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Research paper

Operation of a P300-based brain-computer interface by patients with spinocerebellar ataxia

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ABSTRACT

Objective: We investigated the efficacy of a P300-based brain-computer interface (BCI) for patients with spinocerebellar ataxia (SCA), which is often accompanied by cerebellar impairment.
Methods: Eight patients with SCA and eight age- and gender-matched healthy controls were instructed to input Japanese hiragana characters using the P300-based BCI with green/blue flicker. All patients depended on some assistance in their daily lives (modified Rankin scale: mean 3.5). The chief symptom was cerebellar ataxia; no cognitive deterioration was present. A region-based, two-step P300-based BCI was used. During the P300 task, eight-channel EEG data were recorded, and a linear discriminant analysis distinguished the target from other nontarget regions of the matrix.
Results: The mean online accuracy in BCI operation was 82.9% for patients with SCA and 83.2% for controls; no significant difference was detected.
Conclusion: The P300-based BCI was operated successfully not only by healthy controls but also by individuals with SCA.
Significance: These results suggest that the P300-based BCI may be applicable for patients with SCA.

1. Introduction

A brain-computer interface (BCI) is a technology that uses neurophysiological signals from the brain, enabling communication and environmental control without muscle movement (Wolpaw et al., 2002; Birbaumer and Cohen, 2007). There are two types of BCIs: invasive and noninvasive. An invasive BCI uses unit recording or electrocorticography, which requires neurosurgery (Leuthardt et al., 2004; Hochberg et al., 2006). A noninvasive BCI uses electroencephalography (EEG) signals recorded from scalp electrodes: slow cortical potentials, sensorimotor rhythms, steady-state visually evoked potentials, and P300 event-related potentials (ERPs) have been proposed and used (Birbaumer et al., 1999; Donchin et al., 2000; McFarland and Wolpaw, 2005; Sakurada et al., 2015).

One popular noninvasive BCI is a P300-based system. The P300's responses to random rare stimuli (e.g., oddball paradigm) are attention-related EEG signals and elicited as a positive potential, occurring ~300 ms after stimulus onset (Sutton et al., 1965; Polich, 2007). Farwell and Donchin (1988) originally developed a P300 speller using this response, induced by a visual oddball paradigm that demanded a choice of randomly flashing icons arranged in the rows and columns of a 6 × 6 matrix. In addition to the visual P300-BCI paradigm, P300-BCI paradigms using auditory or tactile stimuli have been applied; however, the accuracy using auditory or tactile P300-BCI spellers is usually lower than that with visual P300-BCI spellers (Riccio et al., 2012).

BCI technology has been applied to patients with severe motor disabilities, such as those with spinal cord injuries (Ikegami et al., 2011), brainstem strokes (Sellers et al., 2014), and amyotrophic lateral sclerosis (ALS). Several research groups have reported clinical experiments in patients with ALS, and reliable performance has been reported (Piccione et al., 2006; Sellers and Donchin, 2006; Hoffmann et al., 2008; Nijboer et al., 2008; Silvoni et al., 2009; McCane et al., 2015). Our research group developed a region-based, two-step P300 speller, which has a larger flashing area than the conventional visual array, and showed that the two-step

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procedure provided significantly increased accuracy when compared with a conventional row/column speller for patients with ALS (Ikegami et al., 2014). The two-step procedure may also be useful for other patients with neurodegenerative diseases who are potential users of the BCI speller.

Spinocerebellar ataxia (SCA), a neurodegenerative disease, is autosomal dominant and is often accompanied by severe cerebellar impairments (Matsuda et al., 2014; Yasui et al., 2014). Patients with SCA exhibit various slowly progressive symptoms, such as incoordination of gait and hands, speech disorders, and impaired oculomotor control. The patients often show deterioration in their activities of daily living (ADL) (Harding, 1982; D'Abreu et al., 2010; Yasui et al., 2014; Jacobi et al., 2015; Park et al., 2015) and often have difficulty with purposeful movements, such as typing and writing and speaking over the phone because of scanning speech disorders. With disease progression, these patients might potentially have difficulty using augmentative and alternative communication devices. Therefore, patients with severe SCA may be candidates for the use of BCI technologies.

