period, these subjects were unable to become familiar with or perform adequately in the internal NFB process, and this could distort the findings erroneously. Eight 1-day sessions were grouped into good NFB performance and nine sessions were into poor NFB performance. In normal controls, out of a total of 31 1-day sessions, the first 1-day session in 11 subjects was excluded automatically from further analysis. Twelve 1-day sessions were grouped into good NFB performance and eight 1-day sessions were into poor NFB performance. To compare the good performance rate between the first 1-day sessions and the second to fourth 1-day sessions, 10 and 11 1-day sessions in the first day were also judged for performance in PD and normals, respectively. The good performance rate was

higher in the second to fourth 1-day sessions than in the first 1-day sessions (30% vs. 47% in PD, 36% vs. 60% in normals, though this did not reach statistical significance).

The number of finally accepted 1-day sessions of NFB was similar in both the patient and control groups (17 vs. 20). The number of 1-day sessions with good NFB performance was 47% and 60% in the two groups, respectively.

4.2. Effects of NFB on BP

4.2.1. Session-based analysis

E-BP (Fig. 5, Fig. 6): Two-way ANOVA revealed significant main effect of NFB performance ($F (1,26) = 21.077$, $p < 0.001$). No main effect of disease or interaction attained significance. This means that regardless of PD or normal controls, the second E-BP tended to be larger than the first one in the good NFB 1-day sessions, whereas in the poor NFB performance the second E-BP tended to be smaller than the first one.

N1 (Fig. 5): Two-way ANOVA revealed significant main effect of NFB performance ($F (1,26) = 18.389$, $p < 0.001$). No main effect of disease or interaction attained significance. The result of N1 turned out to have a similar tendency as that of E-BP.

L-BP (Fig. 5): Two-way ANOVA revealed no significant main effect or interaction.

4.2.2. Subject-based analysis (Table 2: lower half)

As the subject-based analysis, four PD patients were grouped into the good NFB group, and three patients were into the poor one. In normal controls, five subjects were placed into the good group and four were into the poor one.

Two-way ANOVA revealed significant main effect of NFB performance on E-BP ($F (1,15) = 12.607$, $p = 0.006$) and N1 ($F (1,15) = 18.800$, $p = 0.002$). No main effect of disease or interaction attained significance. Similar to session-based analysis, this means that regardless of PD or normal controls, the second E-BP and N1 tended to be larger than the first ones in the good NFB group, whereas the poor NFB group tended to have smaller E-BP and N1 in the second BP than in the first one. By contrast, no significant differences were observed in the L-BP (no figures shown).

4.3. Comparison of BP between PD patients and normal controls (Fig. 8

The Mann–Whitney U test revealed significant difference of the session-based first BP between PD patients and normal controls in N1 ($p = 0.035$) and E-BP ($p = 0.039$). No significant difference was found in L-BP. This means that the first E-BP and N1 were smaller in PD than those in normal controls, whereas L-BP did not reach the significant difference. The result of the second N1 and E-BP turned out to be a similar significant difference as the first one (N1: $p = 0.021$, E-BP: $p = 0.039$, L-BP: not significant).

5. Discussion

Brain plasticity, brain–computer interface and neuromodulation are the most important concerns in current clinical neuroscience. Deep-brain stimulation in patients with PD provided the great success at least to lessen the patients' symptoms. It belongs to the externally regulated or exogenous procedure of neuromodulation. BP was modulated by TMS previously (Rossi et al., 2000); however, little has been investigated regarding an intrinsic, endogenous procedure for BP modulation.

