Original Article

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Impaired anticipatory hand movement during a loading task in patients with schizophrenia

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Abstract

In patients with schizophrenia, a wide range of motor symptoms and functional and morphological abnormalities of the cerebellum have been reported. An attractive hypothesis, called the "cognitive dysmetria" hypothesis, has been proposed to emphasize the role of the cerebellum in schizophrenia. The cerebellum plays an essential role in prediction-based, feed-forward motor control - which is important for performing movements smoothly, precisely, and skillfully. In the present study, we tested the possibility that feed-forward motor control is impaired in schizophrenia, by comparing predictive components of hand movements during a weight-loading task between 10 healthy volunteers and 10 patients with schizophrenia. Using a haptic device named the Space Interface Device for Artificial Reality (SPIDAR), which enables us to perform a ball-catching or weight-loading task in a virtual environment, a downward force (4.9 N) was applied to the right hand (loading) and the vertical deflection of the hand was monitored. The hand movement was also monitored by the accelerometer attached to the dorsal surface of the right hand. Loading was started by pressing a start key, which was pressed by either the subject (predictable condition) or an examiner (unpredictable condition). To assess feed-forward motor control, we measured the upward movement just before the start of loading. This upward movement (anticipatory response) was observed only in the predictable condition, confirming that it is based on prediction. We found that the amplitude of anticipatory response was significantly smaller in the patients than in the healthy volunteers, indicating the impairment of feed-forward motor control in schizophrenia. We also found that the amplitude of anticipatory response was negatively correlated with age in both the healthy and patient groups. These results suggest that feed-forward motor control is impaired in patients with schizophrenia, and that aging might exaggerate the impairment. Our results are consistent with the "cognitive dysmetria" hypothesis that emphasizes the role of the cerebellum in schizophrenia.

Key Words

schizophrenia, feed-forward motor control, prediction, anticipatory response, loading task

Introduction

Motor abnormalities have been reported in patients with schizophrenia[1,2]. Almost a century ago, early schizophrenia researchers described a wide range of motor symptoms to be associated with schizophrenia[3]. Later, diagnostic and pathological concepts of schizophrenia focused on cognitive symptoms, such as delusions and hallucinations, while motor symptoms were interpreted as secondary phenomena[3]. In the 1970s, neurological soft sign (NSS), which refers to neurological abnormalities in several domains including sensory integration, motor coordination and motor sequencing, were investigated in schizophrenia[3]. Since then, several signs related to motor functions have been demonstrated to be specific

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to schizophrenia [1] , and researchers regained interest in movement abnormalities in schizophrenia [2] .

In line with these clinical observations, the "cognitive dysmetria" hypothesis has been proposed to emphasize the role of the cerebellum in schizophrenia. According to this model, a disruption in the connectivity among nodes located in prefrontal cortical regions, the thalamic nuclei, and the cerebellum produces "cognitive dysmetria," and can account for a broad diversity of symptoms in schizophrenia [4] . This hypothesis has been supported by many studies reporting functional and morphological abnormalities of the cerebellum in patients with schizophrenia [5, 6] . Volumetric magnetic resonance imaging showed that patients with schizophrenia have significantly smaller cerebellar volumes compared with healthy subjects, and that NSS in patients with schizophrenia is inversely correlated with cerebellar volumes [6] . fMRI studies demonstrated that patients with schizophrenia show decreased activation in the cerebellum during recognition and memory tasks [7] .

The cerebellum makes an essential contribution to motor control, and is generally thought to play a more important role in feed-forward control than in feedback control [8] . Feed-forward motor control is important for performing movements smoothly, precisely, and skillfully. When catching a falling ball, for example, we predict the weight of the ball and the timing of contact, and generate motor commands in advance of the estimated time to contact before feedback motor control begins to compensate for the perturbation through the sensory system [9] . Feed-forward control has been evaluated by measuring predictive components of movement. In a ball-catching task, for example, muscle activity starts to increase before the ball strikes the hand. Learning this predictive muscle activation was reported to be impaired in patients with cerebellar damage [10] . In a grasping task, generating predictive finger forces to resist a self-generated perturbation was reported to be impaired in patients with cerebellar damage [11] . These results show that predictive components of movements depending on feed-forward motor control are actually affected by cerebellar dysfunction.