In this study, we applied a region-based, two-step P300 speller to eight patients with SCA who needed some ADL assistance. We showed that patients with SCA could use the two-step P300 speller successfully.

2. Methods

2.1. Participants

We studied eight patients with SCA (aged 38–69 years; mean 60 years old; 4 males), whose SCA categories were type 3 ($n = 5$), type 6 ($n = 2$), and sporadic type ($n = 1$) (Table 1). As a control group, eight age- and gender-matched healthy subjects (aged 35–69 years old; mean 57.6 years; 3 males) were included. No participant had any prior training with BCI devices. The mean time since disease onset was 20.9 (range, 7–57) years. Seven patients were diagnosed genetically with SCA. All patients presented the chief symptom of ataxia, resulting from cerebellar impairments. Incoordination of gait, hands, and speech were apparent. Clinical assessments of nystagmus testing showed that 6 of the 8 patients had obvious oculomotor impairment. Horizontal nystagmus was dominant in these patients. They all had to depend on some assistance in their daily life (modified Rankin scale: mean 3.5). Neurocognitive deterioration was not observed.

This study was approved by the institutional ethics committee. We obtained written informed consent regarding study participation according to our institutional guidelines from the participants or their representatives if they were not able to write. All experiments were performed in accordance with the approved guidelines.

2.2. Experimental setting

The experimental conditions were based on our previous study (Ikegami et al., 2014). The P300 speller used the P300 paradigm and involved the presentation of a selection of icons arranged in a matrix. The participant focused on one icon of the matrix as the target, and focusing on the target presented as a rare stimulus enhanced the P300 response. The conventional P300 speller uses a 6×6 matrix of icons consisting of 26 English alphabets and 10 numeric characters or symbols (Farwell and Donchin, 1988). In this study, we used a region-based, two-step P300-based spelling paradigm with green/blue flickers to elicit the P300 response to a target stimulus (Takano et al., 2009; Ikegami et al., 2014). This system had a 6×9 matrix, and all matrices had 48 hiragana characters and six symbols in total. The regions were intensified individually with green on a blue background. We set the duration of the intensification at 100 ms and the rest period at 75 ms, and each intensification was repeated eight times for each circled region. In the first step, which had 2×3 circled regions that contained nine characters and symbols, participants were required to focus on the target circle, including the character that the experimenter identified verbally. When the region was selected using the P300 algorithm, the selected circle that contained nine characters or symbols was enlarged, and this spelling matrix shifted toward the second step. In the second step, which had 3×3 circled regions of the same size as in the first step, each containing one character or symbol, each region was pseudorandomly intensified. Each circle was selected in a series of eight flashes (eight sequences) for a total of 48 flashes in the first step or 72 flashes in the second, where we defined every region that was intensified once as a sequence. Repeating this two-step procedure, the patients were able to input hiragana characters (Fig. 1A).

All participants sat on chairs or in wheelchairs that were approximately 100 cm from the display that presented a flickering matrix and an input window. Before starting a spelling session, we needed to collect EEG data to derive feature vectors in a preparatory session for each participant. In this preparatory session, we used a 3×3 matrix, and participants were required to attend to the nine regions sequentially to derive feature vectors, where each region was intensified eight times. After the preparatory session, we started the spelling session, during which all participants were required to input the hiragana characters for their own names using the two-step procedure. Healthy participants repeated the spelling task twice, whereas the SCA group did it once (mean SCA: 6.3 characters, control: 13.6 characters).