We previously reported that, after enough training to regulate their SCPs by means of NFB, young normal controls produced a larger early component of BP while they were trying to produce negative SCP shifts (negativation), as compared with BP obtained
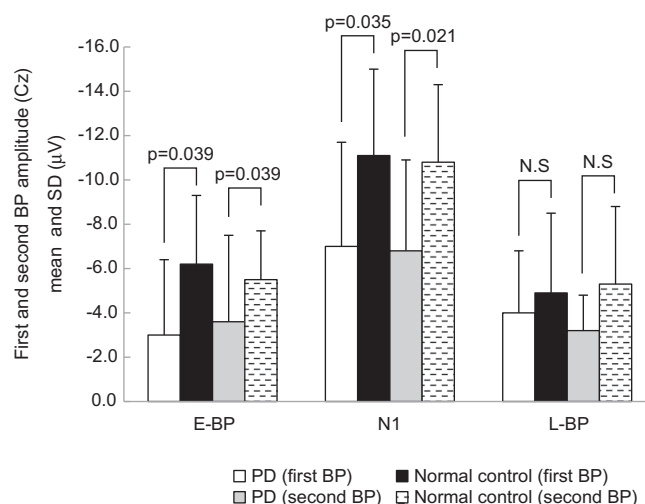

Fig. 8. Comparison of BP at Cz between PD patients and normal controls. Each bar indicates the mean BP amplitude at Cz. PD patients had smaller early BP than aged normal controls, but not for late component of BP.

before NFB training (Fumuro et al., 2010). By contrast, no significant differences were observed in the late component of BP between the two conditions. These results suggested that the self-regulated negative SCPs (negativation) could activate the generators of early component of BP.

The aim of this study was to clarify whether PD patients could restore their BP amplitude by means of NFB to control negative SCPs (negativation). This study presented the first scientific evidence that MRCPs could be restored by the subject's own effort, instead of the external stimuli or medication in patients with PD and aged normal controls. As results, with regard to BP, similar to the previous study (Dick et al., 1989), PD patients had smaller E-BP than aged normal controls, but not for the late component of BP (Fig. 8). This suggests that the situation in the present study of MRCP is very consistent with the previous study.

We could summarise the main finding as follows. Good NFB performance had the tendency of larger, E-BP in the second BP than in the first one, whereas the E-BP tended to be smaller in the second BP than in the first one in the poor NFB performance in both PD and normal control (Figs. 5–7).

The present study provides us with the very important concerns as follows: (1) decreased BP in patients with PD could be potentially reversible as long as NFB was well performed or the non-pharmacological process optimally works in the brain and (2) neurophysiological BP modulation is mainly for its early component rather than the late one immediately before voluntary movement onset. With regard to (1), it was previously reported that administration of L-DOPA in normal controls could significantly increase the amplitude of BP (Dick et al., 1987). Namely, not only administration of dopaminergic drugs but also neurophysiological intrinsic activity commonly modify brain activity. Deep-brain stimulation could lessen the clinical symptoms of patients with PD, but it remains to be solved whether the present study or neuromodulation of BP would lessen the symptoms of patients with PD (or not) in future studies. As regards (2) or generators of BP, surface-negative BP is assumed to reflect field potential, probably excitatory postsynaptic potentials (EPSPs) in the superficial layer of the apical dendrite of cortical pyramidal neurons as the result of the thalamo-cortical input (Hashimoto et al., 1979). The current consensus of the generators of the early component of BP is that it begins in the pre-SMA with no site specificity and is followed by the SMA proper according to the somatotopic organisa-

tion, as well as in the lateral motor cortices bilaterally, again with relatively clear somatotopy (Ikeda et al., 1992, 1995; Yazawa et al., 2000).

The late component of BP occurs in the contralateral M1 and the lateral motor cortices with precise somatotopy (Neshige et al., 1988; Shibasaki and Hallett, 2006). With regard to the effect of NFB on the E-BP component, the contribution of electrical fields arising from at least bilateral pre-SMA and SMA proper for the midline component was most likely. From this point of view, SMA activation by means of the self-regulated negative SCPs would act to restore E-BP in PD patients, which showed hypofunction in the SMA as reported before. This implication is consistent with previous study by using functional magnetic resonance imaging (fMRI): a strong positive correlation between negativation of SCP and blood oxygenation level-dependent (BOLD) contrasts was found in the hippocampus and the SMA (Hinterberger et al., 2003). According to these findings, the increased amplitude of E-BP while the negativation task was performed can be interpreted as efficient thalamo-cortical modulation via at least SMA.

