Table 1
Patients' clinical characteristics.

Patient	Age, y	Sex	Stroke	Pain duration, month	Current medication	Motor weakness	Sensory deficit	Allodynia	Hyperpathia	Baseline VAS score	VAS reduction after rTMS,%
1	61	M	Lt brain stem infarction	29	TCA, SSRI, BZD	Mild	Severe	+	–	95	21.1
2	65	F	Rt subcortical infarction	37	TCA, BZD, NSAID	Moderate	Mild	+	+	83	33.3
3	56	M	Rt subcortical hemorrhage	7	CZP	Mild	Mild	+	–	97	0
4	64	F	Rt putaminal hemorrhage	37	TCA, GBP	Moderate	Mild	+	+	100	0
5	48	M	Rt thalamic hemorrhage	7	GBP, PB, BZD, NSAID	Mild	Mild	–	–	59	41.5
6	48	M	Rt putaminal hemorrhage	6	TCA, GBP, MEX	–	Severe	+	–	80	100
7	64	M	Lt putaminal hemorrhage	16	CZP, ZNS, BZD, NSAID	Mild	Mild	+	+	86	21.4
8	57	F	Lt putaminal hemorrhage	30	CZP	Mild	Severe	+	+	100	65
9	59	F	Rt putaminal hemorrhage	180	CZP	–	Mild	+	–	77	22.2
10	76	M	Lt thalamic hemorrhage	216	TCA, GBP, MEX	Moderate	Severe	–	–	56	57.1
11	64	M	Lt thalamic hemorrhage	37	TCA, GBP	Moderate	Severe	–	–	81	62.5
12	63	M	Rt thalamic hemorrhage	88	SSRI, GBP, BZD	Moderate	Mild	–	–	89	50
13	52	F	Rt thalamic hemorrhage	8	TCA, GBP	–	Mild	+	+	98	0
14	51	F	Rt putaminal hemorrhage	46	PHT	Mild	Severe	+	–	52	16.7
15	35	M	Rt thalamic hemorrhage	14	GBP	–	Mild	+	+	45	14.3
16	66	F	Lt thalamic hemorrhage	18	GBP	Mild	Mild	+	–	76	7.1
17	58	F	Rt brain stem hemorrhage	86	SSRI, CZP, CBZ, BZD	Mild	Mild	–	–	99	75
18	73	M	Rt thalamic infarction	40	NSAID	Mild	Severe	–	–	89	0
19	65	M	Lt brain stem hemorrhage	39	TCA, GBP	–	Mild	–	–	53	0
20	65	F	Rt brain stem infarction	20	SSRI	Mild	Severe	+	+	75	11.8
21	62	M	Lt putaminal hemorrhage	20	TCA, GBP	Mild	Mild	–	–	50	19

Rt, right; Lt, left; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; BZD, benzodiazepine; NSAID, nonsteroidal anti-inflammatory drug; CZP, clonazepam; GBP, gabapentin; PB, phenobarbital; MEX, mexiletine; ZNS, zonisamide; PHT, phenytoin; CBZ, carbamazepine; VAS, visual analog scale; rTMS, repetitive transcranial magnetic stimulation.

to M1, corresponding to the painful hand, for 10 s with 50 s of intertrain interval. Thus, a total of 500 pulses were applied in an rTMS session. The details of this rTMS protocol have been reported previously [14,41]. This protocol was carried out in accordance with the guidelines for safe use of rTMS [38].

2.5. Statistical analysis

Patients were assigned to 1 of 2 groups: responders ($\geqslant$30% pain reduction after rTMS) and nonresponders (<30% pain reduction) [8]. Differences of cortical excitability indices between each group at baseline were evaluated by Mann-Whitney *U* test. Alterations of these indices after rTMS were evaluated by Wilcoxon's signed-rank test. Nonparametric tests were adopted because the analyzed groups were not estimated to have a normal distribution. In all comparisons, findings with $P < .05$ were considered statistically significant.

3. Results

All patients completed the study without adverse effects. Eight of 21 patients experienced $\geqslant$30% pain reduction in their VAS after rTMS, and these patients were categorized as responders. Between responders and nonresponders, there were no significant differences in any patient characteristics (age, sex, duration of pain, stroke type, pain laterality, severity of motor and sensory disturbances, and VAS at baseline) and the stimulus intensities of rTMS.