2.3. EEG data acquisition and analyses

We used an environmental control system consisting of a laptop PC with in-house software on the 64-bit Windows platform and an in-house EEG amplifier (24 bit, 8 ch, 1024 Hz, USB connected). EEG data were recorded from eight channels (Fz, Cz, Pz, P3, P4, Oz, PO7, and PO8, Fig. 1B) using an in-house cap and in-house solid-gel electrodes, which had comparable impedance to those of conventional paste-based electrodes and an impedance lower than that of pin-based electrodes (Toyama et al., 2012). We applied a band-pass filter (0.1–50 Hz) to the derived EEG signals, and these signals were

Table 1
Clinical characteristics of patients with SCA.

No.	Age	Gender	mRs	Time since onset (years)	Oculomotor impairment	Type
1	69	Male	4	57	N	SCA6
2	67	Female	4	12	Y	SCA3
3	66	Male	4	16	Y	SCA6
4	64	Female	4	7	Y	Sporadic
5	54	Female	3	20	Y	SCA3
6	54	Female	3	39	Y	SCA3
7	68	Male	4	8	Y	SCA3
8	38	Male	2	8	N	SCA3

mRs, modified Rankin scale; SCA, spinocerebellar ataxia.

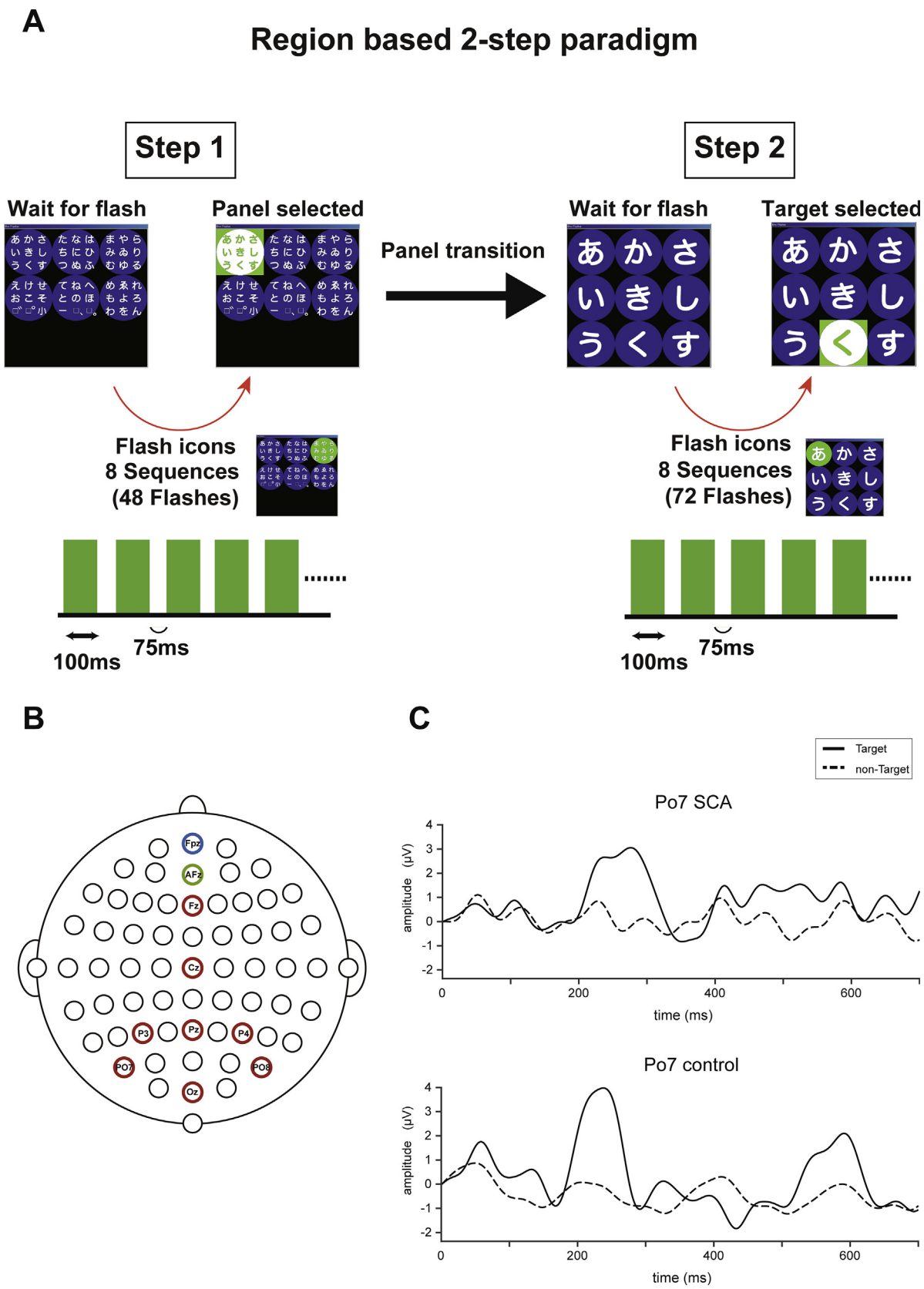

Fig. 1. A region-based, two-step P300-based hiragana speller. (A) This shows a region-based, two-step P300-based hiragana speller. Each visual stimulus flickered 8 times, pseudo-randomly. The interval between the stimuli was 175 ms: 100 ms of intensification and 75 ms of rest. In the first step, 6 circles contained 9 hiragana characters or symbols. In the second step, the selected circle enlarged, and the participants attempted to select the character that they wanted to input. (B) We used 10 electrodes, including eight recording electrodes (Fz, Cz, Pz, P3, P4, Oz, PO7, and PO8). EEG data were collected and used for the classification. (C) The additional averaged EEG waveforms obtained from the Po7 electrode are shown in both groups. The 700 ms waveforms at 100 ms after the onset of intensification were averaged. The solid line indicates the ERP when attending to the target, while the dashed line indicates the ERP when attending to the non-target. We found two positive peaks, which corresponded to the early and late components of P300, in both groups.