With regard to the cortical generators of scalp-recorded SCP, NFB in the present study may share the features of pursuit such as visuo-motor performance using a BP trajectory definitely:

(1) It could affect SCP amplitude because of co-occurrence of pursuit related BP. In addition, NFB in the present study also may share the features of the methods of contingent negative variation (CNV), and at least the SMA is activated during the CNV paradigm. During NFB performance, similar to the trials with visual feedback ('sunfish', in Fig. 3), subjects might have had an image of moving fish in their mind even during the trials without visual feedback.
(2) It could affect the amplitude of the second BP because of co-occurrence of memory-guided pursuit imaging CNV.

For (1), the amplitude of scalp-recorded BP is usually rather small (several μV) as compared with SCP amplitude (10–20 μV); its effect could be practically little. For (2), it is still possible and should be carefully taken into account.

There is a different finding in BP between the present study and our previous one (Fumuro et al., 2010) in the poor-performance situation as follows. In the previous study, young subjects showed increased E-BP amplitude with good NFB performance in the second BP recording as compared with the first recording. In the poor NFB performance, they did not show significant difference of E-BP between the first and second BP recording. In the present study, good NFB performance showed more or less a similar tendency of E-BP as seen in young normal controls. However, the E-BP tended to be smaller in the second BP than that in the first one in the poor NFB performance in both PD and normal controls (Figs. 5–7). This tendency may reflect the effects of probably central fatigue in aged normal controls. In the present study, an entire examination of a single session took 2–3 h, including the time for preparation. The repetitive process of button-press would cause fatigue and result in the decrement of the BP usually (Dirnberger et al., 2004). In the good NFB performance, this decrement may be cancelled out or rather more exceed its former state by the good negative SCP performance. By contrast, fatigue may directly affect BP in the poor NFB performance. However, in the young subjects, the degree of fatigue would be just so small that the degree of NFB performance more directly affected the BP amplitude. Another possible cause for this tendency is the different degree of adaptation to the task. As described in previous literature (Shibasaki and Hallett, 2006), more intention would result in larger amplitude of BP. For instance, in sessions with poor NFB performance, the subjects may have higher motor commands to execute the task in the recording of the first BP; then they may gradually adapt to the optimised com-

mands or efforts to adjust the task, resulting in normal motor control. Although sessions with poor adaptability were excluded from the final analysis, we could not completely exclude this possibility.

There are several limitations in the present study. First, the terms of the NFB training were limited to only 2–4 days. Because of the short term of NFB training, we could not verify whether each subject achieved a better NFB performance day by day or not. Therefore, the grouping by 1-day sessions required further validation as to whether the NFB performance improved much more with lesser artefact. In order to have artefact-free data, as described previously (in the Methods), (1) the notion that averaged waveform of the SCPs should show reproducibility was verified in several electrodes, (2) in BP measurement, epochs containing artefacts were excluded in an objective manner and (3) epochs were separately averaged into two BP waveforms and any measurements with poorly reproducible BP were excluded from further analysis. Through these processes, most artefacts should be excluded from the result and final analysis had the minimised artefact effects. In addition, we compared the two BP waveforms that are measured in the same day, for reducing the effect of various factors such as level of intention and preparatory state that affect the magnitude of BP (Shibasaki and Hallett, 2006). Second, we put together all the PD patients with mild-to-severe degree of Hoehn and Yahr grade (H–Y grade) (Hoehn and Yahr, 1967) into one group. It is possible that each grade has different neurobiological mechanisms and therefore different BP characteristics. Third, the underlying working mechanism of NFB training remains to be solved. It is probably closely associated with the guided activation theory, rather than the reinforcement learning theory although there is some overlap between the two. It is also related to free will but partly to the automatically guided action since the dichotic instruction symbols let subjects decide either direction of NFB procedure.

