Comparison of Bereitschaftspotentials (BP) in finger tasks between schizophrenia patients and control subjects

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Key words: schizophrenia, Bereitschaftspotential (BP), complex finger task, motor dysfunction

Abstract

Dysfunction of voluntary motor movements in schizophrenia patients has been clinically observed. It has been suggested that schizophrenia patients have difficulty in programming voluntary movements such as preparation and intention to act. Recording of Bereitschaftspotentials (BP) can provide neurophysiological measure of voluntary movements and can index motor preparatory function. Previous BP studies in schizophrenia patients seem to be contradictory in terms of several points. Thus, we assessed the BP generated prior to a simple finger task and a complex finger task in 11 schizophrenia patients with positive symptoms, 13 schizophrenia patients with negative symptoms and 11 normal control subjects. All schizophrenia patients have no drug induced parkinsonism and tardive dyskinesia. We compared the BPs in two different schizophrenia groups with the corresponding data from the control group. To evaluate actual motor performance, we also employed finger tapping task and pegboard tasks. The most prominent result was shown in the complex finger task. During the complex finger task requiring sequential motor processes, we found a significantly smaller late BP in schizophrenia patients with negative symptoms and a significantly larger late BP in schizophrenia patients with positive symptoms, as compared to late BP in normal healthy subjects. During the simple finger task, we found only a significant difference; schizophrenia patients with negative symptoms showed a significantly smaller late BP than that in normal healthy subjects. Both of these patient groups showed poor motor performance in the finger tapping and pegboard tasks. These abnormal neurophysiological changes of BP in schizophrenia patients may be explained by dysfunction of sensorimotor and supplementary motor area generating the BP. Furthermore, since late BP is related to motor preparatory function, we hypothesize that: 1) an inappropriate level of BP particularly during the complex finger task requiring more motor preparatory function in schizophrenia patients may cause the poor motor performances; 2) schizophrenia patients have impaired optimal control of motor preparatory function. The present study may provide further support for motor dysfunction in schizophrenia.

Introduction

Bereitschaftspotential (BP) is a negative potential occurring approximately 1.5 s before voluntary movements. BP is classified into three components; early BP, late BP and peak BP. Early BP occurs 1.6 s prior to voluntary movements. Late BP occurs 0.3 s~0.5 s prior to voluntary movements. In general, these BPs are thought to reflect motor preparatory functions such as motor programming and intention to act.

Dysfunction of voluntary movements has been clinically observed in schizophrenia patients. However, motor tasks, such as voluntary movements, have rarely been investigated in schizophrenia. BP recordings can provide an electrophysiological measure of voluntary movements, and can index motor preparatory function associated with voluntary movements. Several previous studies have found abnormal BP in schizophrenia patients compared with normal healthy subjects. However, those results seem contradictory in terms of the components of BP, its composition in schizophrenia patients (positive or negative symptoms), and complexity of motor tasks (simple or complex motor tasks). Then, the present study intended to reevaluate changes in BP during voluntary movements in schizophrenia patients as compared with that in control subjects.
I. Methods and Materials
Subjects
This study was approved by the Ethics Committee of the Toho University School of Medicine. Written informed consent was obtained from each subject. Thirty patients diagnosed with schizophrenia according to ICD-10 are recruited from the Toho University Omori Hospital. Four patients were excluded due to drug induced parkinsonism and tardive dyskinesia. The data from the remaining 26 patients were used in the analysis. The Scales for the Assessment of Positive and Negative Symptoms were applied to schizophrenia patients. Symptom scales were assessed by an independent psychiatrist. Those patients who had a higher rating of positive symptoms (hallucinations/delusions/formal thought disorder/bizarre behavior) compared to negative symptoms (alogia/affective flattening/asociality/avolition/attentional impairment) were defined as the 'positive schizophrenia group' (11 patients). Those patients who had a higher negative symptoms compared to positive symptoms were defined as the 'negative schizophrenia group' (13 patients).

Mean dose of neuroleptic medication (chlorpromazine equivalents) did not differ significantly between these two groups (positive: 405 mg/day±170.8, negative: 420 mg/day±195.2).