digitized at 1024 Hz. All channels were referenced to Fpz and grounded to AFz, and the impedance was kept at <20 kΩ, which gradually decreased until it was sufficiently low using the solid-gel electrodes (Toyama et al., 2012). The representative EEG waveforms obtained from the Po7 electrode, a channel that seemed to have an important role in P300 BCI with green/blue visual stimuli (Takano et al., 2014), were averaged for patients with SCA and controls (Fig. 1C).

Recorded EEG data for a BCI analysis were downsampled to 21 Hz for analysis. We segmented EEG data in 800 ms per timing of the flash onset. The first 100 ms period, occurring just prior to flash onset, was used for baseline correction, and the remaining 700 ms was used for classification. First, we needed a preparatory session to derive feature vectors. In the preparatory session, target and nontarget characters were discriminated using Fisher's linear discriminant analysis. We could determine the region using the maximum of the summed scores in a phase of classification.

For online analysis, we calculated the accuracy at the eighth sequence. The accuracy was evaluated for both the BCI operation and character inputs. The accuracy of the BCI operation was evaluated from the performance on both the first and second steps in total. We then evaluated the performance on the character input, in which the correct responses in both the first and the successive second step were required for correct character input. The information transfer rate (ITR) for SCA and controls was also evaluated (Wolpaw et al., 2002).

For offline analysis, the accuracy for each sequence (1–8) was calculated. The accuracy was evaluated for both the BCI operation and character inputs. The effects of subject group (SCA vs. control) and the number of sequences (1–8) on accuracy in each sequence were evaluated by a two-way repeated measures analysis of variance followed by *post hoc t*-tests.

3. Results

3.1. Performance on BCI operation

The mean online accuracy of BCI operation, which indicated the accuracy of both steps in total, was 82.9% for patients with SCA and 83.2% for controls; there was no significant difference ($p = 0.68$; Fig. 2A). The mean accuracy of the SCA group in the second step was significantly lower than that in the first step (92.5%, 78.1%; $p = 0.045$), whereas there was no such difference in the control group.