The RMT of all patients was higher than those of controls (65.5 ± 3.0% vs 56.7 ± 2.3%, $P = .035$). There were no significant differences in the other parameters between the patients and controls (Table 2). The ICF of the responders significantly increased after the rTMS session (110.3 ± 12.5% vs 170.0 ± 28.3%, $P = .039$). There were no significant changes in the other parameters (Table 3). The ICF of the responders was significantly lower than those of the controls and the nonresponders at baseline (110.3 ± 12.5% vs 168.0 ± 18.8%, $P = .035$, and vs 188.3 ± 21.7%, $P = .019$) (Fig. 1).

4. Discussion

To our knowledge, this study is the first to document alteration of cortical excitability within M1 in CPSP patients. We studied the cortical excitability changes in CPSP patients and healthy controls by means of single- or paired-pulse TMS methods. Our findings revealed that RMT in patients with CPSP was elevated and the im-

Table 2
Cortical excitability measurements at baseline.

Characteristic	Patients, mean (SEM)	Controls, mean (SEM)	*P*
RMT, %	65.5 (3.0)	56.7 (2.3)	.035*
MEP amplitude, μV	655 (80)	707 (105)	.818
CSP, ms	167.9 (10.4)	148.4 (8.7)	.238
SICI, %	32.0 (8.7)	47.3 (7.0)	.350
ICF, %	158.6 (16.5)	168.0 (18.8)	.530

SEM, standard error of mean; RMT, resting motor threshold; MEP, motor evoked potential; CSP, cortical silent period; SICI, short interval intracortical inhibition; ICF, intracortical facilitation.
* $P < .05$ for differences in mean values between patients and controls by Mann-Whitney *U* test.

Table 3
Changes in cortical excitability measurements after rTMS.

Characteristic	Good response		Poor response	
	Mean (SEM)	*P*	Mean (SEM)	*P*
RMT, %		.171		.833
Baseline	62.9 (5.8)		67.1 (3.1)	
Post-rTMS	64.6 (6.1)		66.8 (2.6)	
MEP amplitude, μV		.945		.455
Baseline	589 (97)		695 (114)	
Post-rTMS	602 (138)		810 (132)	
CSP, ms		.461		.067
Baseline	186.8 (19.8)		156.2 (10.2)	
Post-rTMS	171.3 (20.6)		162.2 (11.1)	
SICI, %		.313		.735
Baseline	40.8 (10.7)		26.7 (12.3)	
Post-rTMS	30.6 (12.1)		16.7 (19.1)	
ICF, %		.039*		1.000
Baseline	110.3 (12.5)		188.3 (21.7)	
Post-rTMS	170.0 (28.3)		183.6 (28.0)	

rTMS, repetitive transcranial magnetic stimulation; SEM, standard error of mean; RMT, resting motor threshold; MEP, motor evoked potential; CSP, cortical silent period; SICI, short interval intracortical inhibition; ICF, intracortical facilitation.
* $P < .05$ for differences in mean values between patients and controls by Mann-Whitney *U* test.

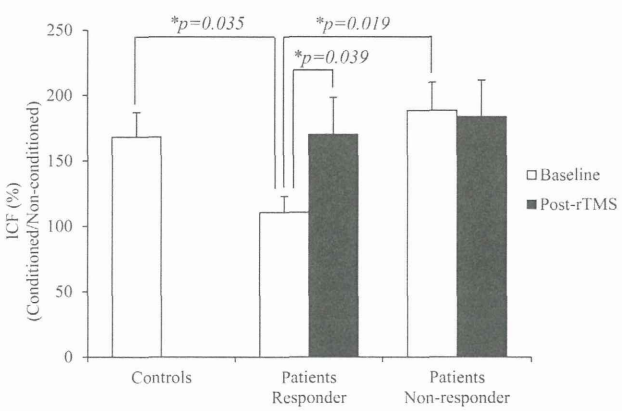

Fig. 1. ICF in responders was lower than ICF in controls and nonresponders at baseline (110.3 ± 12.5% vs 168.0 ± 18.8%, $P = .035$, and vs 188.3 ± 21.7%, $P = .019$). ICF of responders significantly increased after the rTMS session (110.3 ± 12.5% vs 170.0 ± 28.3%, $P = .039$). ICF, intracortical facilitation; rTMS, repetitive transcranial magnetic stimulation.

paired ICF in the responders was restored after high-frequency rTMS of M1. Restoration of a normal ICF value was accompanied by successful pain relief.