In the present study, we examined whether prediction-based, feed-forward motor control is impaired in schizophrenia, by comparing predictive components of hand movements during a weight-loading task between healthy subjects and patients with schizophrenia. We observed that the amplitude of predictive components was significantly smaller in the patients than in the healthy subjects, indicating the impairment of feed-forward motor control in schizophrenia. Our results are consistent with the "cognitive dysmetria" hypothesis.

Methods

1. Subjects

This study was approved by the Medical Ethics Committee of Kanazawa University and was performed according to the Declaration of Helsinki. Informed consent was obtained from 10 healthy volunteers and 10 patients with schizophrenia (Table 1) . The subjects were all right-handed. Patients were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) . The duration of illness was 8.5 ± 6.1 years. All patients were receiving antipsychotic medication (e.g., olanzapine, pariperidone, or quetiapine either alone or in combination) , with mean equivalent doses of the antipsychotic drug chlorpromazine of 680.5 ± 455.2 mg/day (Table 2) . Symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) . The intensity of extrapyramidal symptoms was evaluated by the Simpson and Angus Scale [12] .

Table 1. The number and age of subjects

	Control	Schizophrenia
Number (male / female)	10 (4 / 6)	10 (5 / 5)
Age (year) , mean ± SD (range)	32.9 ± 8.0 (21 - 47)	35.4 ± 7.4 (26 - 50)
Number (20's / 30's / 40's / 50's in age)	(4 / 4 / 2 / 0)	(2 / 5 / 2 / 1)

Table 2. Characteristics of patients with schizophrenia

Characteristics	mean ± SD (range)	unit
Duration of illness	8.5 ± 6.1 (2 - 21)	year
CPZ equivalents	680.5 ± 455.2 (75 - 1675)	mg/day
BPRS	38 ± 11 (23 - 57)	scale
Simpson and Angus Scale	2.4 ± 3.0 (0 - 9)	scale

2. Experimental set-up and procedures

Figure 1 shows experimental set-up and procedures used in the study. To apply a downward force to a hand (loading) and monitor the vertical deflection of the hand, we used a haptic device named the Space Interface Device for Artificial Reality (SPIDAR) , which consists of eight motors and strings attached to the grip (Fig. 1A) [13] . SPIDAR was developed in Tokyo Institute of Technology

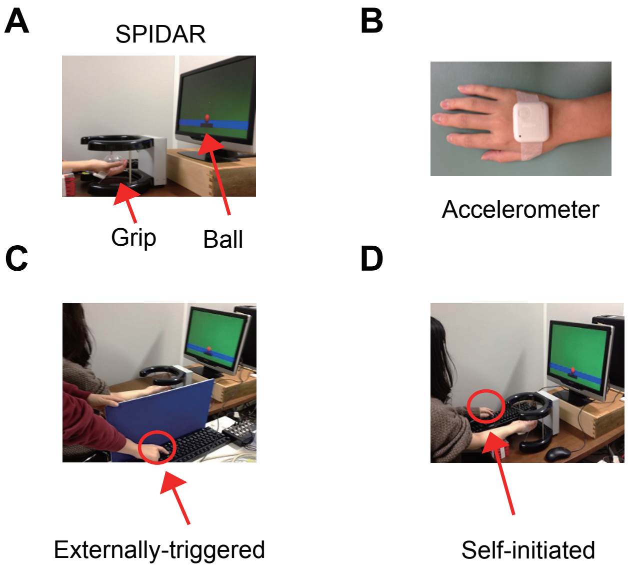

Figure 1. Experimental set-up and procedures. A: A photograph of SPIDAR, which consists of eight motors and strings attached to a ball-shaped grip, and a virtual ball on a display. B: A photograph of an accelerometer attached to the dorsal surface of a right hand. C, D: Loading was started when the start key (red circles) was pressed by an examiner (C: unpredictable condition) or the subject (D: predictable condition).

to perform a ball-catching task in a virtual environment, and kindly provided to us by Y. Koike.