Fig. 2B shows the results of the offline analyses for both groups under each step procedure. We used a two-way repeated-measures ANOVA with group (SCA vs. control) and accuracy for each sequence (1–8). The main effect of group was significant ($p = 0.0045$), as was the main effect of number of sequence ($p < 0.0001$; Fig. 2B). *Post hoc* testing did not detect a significant difference in accuracy in either sequence between patients with SCA and controls ($p > 0.05$; *t*-test). In each step, the accuracy in the SCA group crossed over 70% in the seventh sequence, whereas accuracy in the control group reached 70% in the fourth sequence (Sellers and Donchin, 2006). The SCA group needed more flashing sequences to achieve reliable accuracy than the control group.

Fig. 3 lists the error distribution rate at the region relative to the target region in the SCA group and controls. In the SCA group, 6 of the 8 patients had horizontal nystagmus; however, a horizontal-dominant error distribution was not observed in patients with SCA.

3.2. Character input performance

The mean online accuracy of inputted characters (accuracy for the two-step procedure) in SCA subjects was 71.4% and that in the controls was 69.1% (Fig. 4A). The difference was not significant ($p = 0.87$). Fig. 4B shows the results of ANOVA under conditions for the two-step procedure. We tested a two-way repeated-measures ANOVA with group (SCA vs. control) and accuracy of each sequence (1–8). Main effects of both group and the number of sequences were significant ($p < 0.005$; Fig. 4B). *Post hoc* testing did not detect a significant difference in accuracy in any sequence between the SCA and control groups ($p < 0.05$; *t*-test). The ITR for patients with SCA was 9.29 bits/min and that for controls was 8.84 bits/min; there was no significant difference between the groups ($p > 0.05$).