The normal control group (control group) (n=11) was characterized by normal neurological findings with no family history of schizophrenia or movement disorder.

All subjects were right handed. The three groups were matched for age. (control: 29.1±3.2, positive: 29.2±3.5, negative: 29.3±3.4)

II. Methods
Recording was conducted in an electrically shielded room. The subjects were seated in a comfortable reclining armchair with their eyes closed. Electroencephalographic (EEG) recording was performed with silver-silver chloride electrodes, fixed at three areas of the brain; Cz, C3, and C4 sites, according to the international 10/20 system. Linked earlobes served as the reference. The high frequency cut-off was set at 100 Hz; the low-frequency cut-off was 0.03 Hz, with a time constant of 5 s. Recordings from these areas were amplified by a bioelectric amplifier. The data were stored on a micro-computer and analyzed off-line with Evoked Potential Software.

An electromyogram (EMG) was recorded with silver-silver chloride electrodes, placed approximately 3 cm apart, from the right flexor digitorum superficialis muscle. The signals were amplified by a bioelectric amplifier. For EMG recording a high-frequency cut-off of 3 KHz, a low-frequency cut-off of 50 Hz and a time constant of 0.03 s.

The duration of the sampling window was 3,000 ms before and 1,000 ms after EMG onset.

The sampling rate was 200 Hz.

Experimental procedures
1) BP task
BP was recorded in two experimental tasks: simple finger task and complex finger task. These tasks were modified movement paradigms, originally used by Roland et al. In the simple finger task, the right thumb was repeatedly touched against the tip of the middle finger at a self-paced repetition rate of 0.2 Hz.

In the complex finger task, there were three kinds of sequential movements, as follows: First, the little finger, ring finger and middle finger were touched in sequence with the right thumb; next, with the right thumb against each of the ring finger, middle finger and little finger were touched in sequence with the right thumb; and finally, the middle finger, ring finger and little finger were touched in sequence with the right thumb.

These sequential movements were performed every 5 sec. Subjects performed 5 sessions; one session was composed of 20 sequential finger movements.

2) Motor performances
The Purdue Pegboard task and Finger tapping task were employed to assess fine motor dexterity and motor speed. During the Purdue Pegboard task, subjects were asked to insert as many pegs as possible. All subjects performed three separate trials of the Perdue pegboard task with their right hands. Subjects were required to take white pegs
one by one, turn them upside down, and insert them as quickly as possible using the right hand. The task was performed for 30 seconds, with pegs being inserted line by line, starting at the top left-hand corner of the board. The task score is the mean number of pegs per 30 seconds achieved over three trials. During the finger tapping task, subjects were required to press a button with right index finger as rapidly as possible for 10 seconds. In these sessions, subjects were asked to first tap with their right index finger. The finger tapping score is the mean number of taps per 10 seconds achieved over six trials.

The Purdue pegboard task and Finger tapping task paradigms were used by modified method of Brown et al.9)

Data analysis
1) Analysis of BP
All EEG data were analyzed offline. To define the 0 point of a trial, movement-onset triggers were manually placed where the movement onset began to rise (Fig. 1). Trials affected by excessive EMG activity were rejected. EEG data were recorded for 4,000 ms (3,000 ms before to 1,000 ms after movement onset). BP curves were obtained by averaging 80 sweeps. The baseline was collected from −3,000 to −2,000 ms (Fig. 1).

We analyzed two premovement components of BP; early BP area and late BP area (Fig. 1). To score the two BP components prior to the self-initiated movements, BP areas were obtained using the previously employed modified Kutas method.10) The early BP area was measured from 300 ms before the late BP onset to the late BP onset. Late BP area was measured from −300 ms to EMG onset. These two areas were obtained by integrating the values over each period, relative to the baseline (Fig. 1).

![BP and EMG traces with defined areas](image)

Fig. 1. Definition of early and late bereitschaftspotential (BP) areas (gray areas). The vertical arrow indicates the point (late BP onset), where the late negative slope became steeper than the earlier slope in the BP trace components. See the text for details.
2) Statistical analysis

The data of each component of BP areas were analyzed separately using repeated measure analysis of variance (ANOVA) with a grouping factor of subjects and a within-subject factor of electrode site.