The subject was comfortably seated with the right elbow in 50-90° flexion on an arm rest and was asked to hold the ball-shaped grip of SPIDAR. A force of 4.9 N was vertically applied to the grip (equivalent to loading of 500 g weight), while the vertical position of the grip was displayed on a computer screen (Fig. 1A, ball). Loading was started by pressing a start key (Fig. 1, red circles), which was pressed by either an examiner (unpredictable condition, Fig. 1C) or the subject (predictable condition, Fig. 1D). The subject was asked to hold the ball-shaped grip (Fig. 1A, grip) near the center of the device and keep the initial position during loading. Vertical deflection from the initial position was recorded by SPIDAR at a sampling frequency of 1 kHz ("position" data). Hand movement of the subject was also monitored by an accelerometer (WAA-006, Wireless Technologies, Tokyo, Japan) attached to the dorsal surface of the right hand (Fig. 1B) and the accelerometer signal was recorded at a sampling frequency of 200 Hz (Accel Real Time 2, ATR-Promotions, Kyoto, Japan). The vertical axis signal of the accelerometer ("acceleration" data) was integrated to yield the velocity of vertical hand movement ("velocity" data). The loading task was repeated 10 times in each condition for each subject. The order of predictable and unpredictable conditions was changed in the half of each group of subjects.

3. Data analysis

Results are presented as means ± SD. SPIDAR data were compared between groups by Mann-Whitney U-test, as the samples did not show normal distribution. Correlations between position and velocity values and between age and SPIDAR data were tested by Spearman analysis. Statistical analysis was performed using SPSS (version19.0) with $p < 0.05$. Effect size (d) and statistical power (1- β) were calculated by G*Power 3.1[14].

Results

1. Motor responses in repeated trials of loading

Figure 2A shows representative acceleration, velocity and position traces obtained from a healthy subject in the unpredictable (left) and predictable (right) conditions. In this example, the velocity of downward movement reached its peak around 30-40 ms and the downward deflection of grip position reached its peak around 100 ms after the start of loading in both conditions. To examine

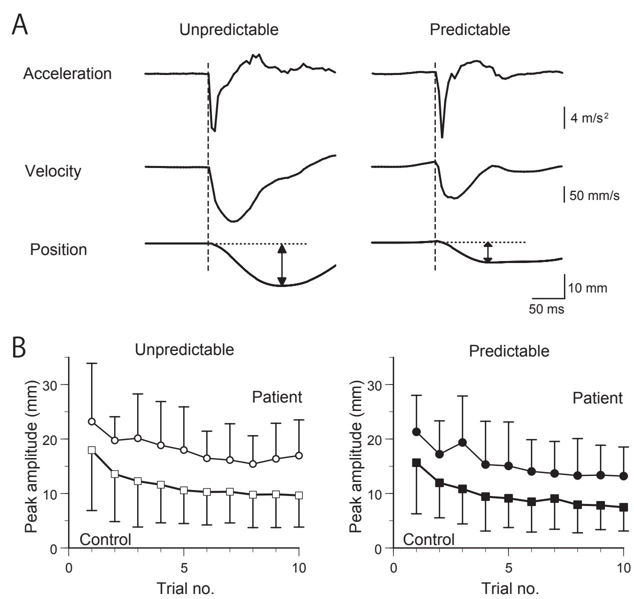

Figure 2. Hand movements during repeated trials of loading. A: Examples of acceleration, velocity and position traces obtained from a healthy subject in the unpredictable (left) and predictable (right) conditions. Loading started at the time indicated by vertical dashed lines. The peak amplitude of downward deflection (vertical arrows) was measured in each trial. B: The peak amplitude was plotted as a function of the trial number. Each symbol is the mean value from 10 healthy subjects (squares) or patients (circles) under the unpredictable (open symbols) or predictable (closed symbols) conditions.

whether hand movements during loading are stable or show adaptation, the peak amplitude of downward deflection (Fig. 2A, vertical arrows) was measured in each trial. Figure 2B shows the averaged data obtained from healthy subjects (squares) and patients (circles) in the unpredictable (left) and predictable (right) conditions. In both conditions, the peak amplitude became smaller with repeated trials, and reached a relatively stable level around the sixth trial. Thus, we used the data acquired between the sixth and the tenth loading trials for the following analysis.