In patients after stroke, it is well known that damage of motor tracts resulted in elevation of the motor threshold in the affected hemisphere [5]. Fifteen of 21 patients studied in this study had mild or moderate motor weakness. The elevated RMT in this study seemed to reflect the condition with motor weakness after stroke.

SICI and ICF are considered to reflect the functions of interneurons within M1. SICI is likely to reflect GABAergic inhibitory interneurons, especially $GABA_A$ function [23,37], while ICF is thought to mainly reflect glutamatergic excitatory interneurons within M1 [37,47]. Several studies have investigated ICF and SICI alterations in patients with various chronic pain conditions: various neuropathic pain [27,45], complex regional pain syndrome type I [9], or fibromyalgia [44]. These studies have demonstrated that a chronic pain state is reflected by a decrease in SICI and a tendency for ICF to decrease as a whole. Our results are consistent with previous reports in that ICF and SICI tended to decrease.

High-frequency (eg, 5 Hz) rTMS is referred to as excitatory rTMS and is thought to increase cortical excitability. Several studies applying high-frequency rTMS to M1 have reported an immediate increase of excitability in healthy volunteers (increased MEP amplitude, decreased SICI, and increased ICF), although the other studies have reported no change [10]. We first demonstrated an increase in ICF in the responders of CPSP patients after 5 Hz rTMS of M1. In this study, SICI did not significantly change after rTMS; however, there was a tendency for SICI to decrease. These findings were consistent with the previous reports, revealing high-frequency rTMS, increased ICF, and decreased SICI. Lefaucheur et al. reported that defective SICI was restored in parallel with pain relief after 10 Hz rTMS of M1 in 22 patients with various types of neuropathic pain (10 strokes, 4 peripheral nerve lesions, 4 brachial plexus lesions, and 4 spinal cord lesions) [27]. These results can fit to the deafferentation theory with cortical and subcortical hyperactivities, and the potential therapeutic action of motor cortex stimulation on pain processing areas [13,22,35], although SICI increase due to the high-frequency rTMS was the opposite to results in healthy subjects. Our results seem to be contrary to the results from the study reported by Lefaucheur et al. However, according to the theory of cortical hyperactivity, motor cortex hyperactivity may result in a compensatory decrease in ICF. Furthermore, rTMS might reduce pain-related hyperactivity, resulting in restoration of the compensatory decrease in ICF along with pain relief. A study demonstrated that rTMS effects on cortical excitability depended more on baseline individual values than on stimulation frequency [6]. The difference between our results and those reported by Lefaucheur et al. may be rooted in the different sources of neuropathic pain and the difference of the baseline individual values in cortical excitability.

rTMS stimulates the neuronal tissue electrically in a manner similar to EMCS, evoking eddy current within the cortex [25], and similar descending volleys were evoked by TMS and EMCS [7]. The frequency and duration of pulses are different between rTMS and EMCS; nevertheless, the analgesic effects produced by rTMS and EMCS have many common points. For instance, pain relief often delayed and prolonged after the stimulation period of rTMS in a similar time course as EMCS [26,33,42], and the efficacy of rTMS on pain relief has been reported to correlate with EMCS efficacy [15,29]. Therefore, the mechanism behind pain relief through high-frequency rTMS may be similar to that of EMCS. According to PET activation studies, EMCS seems to activate several brain areas related to pain perception, affective–emotional components, and the descending pain inhibitory system, such as the posterior thalamus, insula, anterior cingulate cortex, orbitofrontal cortex, and upper brain stem [11,19]. rTMS also activated remote and widespread areas in a PET study [40]. A recent study suggested that inhibition of thalamic sensory neurons and disinhibition of the neurons in the periaqueductal gray played a role in pain relief induced by the motor cortex stimulation in naive rats [35]. The process of pain relief resulting from rTMS or EMCS suggests that the