For analysis of actual motor performances, ANOVA was carried out for number of pegs, number of taps, separately in groups, as within subjects factors.

Dunnett's post hoc examination was used following analysis.

III. Results

1. Grand average waveform of BP (Fig. 2)

   1) Grand average waveform of BP in the simple finger task

   In the simple finger task performed by the control group, BP at C3 started at about $-2000$ ms and increased gradually in amplitude until the movement onset. There was a steeper rise in amplitude during the approximately late 800 ms before movement onset.

   In the simple finger task performed by the negative schizophrenia group, there was little increase in the amplitude of BP until approximately $-500$ ms.

![Fig. 2. Grand averages of BP at C3 and C4 during simple finger task (upper panel; A) and during complex finger task (lower panel; B) in control group (black line), negative schizophrenia group (green line), positive schizophrenia group (red line).]
The general shape of the BP in the positive schizophrenia group was similar to that in the control in terms of the start of BP, and showed a steeper rise in slope during 800 ms before movement onset.

2) Grand average wave form of BP in complex finger task

In the complex finger task, the general shape of BPs in all groups was not much different from that in the simple finger task, except for the following aspect: the maximum negative potentials observed at movement onset in the positive schizophrenia group were larger both at C3 and C4 than those with the simple finger task.

2. Statistical analysis of BP area

We compared the early and late BP areas in the positive and negative schizophrenia groups with the corresponding data from the control group.

1) The late BP area in the complex finger task

For the late BP area in the complex finger task, the main effects of groups (F = 5.6, p < 0.01) electrode site (F = 5.5, p < 0.01) and group×electrode site interaction (F = 3.9, p < 0.01) showed a significant difference. Post hoc test revealed that 1) the late BP area in the negative schizophrenia group was significantly smaller than that in the control group (p < 0.01), and 2) the late BP area in the positive schizophrenia group was significantly greater than that in the control group (p < 0.01).

Further analyses of the two main effects were carried out separately by individual ANOVA. As for the main effects of group, individual ANOVA revealed significant effects of group at C3 and C4 (p < 0.01). Post hoc tests revealed that the late BP area in the negative schizophrenia group was smaller (p < 0.01) than that in control group at C3. Also, the late BP area in the positive schizophrenia group was larger than that in the control group at C3 and C4 (p < 0.01). As for main effect of electrode site, individual ANOVA revealed a significant effect of electrode site in the control group (p < 0.01), but not in the schizophrenia groups (p > 0.05).

2) Late BP area in the simple finger task

For the late BP area in the simple finger task, the main effects of group (F = 5.6, p < 0.01) was significant, but the main effect of electrode site and group×electrode site interaction was not significant (p > 0.05). Post hoc tests revealed only one significant difference; the late BP area in the negative schizophrenia group was significantly smaller than that in the control group (p < 0.01).

3) Early BP area in the complex and simple finger task

For the early BP area the main effects of group (F > 0.05), electrode site (p > 0.05), and group×electrode site interaction (p > 0.05) were not significant.

3. Statistical analysis of actual motor performance

For both the right finger tapping and pegboard tasks (Table 1), there were significant effects of group (F = 3.4, p < 0.05). Post hoc tests revealed that both the number of taps and pegs in the positive schizophrenia and negative schizophrenia groups were significantly smaller than that in the control group (p < 0.05).

IV. Discussion

The present experimental study had the following two features: first, we employed a simple finger task and a complex finger task to evoke changes in BP; and second, we classified schizophrenia patients into two groups according to clinical symptoms. The prominent result was shown in the complex finger task.

Several reports have evaluated the late BP in schizophrenia patients with negative symptoms. Previous reports have demonstrated that the late BP in the simple and complex finger task is statistically significant smaller in negative schizophrenia groups than that in control groups. The same results were obtained in the present study.