2. Analysis of the position data

We first analyzed the position data measured by SPIDAR. Figure 3A shows representative position traces obtained from a healthy subject (top) and a patient (bottom) in the unpredictable and predictable conditions. Each trace is the average of five trials. In Figure 3A, two traces acquired in the unpredictable and predictable conditions are superimposed (middle), and then amplified (right). To examine feed-forward motor control, we measured the upward deflection just before the start of loading in the predictable condition (P-up) as a predictive component.

Figures 3B shows individual data for P-up obtained from 10 healthy subjects and 10 patients. P-up ranged from 0.2 to 1.1 mm in the controls, and from 0.0 to 0.2 mm in the patients except one (1.3 mm), showing almost no overlap. The averaged P-up value even including the exception was significantly smaller ($p = 0.02$, $d = 0.96$, $1-\beta = 0.50$) in the patients than in the healthy subjects.

3. Analysis of the velocity data

We next analyzed the velocity data that were calculated from the accelerometer signal, and obtained similar results. Figure 4A shows representative velocity traces obtained from a healthy subject (top) and a patient (bottom). Two traces obtained in the unpredictable and predictable conditions are superimposed and amplified. As a predictive component, we measured the peak velocity of upward movement just before the start of loading in the predictable condition (V-up).

Figures 4B shows individual data for V-up obtained from 10 healthy subjects and 10 patients. V-up ranged from 1.4 to 14.3 mm/s in the healthy subjects, and from 0.0 to 5.8 mm/s in the patients except one (22.4 mm/s). The averaged V-up value including the exception was significantly smaller in the patients ($p = 0.04$, $d = 0.65$, $1-\beta = 0.27$).

4. Comparison between position and velocity data

We compared the position and velocity data described above. As shown in Fig. 5, there was a good correlation between P-up and V-up, both of which reflect feed-forward motor control ($p < 0.001$, $1-\beta = 0.99$). This result indicates that feed-forward motor control can be assessed by measuring either the peak amplitude of upward