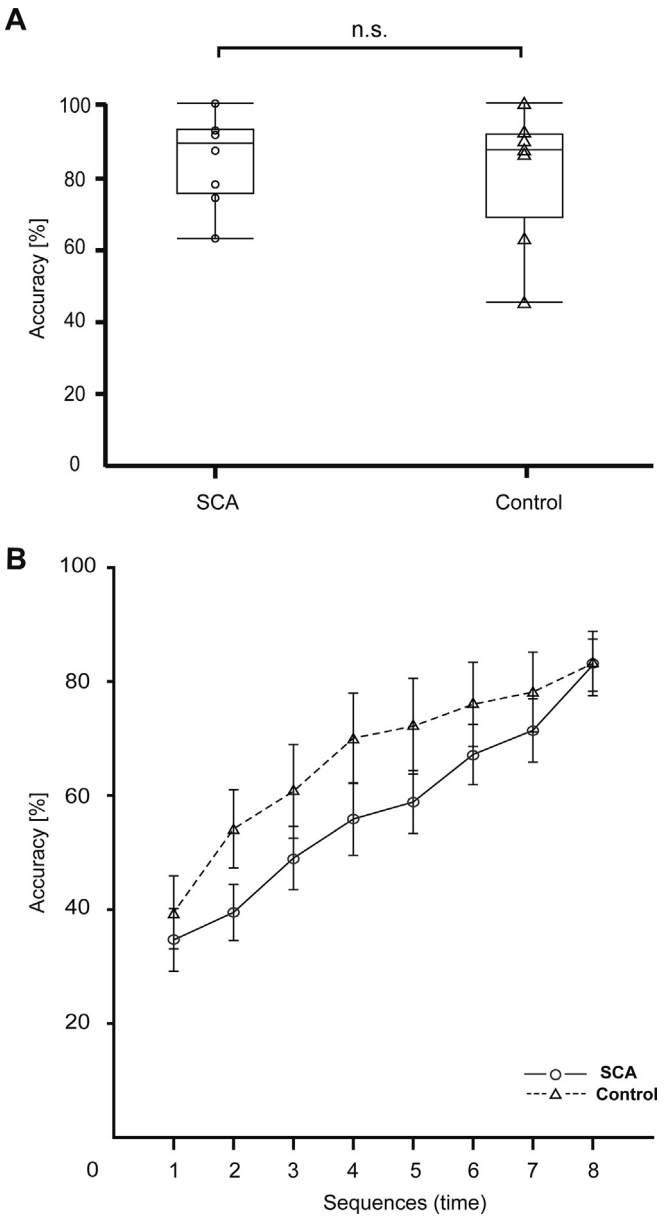

Fig. 2. Performance in BCI operation. (A) Online BCI accuracy was evaluated from the total performance on both the first and second steps. Accuracy in BCI operation by patients with SCA and controls is plotted with box plots. The central black solid line represents the median, the edges of the box are the 25th and 75th percentiles, and the whiskers extend to the most extreme data points. Each gray dot represents an actual subject's accuracy score. We found no significant difference between the SCA and control groups (mean 82.9% and 83.2%, respectively; $p = 0.68$). (B) Offline evaluation of each sequence. Mean accuracies of the SCA and control groups are plotted in each sequence. Each circle represents the accuracy of each sequence in the SCA group, while each square represents that in the control group. Two-way repeated-measures ANOVA revealed that the main effect of group (SCA vs. control) and the main effect of number (1–8) of sequence were significant ($p = 0.0045$ and $p < 0.0001$, respectively).

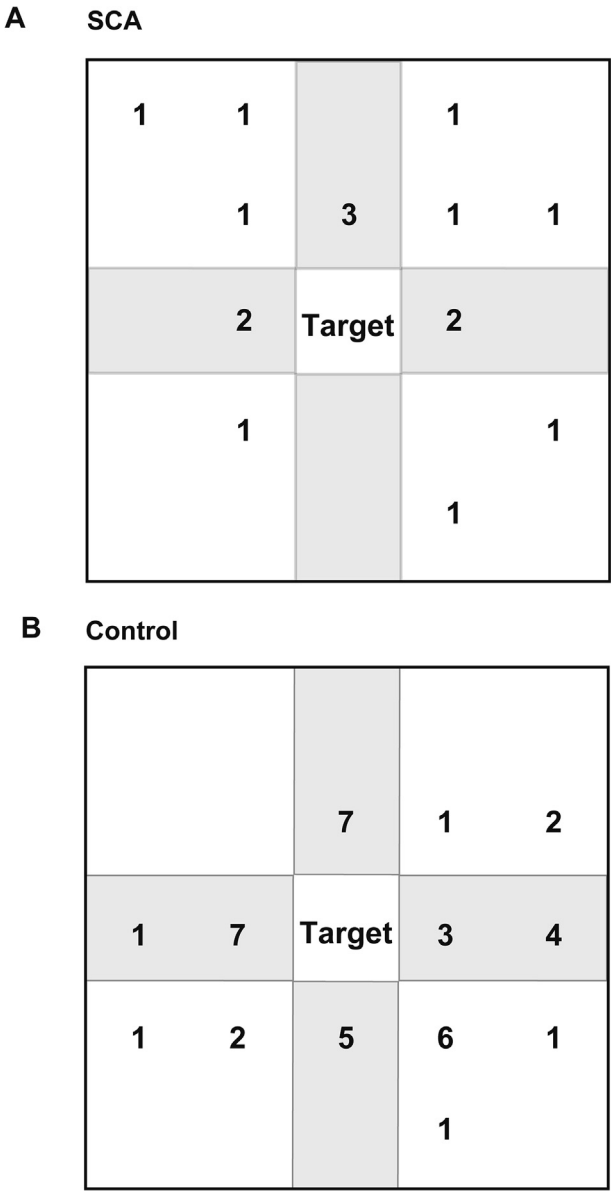

Fig. 3. Distribution of errors in BCI operation. This figure lists the error distribution rate at the region relative to the target region in the SCA and control groups during BCI operation. The position in the figures represents the relative location, and the numbers indicate error ratios. In the SCA group, 7 of the 8 patients showed horizontal nystagmus, but horizontal-dominant error distribution was not observed in the patients with SCA.