stimuli act locally in M1, then modulate the interconnected remote deep brain structures through the subcortical fibers. Our diffusion tensor fiber tracking study demonstrated that the rTMS efficacy in pain relief related to good preservation of the thalamocortical tract and corticospinal tract [12]. In addition, we reported that rTMS and EMCS provided better pain relief in patients without cerebral lesions [15,41]. These results suggest that subcortical fibers and various remote deep brain structures play an important role in pain reduction by rTMS. High-frequency rTMS may reinforce propagation from M1 to such remote regions resulting in pain relief and strengthening the function of intracortical excitatory interneurons within M1.

Our findings demonstrated that ICF in responders was significantly lower compared with that in nonresponders and controls at baseline. The basis for these differences is difficult to explain with certainty. The physiology of ICF is not clear compared to that of SICI, and only a small number of studies have reported ICF alterations in patients with neurological disease. One study investigating intracortical excitatory mechanisms in patients with stroke found reduced SICI but normal ICF in the affected hemisphere [31]. Furthermore, there were no significant differences in patient characteristics or medications between the responders and nonresponders in the present study. Therefore, our findings demonstrating ICF decrease were not simply caused by a poststroke condition, by patient characteristics, or by medication. The state of low ICF at baseline may be associated with the clinical efficacy of rTMS in patients with CPSP, and the patient with low ICF may be a good candidate for the rTMS intervention.

In conclusion, we found alterations of cortical excitability in M1 in CPSP patients with high-frequency rTMS in M1. Our findings suggest that restoration of abnormal cortical excitability might be one of the mechanisms underlying pain relief as a result of rTMS in CPSP.

Conflict of interest statement

The authors report no conflict of interest.

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Systems/Circuits

Cancelling Prism Adaptation by a Shift of Background: A Novel Utility of Allocentric Coordinates for Extracting Motor Errors

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Many previous studies have reported that our brains are able to encode a target position not only in body-centered coordinates but also in terms of landmarks in the background. The importance of such allocentric memory increases when we are forced to complete a delayed reaching task after the target has disappeared. However, the merit of allocentric memory in natural situations in which we are free to make an immediate reach toward a target has remained elusive. We hypothesized that allocentric memory is essential even in an immediate reach for dissociating between error attributable to the motor system and error attributable to target motion. We show here in humans that prism adaptation, that is, adaptation of reaching movements in response to errors attributable to displacement of the visual field, can be cancelled or enhanced simply by moving the background in mid-flight of the reaching movement. The results provide direct evidence for the novel contribution of allocentric memory in providing information on "where I intended to go," thereby discriminating the effect of target motion from the error resulting from the issued motor control signals.

Introduction

Our brains are able to memorize target positions not only in body-centered coordinates but also in terms of landmarks, such as a square (Fig. 1*a*), in the background (McIntyre et al., 1998; Burgess et al., 2004; Krigolson and Heath, 2004; Lemay et al., 2004; Sheth and Shimojo, 2004; Obhi and Goodale, 2005; Krigolson et al., 2007; Byrne and Crawford, 2010; Byrne et al., 2010; Chen et al., 2011). These studies have often adopted delayed reaching tasks in which participants reach for a target that disappeared a moment ago. The errors generally decreased when landmarks were available compared with when they were unavailable. However, the effect of the landmarks was much reduced when subjects made an immediate reach and became obvious only when the delay was as long as ~2 s or more (Carrozzo et al., 2002; Sheth and Shimojo, 2004; Obhi and Goodale, 2005). Admitting that the allocentric coordinate is useful in memorizing "where to go" (Fig. 1*a*, left), there are few natural situations that involve reaching for a target that disappeared >2 s ago. Thus, the realistic utility of the allocentric memory is yet to be discovered.