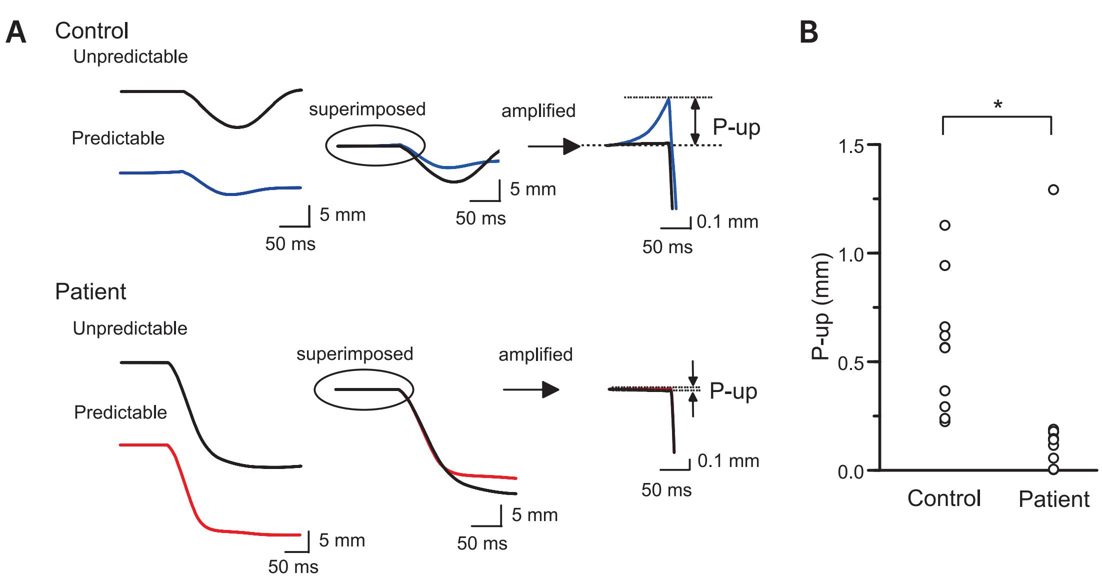

Figure 3. Analysis of the position data. A: Examples of position traces obtained from a healthy subject (top) and a patient (bottom) in the unpredictable (black) and predictable (blue or red) conditions. Each trace is the average of five trials. The peak amplitude of upward deflection just before the start of loading obtained in the predictable condition (P-up) was measured in each subject. B: Individual data for P-up. *, $p < 0.05$.

deflection or the peak velocity of upward movement.

5. Age-related decline in feed-forward motor control

It is known that with aging there are performance declines in a wide variety of motor and cognitive behaviors [15]. We therefore examined whether there are age-related changes in feed-forward motor control. We found that P-up and V-up values were negatively correlated in both healthy subjects (P-up: $p = 0.03$, $1-\beta = 0.62$; V-up: $p = 0.04$, $1-\beta = 0.58$) and patients (P-up: $p = 0.03$, $1-\beta = 0.67$; V-up: $p = 0.03$, $1-\beta = 0.65$) (Fig. 6).

Discussion

In the present study, we examined whether prediction-based motor control is impaired in patients with schizophrenia. We monitored hand movements during a simple loading task, where the subject was required to hold the ball-shaped grip and keep the hand at the original vertical level during predictable or unpredictable sudden loading. In healthy subjects, a small upward movement was consistently observed just before the start of predictable - but not unpredictable - loading, confirming that this response (anticipatory response) reflects prediction-based motor control. In the patients, the anticipatory response was significantly reduced, indicating that prediction-based motor control is impaired in patients with schizophrenia. These results are consistent with the "cognitive dysmetria" hypothesis that emphasizes the role of the cerebellum in schizophrenia.

Among 10 patients with schizophrenia, one patient showed a large anticipatory response comparable to healthy subjects (Fig. 3B and Fig. 4B). We checked clinical parameters including duration of illness, mean dosage of neuroleptic medication, symptoms of schizophrenia and intensity of extrapyramidal symptoms, but found no unique feature that can explain the exceptionally large response in this patient. Moreover, we found no significant correlations between the amplitude of anticipatory response and these clinical parameters. Further studies with increased number of patients will be required to examine the heterogeneity of schizophrenia with respect to impairment of feed-forward motor control.

Prediction-based motor control has been evaluated in several different tasks, including ball-catching, loading and grasping tasks[16, 17]. In the present study, we used SPIDAR, which was originally developed for a ball-catching task and can control the initial velocity, height and acceleration of a falling ball in a virtual environment[13]. However, we used SPIDAR for a loading task by setting the initial height of the ball at zero, because patients with schizophrenia often experience oculomotor disturbances, and those are expected to make the interpretation of anticipatory responses difficult in a ball-catching task.

The cerebellum plays an important role in feed-forward motor control by forming internal models that predict