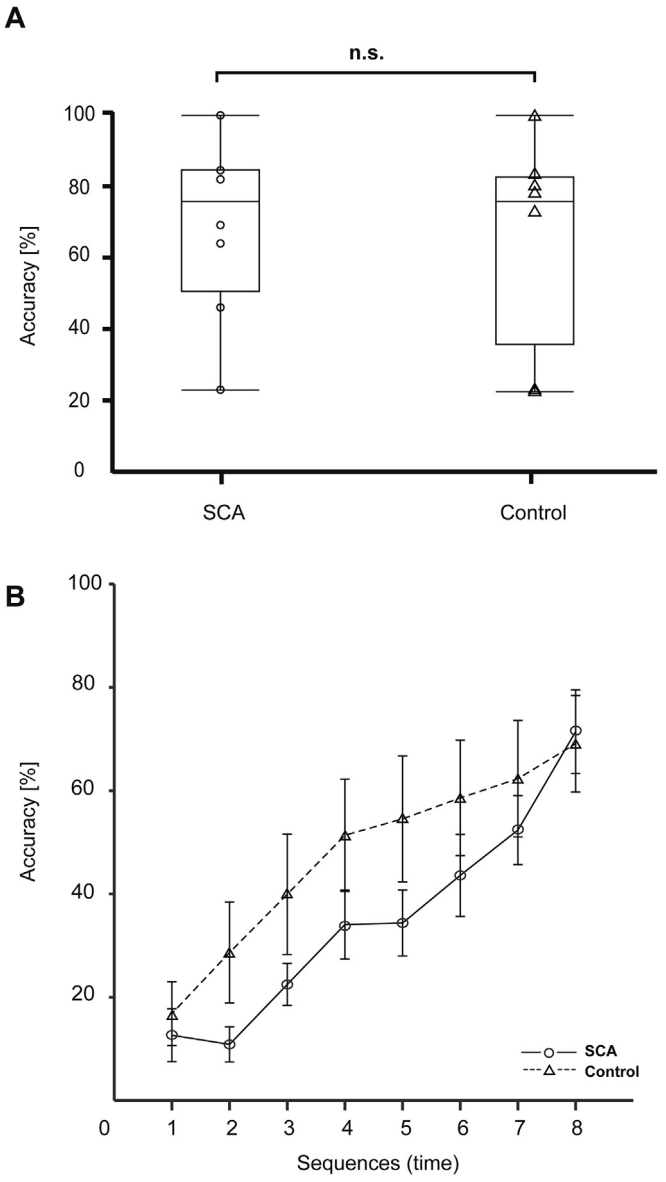

Fig. 4. Performance on character input. (A) Performance on character input was evaluated, in which correct responses in both the first and second steps were required for correct character input. The accuracy of each SCA and control participant was plotted with box plots. We found no significant difference between the SCA and control groups (mean 71.4% and 69.1%, respectively; $p = 0.87$). (B) Offline evaluation for each sequence. Mean accuracies of the SCA and control groups were plotted in each sequence. The main effects of group (SCA vs. control) and number of sequences (1–8) were significant ($p < 0.01$, two-way repeated-measures ANOVA).

4. Discussion

In this study, we applied a region-based, two-step P300-based BCI to patients with SCA who had accompanying cerebellar impairments. We showed that patients with SCA could control the BCI system.

4.1. Successful control of the visual P300-BCI by patients with SCA

The patients with SCA could control the BCI system, and their performance was not significantly different from that of age- and gender-matched healthy controls. In the SCA group, 6 of 8 patients showed horizontal nystagmus; however, a horizontal-dominant error distribution was not observed in patients with SCA. In addition, the mean accuracy of the SCA group in the second step (9 choices) was significantly lower than the accuracy in the first step (6 choices), whereas we did not observe this difference in the control group. The use of the region-based, two-step P300-based BCI with fewer choices may have contributed to the successful operation in patients with SCA.