Good and poor outcome are in almost the same possibilities not only in the present but also previous study (Kotchoubey et al., 1999). About 50% of the good outcome may be criticised as it is by chance or chance-level. However, this is unlikely because of the following two reasons: (1) when we compared good outcome rate between the first 1-day sessions and the second to fourth 1-day sessions, it was higher in the second to fourth 1-day sessions than in the first 1-day sessions (30% vs. 47% in PD, 36% vs. 60% in normal controls) (although it did not reach statistical significance) and (2) Kotchoubey et al. (1997) showed that many training sessions produced higher rate of good outcome; namely, after 35 training sessions, 13 among 18 patients (=72%) showed so-called good training performance. This suggests that longer training is needed to obtain a higher rate of good training outcome.

As a better successful rate in NFB training is essential for clinical applications, a more effective training method should be developed. Good regulation of the SCP could provide us with better clinical application. Therefore, it is also very important to delineate any factors to enhance or predict good training performance for clinical application. For example, since event-related synchronisation or desynchronisation of background EEG could reflect the intercortical or cortico-subcortical network interaction, a further analysis with SCP may provide us with any predictable information in this regard in the future. Furthermore, future studies could clarify the effect of NFB on BP in PD patients with different degree of symptoms.

6. Conclusions

Good NFB performance of negative shifts (negativation) could increase excitatory field potential, probably EPSP of pyramidal cells for the early component of BP generation in PD patients and aged normal controls. NFB could enhance the excitability of cortices re-

lated to voluntary movement preparation, and a further investigation will be warranted for improvement of clinical motor function of PD in relation to BP restoration.

Acknowledgements

References

Benecke R, Rothwell JC, Dick JP, Day BL, Marsden CD. Disturbance of sequential movements in patients with Parkinson's disease. Brain 1987;110:361–79.

Birbaumer N, Elbert T, Canavan AG, Rockstroh B. Slow potentials of the cerebral cortex and behavior. Physiol Rev 1990;70:1–41.

Cooper R, Osselton JW, Shaw JC. EEG technology. 3rd ed. London: Butterworths; 1980.

Deecke L, Kornhuber HH. An electrical sign of participation of the mesial 'supplementary' motor cortex in human voluntary finger movement. Brain Res 1978;159:473–6.

Dick JPR, Benecke R, Rothwell JC, Day BL, Marsden CD. Simple and complex movements in a patient with infarction of the right supplementary motor area. Mov Disord 1986;1:255–66.

Dick JPR, Cantello R, Buruma O, Gioux M, Benecke R, Day BL, et al. The Bereitschaftspotential, L-DOPA and Parkinson's disease. Electroencephalogr Clin Neurophysiol 1987;66:263–74.

Dick JPR, Rothwell JC, Day BL, Cantello R, Buruma O, Gioux M, et al. The Bereitschaftspotential is abnormal in Parkinson's disease. Brain 1989;112:233–44.

Dirnberger G, Duregger C, Trettler E, Lindinger G, Lang W. Fatigue in a simple repetitive motor task: a combined electrophysiological and neuropsychological study. Brain Res 2004;1028:26–30.

Fumuro T, Matsuhashi M, Mitsueda T, Inouchi M, Matsumoto R, Fujita M, et al. Neuro-feedback training of slow cortical potentials improves Bereitschaftspotential in normal controls. Jpn, J Clin Neurophysiol 2010;38:172–80 (abstract in English).

Hashimoto S, Gemba H, Sasaki K. Analysis of slow cortical potentials preceding self-paced hand movements in the monkey. Exp Neurol 1979;65:218–29.

Hinterberger T, Veit R, Strehl U, Trevorrow T, Erb M, Kotchoubey B, et al. Brain areas activated in fMRI during self-regulation of slow cortical potentials (SCPs). Exp Brain Res 2003;152:113–22.

Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–42.