In natural situations, a target often moves (Fig. 1*a*, right). However, we are never able to compensate for a target motion that occurred within the last ~150 ms of a reaching movement (Day and Lyon, 2000). Thus, the apparent discrepancy between the target and the hand (apparent error) consists of two components: one attributable to the error in the motor system (here termed "motor error") and another attributable to the target motion. For improving motor skill, it is essential to estimate the net motor error by discounting the error attributable to target motion. We here hypothesize that the allocentric memory is essential for dissociating error attributable to the motor system from error attributable to target motion by encoding "where I intended to go" (Fig. 1*a*, right).

To test this hypothesis, we introduced a large apparent error using a lateral displacing prism and presented a frame in the background (Fig. 1*b*). In a control condition, the frame remained still (no shift): the apparent error itself was expected to serve as the motor error to be corrected, and the error decreased trial by trial as in the traditional prism adaptation paradigm. In another condition, the frame was displaced in the direction of prism displacement in mid-flight of reaching (ipsilateral shift), with no movement of the target itself. In this condition, the original target position decoded in the frame coordinate would shift with the frame (dotted circle), and the hand would be likely to land on the decoded position. The motor error would then be judged as much smaller than the apparent error, and prism adaptation would be expected to be reduced. In a third condition, the frame was displaced in the opposite direction (con-

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tralateral shift). In this case, prism adaptation was likely to be enhanced. We show in the following that the prism adaptation was modulated as predicted.

Materials and Methods

Participants. Thirty-seven young adults (33 men and four women, aged 19–28 years) with normal vision or vision that was corrected to normal with contact lenses participated in the study. Participation was discontinued for seven participants because of low success rates during a training session in terms of reaction time and movement duration. All participants were naive to the purpose of the experiments, and none reported neurological history. All participants were right-handed (laterality quotient, +80 to +100) according to the Edinburgh Inventory (Oldfield, 1971). The study received approval from the institutional ethics committee, and all participants gave informed written consent before the experiments.

Apparatus and general task procedures. The participants were seated facing a tangent 22-inch LCD screen 360 mm from their eyes with their heads restrained by a chin rest and a head band; they viewed the screen through a refractor (with two pairs of motor-driven wedge prisms, one for each eye) that restricted their view of the screen within the visual field to ~30° (Fig. 2*a*). Liquid crystal shutters were placed between the prisms and the eyes of the participants. The refractor was designed to achieve a desired displacement of 0–20 diopter (0–11.3°) in any direction by rotation of the prisms with a command from a personal computer (Interface Corporation). The shutters were opened at the initiation of each trial when the participants pressed a button with their index fingers. The button was positioned 300 mm below and 100 mm ahead of the subject's eyes in the midsagittal plane. A target (a red cross, 15 mm = 2.4° wide) and background figures drawn with blue lines then appeared on a white background after a random delay (900–1200 ms). The position of the background figures was randomized from one trial to another so that the centers of the figures fell within a circular zone (20 mm radius, 3.2°) in the center of the visual field. A target was presented at a random location within a target zone (20 mm radius, 3.2°) placed in the center of the background figures. The participants were required to release the button within 300 ms (but after 150 ms) from the appearance of the target and to touch the screen within 300 ms of the release. The shutters were closed at the release to block the vision of the hand and the target during the reach and were opened again at the touch, which was detected with a touch sensor (Touch Panel Laboratories), to allow the participants to see the target and the final position of the hand for 300 ms. The participants were required to hold the final position of the hand for 1000 ms after the touch and were allowed to return the hand to the starting position when they heard a beep. The prisms were rotated for 500 ms during each intertrial interval even in blocks with no visual displacement so that the participants would not be able to infer the size of visual displacement from the sound of the motors. It took 5–6 s to complete one trial. When the reaction time or the movement time was outside the required range (failure trial), the shutters were kept closed at the touch with a low beep sound.