We previously reported that patients with late-stage ALS, who could not use a conventional row/column matrix P300 speller well, could operate a region-based, two-step speller that had a larger flashing area than the conventional visual array (Ikegami et al., 2014). Patients with late-stage ALS also showed various oculomotor impairments, such as dysfunction in smooth pursuit and slowing fixation (Nijboer et al., 2008). Similar to the patients with ALS, a larger matrix size and green/blue color intensification of icons may have also contributed to the successful performance in the SCA group with oculomotor impairments.

Although the online evaluation did not detect a significant difference in BCI performance between the SCA and control groups, the offline evaluation revealed that SCA patients needed more flashing sequences to achieve reliable accuracy than the controls. Patients with accompanying cerebellar impairments often present with various oculomotor symptoms, such as saccadic dysmetria. Matsuda et al. reported that some SCA patients suffered from an inability to recognize various objects in daily life because of impaired saccade control and impaired eye fixation (Matsuda et al., 2015). With respect to eye gaze and BCI performance, Brunner et al. reported that the performance with a visual P300 BCI speller in healthy participants depended in great measure on gaze direction (Brunner et al., 2010). Treder and Blankertz also showed that healthy participants could drive an ERP-based visual BCI system in both conditions, with the eye fixed to a fixation point and not; however, their performance was markedly worse in the eye-fixed condition (Treder and Blankertz, 2010). Those reports indicated that eye movement had a close relationship with performance in the case of the visual P300 speller. The fact that patients with SCA needed more flashing sequences to achieve reliable accuracy than the controls may be related to impaired saccade control and eye fixation.

It has also been reported that cerebellar impairment may be accompanied by an attention disorder referred to as attentional dysmetria (Ivry and Diener, 1991; Nawrot and Rizzo, 1995; Thier et al., 1999; Jokisch et al., 2005), although the concept of attentional dysmetria caused by cerebellar damage remains controversial. Townsend et al. showed that a lesion in the cerebellum induced a slow shift of attention in both overt and covert situations, whereas Golla et al. demonstrated that attention was basically preserved with cerebellar impairments (Golla et al., 2005). Our results of the successful performance of patients with SCA with the visual P300-BCI may indicate that the basic attentional system in patients with severe SCA is largely preserved.

4.2. Other BCI options for patients with cerebellar impairment

There may be other possible BCI options for patients with cerebellar impairments. For example, several gaze-independent BCIs have been reported previously; visual BCIs, auditory BCIs, and tactile BCIs are three main categories (Riccio et al., 2012). A Hex-O speller, which needed covertly directed attention to a target, is a gaze-independent visual BCI (Treder and Blankertz, 2010; Marjolein van der et al., 2012). Severens et al. showed that patients with moderate ALS could achieve high performance in a copy-spelling task with the Hex-O speller (Severens et al., 2014).

In a P300 auditory BCI speller, instead of visual stimuli, a series of different auditory stimuli (target and nontarget) is presented and the participant is asked to concentrate on a target stimulus. Kubler et al. demonstrated a 25-choice P300 auditory BCI speller (Kubler et al., 2009), and Halder et al. reported a 50-choice P300 auditory BCI speller (Halder et al., 2016). The reported accuracies with P300 auditory BCI spellers are usually lower than those with P300 visual BCI spellers, but an auditory BCI speller may be useful for patients who are unable to use a visual one. Tactile BCIs may be another option for gaze-independent use. Kaufmann et al. evaluated the efficacy of a BCI that had binary choices in an oddball paradigm according to three different modalities, auditory, visual, and tactile, in a patient with a locked-in state and concluded that the tactile modality showed higher offline accuracy (Kaufmann et al., 2013). To date, no study using a gaze-independent BCI applied to patients with cerebellar impairment has been reported, but some of these techniques may be applicable to these patients.

5. Conclusions

We applied a region-based, two-step P300 speller to patients with SCA who had accompanying cerebellar impairments and showed that these patients could control the BCI system. The larger matrix and green/blue color intensification of icons may have contributed to successful performance in patients with SCA with accompanying oculomotor impairments. Patients with SCA may be potential BCI user candidates.

Competing financial interests

The authors have no competing financial interests to declare.

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