Ikeda A, Luders HO, Burgess RC, Shibasaki H. Movement-related potentials recorded from supplementary motor area and primary motor area. Role of supplementary motor area in voluntary movements. Brain 1992;115:1017–43.

Ikeda A, Luders HO, Shibasaki H, Collura TF, Burgess RC, Morris 3rd HH. Movement-related potentials associated with bilateral simultaneous and unilateral movements recorded from human supplementary motor area. Electroencephalogr Clin Neurophysiol 1995;95:323–34.

Ikeda A, Terada K, Mikuni N, Burgess RC, Comair Y, Taki W, et al. Subdural recording of ictal DC shifts in neocortical seizures in humans. Epilepsia 1996;37:662–74.

Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368–76.

Jurgens U. The efferent and afferent connections of the supplementary motor area. Brain Res 1984;300:63–81.

Kotchoubey B, Blankenhorn V, Froscher W, Strehl U, Birbaumer N. Stability of cortical self-regulation in epilepsy patients. Neuroreport 1997;8:1867–70.

Kotchoubey B, Strehl U, Holzapfel S, Blankenhorn V, Froscher W, Birbaumer N. Negative potential shifts and the prediction of the outcome of neurofeedback therapy in epilepsy. Clin Neurophysiol 1999;110:683–6.

Kotchoubey B, Strehl U, Uhlmann C, Holzapfel S, Konig M, Froscher W, et al. Modification of slow cortical potentials in patients with refractory epilepsy: a controlled outcome study. Epilepsia 2001;42:406–16.

Neshige R, Luders H, Shibasaki H. Recording of movement-related potentials from scalp and cortex in man. Brain 1988;111(Pt 3):719–36.

Roland PE, Larsen B, Lassen NA, Skinhoj E. Supplementary motor area and other cortical areas in organization of voluntary movements in man. J Neurophysiol 1980;43:118–36.

Roland PE, Meyer E, Shibasaki T, Yamamoto YL, Thompson CJ. Regional cerebral blood flow changes in cortex and basal ganglia during voluntary movements in normal human volunteers. J Neurophysiol 1982;48:467–80.

Rossi S, Pasqualetti P, Rossini PM, Feige B, Ulivelli M, Glocker FX, et al. Effects of repetitive transcranial magnetic stimulation on movement-related cortical activity in humans. Cereb Cortex 2000;10:802–8.

Schell GR, Strick PL. The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. J Neurosci 1984;4:539–60.

Schellhorn K, Markert S, Berkes S, Bolten J, Schlegelmilch F. A multifunction EEG-feedback system. Biomedizinische Technik 2004;49:766–7.

Shibasaki H, Shima F, Kuroiwa Y. Clinical studies of the movement-related cortical potential (MP) and the relationship between the dentatorubrothalamic pathway and readiness potential (RP). J Neurol 1978;219:15–25.

Shibasaki H, Barrett G, Halliday E, Halliday AM. Cortical potentials following voluntary and passive finger movements. Electroencephalogr Clin Neurophysiol 1980;50:201–13.

Shibasaki H, Hallett M. What is the Bereitschaftspotential? Clin Neurophysiol 2006;117:2341–56.

Tallgren P, Vanhatalo S, Kaila K, Voipio J. Evaluation of commercially available electrodes and gels for recording of slow EEG potentials. Clin Neurophysiol 2005;116:799–806.

Tamas LB, Shibasaki H. Cortical potentials associated with movement: a review. J Clin Neurophysiol 1985;2:157–71.

Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649–53.

Yazawa S, Ikeda A, Kunieda T, Ohara S, Mima T, Nagamine T, et al. Human presupplementary motor area is active before voluntary movement: subdural recording of Bereitschaftspotential from medial frontal cortex. Exp Brain Res 2000;131:165–77.

Zaidel A, Arkadir D, Israel Z, Bergman H. Akineto-rigid vs. tremor syndromes in Parkinsonism. Curr Opin Neurol 2009;22:387–93.