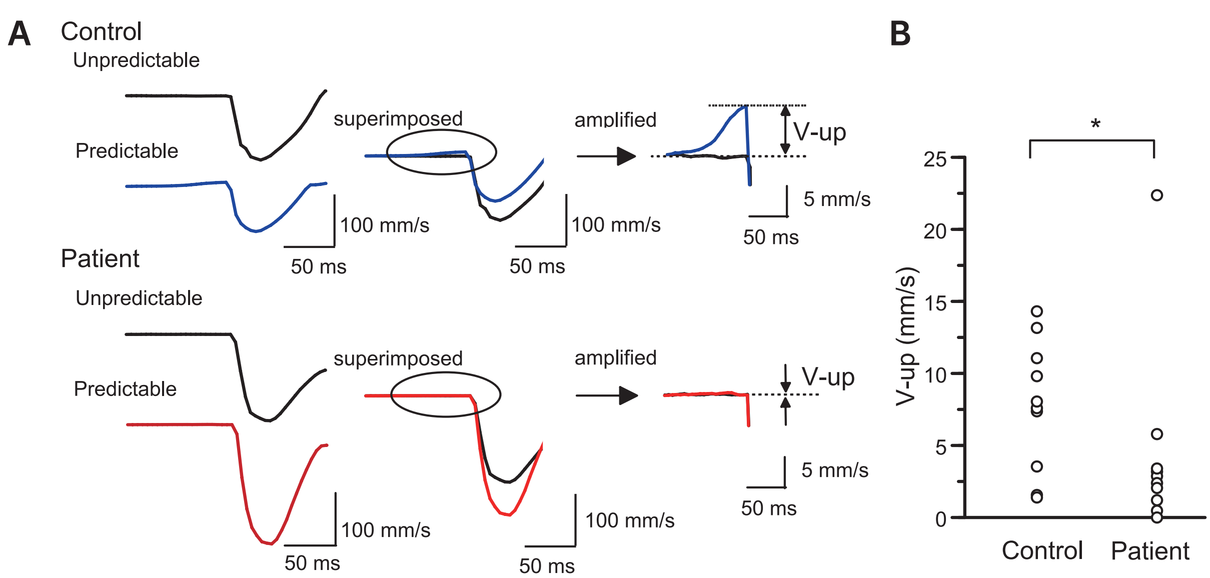

Figure 4. Analysis of the velocity data. A: Examples of velocity traces obtained from a healthy subject (top) and a patient (bottom) in the unpredictable (black) and predictable (blue or red) conditions. Each trace is the average of five trials. The peak velocity of upward movement just before the start of loading obtained in the predictable condition (V-up) was measured in each subject. B: Individual data for V-up. *, $p < 0.05$.

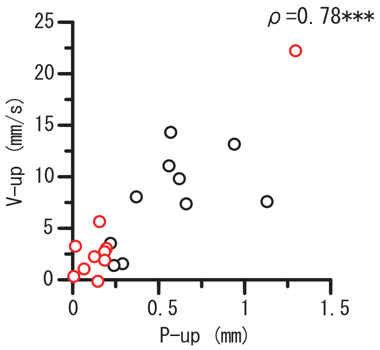

Figure 5. A significant correlation between P-up and V-up. Spearman correlation coefficient (ρ) is shown. ***, $p < 0.001$. Black and red circles are the data in healthy subjects and patients, respectively.

sensory outcomes of motor commands and correct motor commands through internal feedback[18] . The cerebellar internal models are also involved in providing the signals that are used to attenuate the somatosensory response to self-produced stimulation[19] . Positive symptoms of schizophrenia, such as auditory hallucinations and delusions of control, which are when the subject experiences his or her will as replaced by that of some other force or agency, have been postulated to be caused by dysfunction of internal models[19-21] . Defects of self-monitoring and sensory prediction have been reported in patients with schizophrenia. It is known that tactile stimuli are perceived as weaker when self-produced rather than externally produced. fMRI data show that the activity in the somatosensory cortex is attenuated when the stimulus is self-produced through the mechanisms involving the cerebellum[19, 22] . This sensory attenuation during self-produced stimulation is impaired in patients with schizophrenia, especially patients with auditory hallucinations and/or delusions of control[21, 23, 24] . Whether impaired anticipatory responses observed in the present study are related to these positive symptoms remains to be elucidated.

In the present study, we measured hand movements by using the SPIDAR and accelerometer. It was already shown that the SPIDAR is useful for monitoring hand movements in a ball-catching task[13] . The present study demonstrates that the impairment of anticipatory responses in the patients can easily be detected by an accelerometer, which is inexpensive and convenient, as well as a SPIDAR. Our data clearly showed that the velocity data derived from accelerometer (V-up) was lineally correlated to the position data derived from SPIDAR (P-up) (Fig 5) . These results indicate that feed-forward motor control can be reliably assessed by accelerometer, which might be clinically useful.