There have been several previous studies using neuroimaging techniques to evaluate the brain areas generating

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Results of motor performance</th>
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<tbody>
<tr>
<td></td>
<td>control Mean (SD)</td>
</tr>
<tr>
<td>Finger tapping Number of taps</td>
<td>78 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Pegboard Number of pegs</td>
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</table>

Significant difference (*p < 0.05) compared with control group score.
the BP. Shibasaki et al.\textsuperscript{11) found using PET that both the SMA and the sensorimotor area play an active role in preparation for complex voluntary finger movements. This neuroimaging data indicate that suppression of the late BP may be derived from dysfunction in the SMA and sensorimotor area. This notion was confirmed by fMRI study (Schroder et al.\textsuperscript{12}), which demonstrated that activation in the SMA and sensorimotor area during the simple finger task was reduced in negative schizophrenia group as compared with that in control group. It is reasonable to conclude that the statistically significant smaller late BP area observed in negative schizophrenia group as compared with that in control group. This new finding may be explained by the hyperexcitability of the SMA and sensorimotor area. Gunther et al.\textsuperscript{13} have demonstrated that hyperactivation of the sensorimotor area in positive schizophrenia patients during finger movements. Based on this finding, we hypothesize that hyperactivity of the SMA and sensorimotor area may be associated with a statistically significant larger late BP area during the complex finger task in the positive schizophrenia group as compared with that in control group.

In contrast to the negative schizophrenia group, the present results revealed the new finding that the late BP area in the complex finger task was statistically significant larger in positive schizophrenia group than that in control group. This new finding may be explained by the hyperexcitability of the SMA and sensorimotor area. To evaluate motor performance, we also employed the finger tapping task and pegboard tasks. We found that both the negative schizophrenia and positive schizophrenia groups showed significantly poorer performance compared with the control group. Westphal et al.\textsuperscript{14} suggested that inadequate control of movement related EEG changes in schizophrenia patients might cause dysfunction of voluntary movements. The complex finger task used in the present study involves more motor preparatory processes compared with simple finger task. Considering these findings as a whole, we hypothesize that: 1) schizophrenia patients have impaired optimal control of motor preparatory function particularly during complex finger task; 2) motor preparatory dysfunction may cause poor motor performances.

A limitation of the current study must be noted. Although all schizophrenia patients have no drug induced parkinsonism and tardive dyskinesia in the present study, neuroleptic drugs influence the motor function. However, Karaman et al.\textsuperscript{5} have reported abnormal amplitude of the BP in both medicated and unmedicated patients with schizophrenia.

V. Conclusion

The present neurophysiological results suggest that 1) inadequate level of BP in schizophrenia patients can be explained by dysfunction of SMA and sensorimotor area generating the BP; 2) impaired control of motor preparatory function (inadequate level of BP) particularly during the complex finger task in schizophrenia patients may be related to poor motor performances (dysfunction of voluntary movements).

References


統合失調症患者と健常者との間の手指運動を課題とした
運動関連電位の比較

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【要旨】統合失調症における自発的運動の障害は臨床的にもみられる。統合失調症では運動の準備や意図などの運動プログラムにおいて困難があるとされている。運動関連電位（BP）は運動準備機能を反映する。しかし、過去の統合失調症におけるBP研究にはいくつかの矛盾した結果が報告されている。そこで、我々は、統合失調症のBPについて再評価を行った。

薬剤性の影響がある患者を対象から除外した上で、単純および複雑な手指運動のBPを陽性症状の強い患者（11人）、陰性症状の強い患者（13人）、そして健常（11人）にて測定した。健常群と2つの患者群との間において比較を行った。実際の運動パフォーマンスの評価としてペグボードやタッピングを用いた。複雑な手指運動の後期BP成分において、健常群と比し陽性症状の強い群では統計学的に有意に振幅が大きく、陰性症状の強い群では有意に振幅が小さいという顕著な結果が得られた。また2つの統合失調症群はともに健常群より統計学的に有意に運動パフォーマンスが悪かった。この異常なBP変化は、BPの起源とされる補足運動野や感覚運動野に統合失調症にて機能障害があることが推察できる。さらにBPは運動準備機能を反映するので、統合失調症においてみられる運動パフォーマンスの悪さは、運動準備機能を必要とする複雑な課題での統合失調症群における不適切なBPの水準がその一要因となっていると考えた。

Key words：統合失調症、運動関連電位、複雑手指課題、運動機能障害