Conclusion

In the present study, we monitored hand movements during predictable or unpredictable sudden loading. The

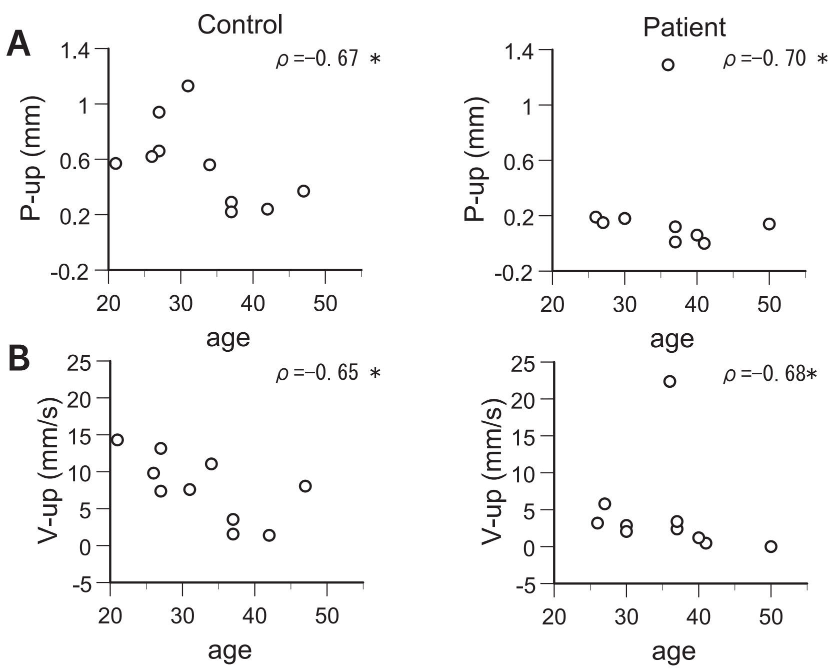

Figure 6. Correlations of age with P-up (A) and V-up (B) in the healthy subjects (left) and the patients (right) . In each graph, Spearman correlation coefficient (ρ) is shown. *, $p < 0.05$.

amplitude of anticipatory responses that occurred just before the start of loading was significantly smaller in patients with schizophrenia than in healthy subjects. These results suggest that prediction-based, feed-forward motor control, which depends on the cerebellum, is impaired in patients with schizophrenia, supporting the "cognitive dysmetria" hypothesis that emphasizes the role of the cerebellum in schizophrenia. In the present study, however, the number of patients used for analysis was not enough to provide a statistical power of 0.8. Further studies with optimal sample size, which can be calculated from the effect size obtained here, will be necessary to generalize the present results.

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統合失調症者の予測に基づく運動制御の障害

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要　旨

統合失調症者では、小脳の機能的および形態学的異常所見が報告されている。小脳は予測に基づく運動制御、あるいは、運動のフィードフォワード制御において重要な役割を担っている。よって、統合失調症者では予測に基づく運動制御に障害がみられる可能性が考えられる。予測に基づく運動制御は、外から力を加えた時の体の動きを調べる課題においては、力を加える前に起こる筋活動（先行反応）として捉えることができる。そこで本研究では、先行反応を指標とし、統合失調症者の予測に基づく運動制御の障害の可能性について検討した。実験は、任意のタイミングで手に垂直方向の力を加えることのできる装置 SPIDAR を使用し、手に 4.9N の力を負荷する課題を行った。その時の垂直方向の手の動きを SPIDAR と加速度計で計測した。健常者 10 名、統合失調症者 10 名を対象に、負荷直前の手の動き（先行反応）の大きさを計測したところ、両群間で有意な差が認められた。健常群では、負荷のタイミングが予測できる条件では、負荷前に手がわずかに上昇するという先行反応がすべての被験者で観察された。一方、患者群では、10 名中 9 名においては先行反応がほとんどない、またはきわめて小さく、健常者と同等の先行反応がみられたのは 1 名のみであった。また、どちらの群においても、先行反応の大きさは加齢とともに小さくなる傾向を示した。以上の結果より、予測に基づく運動制御は統合失調症者で障害されている可能性、また、加齢とともにその機能が低下する可能性が示された。