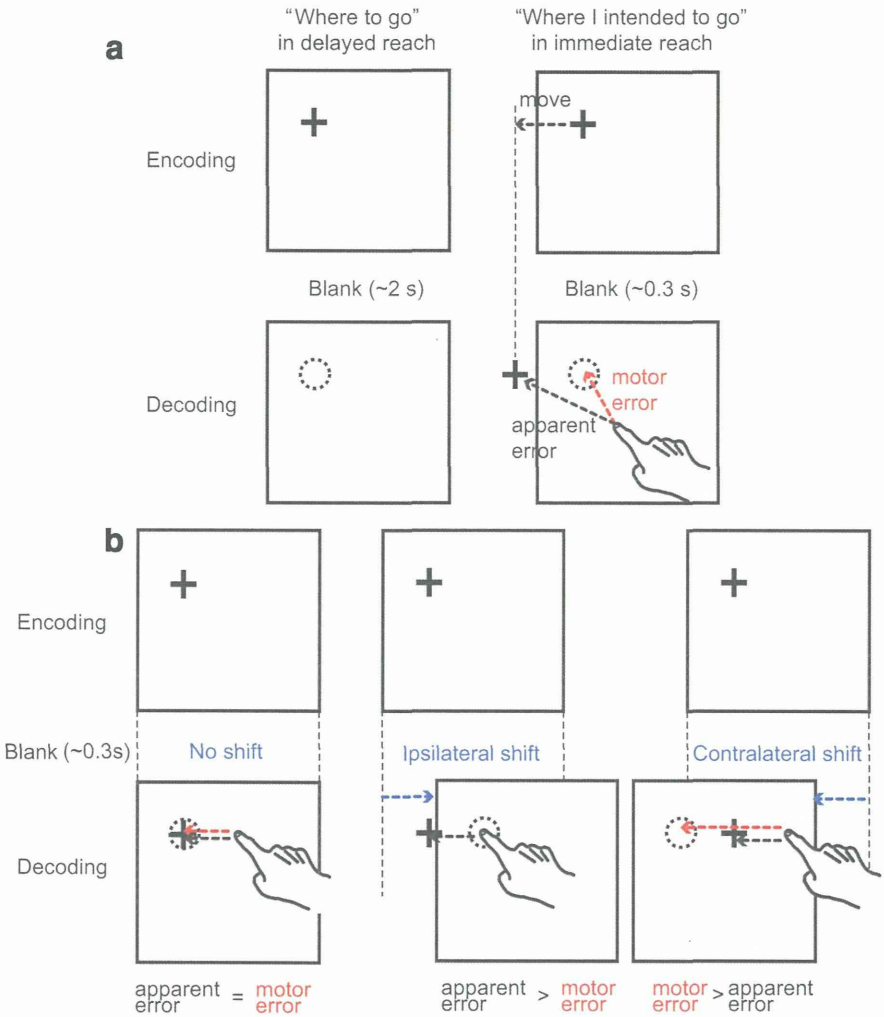

Figure 1. A novel utility of the allocentric memory of a target position. ***a***, Allocentric memory in terms of the background frame has been believed to be useful in memorizing "where to go" in delayed reaching when a blank (delay) is as long as 2 s (left). We propose a novel use of the allocentric memory in an immediate reach (right). We hypothesize that the allocentric memory is essential for dissociating error attributable to the motor system (red arrow) from error attributable to target motion by encoding "where I intended to go" (dotted circle). ***b***, Basic design of the experiments. A large apparent error (black arrow) was introduced using a lateral displacing prism. The frame remained still (left) or was displaced in the direction of prism displacement (ipsilateral shift, middle) or in the opposite direction (contralateral shift, right) during a reaching movement. Assuming that our hypothesis is correct, the original target position decoded in terms of the frame would shift with the frame (dotted circle), and the motor error (red arrow) would be underestimated in the ipsilateral condition and overestimated in the contralateral condition.

One session consisted of three periods of 30 trials. In the first and the third periods (pretest and posttest periods), the participant performed the reaching task without visual displacement or any shift of background figures. In the second period (exposure period), the visual field was displaced to the right or to the left by 20 mm (3.2°), and the background figures were shifted by 20 mm in the same (ipsilateral shift condition) or the contralateral direction (contralateral shift condition) while the participant's vision was blocked with shutters. The size of visual field was restricted within ~30° so that objects in the background other than the background figures, such as the edges of the LCD screen, cannot be seen by the participants. The directions of visual displacement and the background figures were kept constant through the 30 trials in each exposure period. Failure trials were discarded, and each period was continued until the participants completed 30 successful trials. It took ~8–10 min to complete one session.

The participants were instructed to ignore the background figures and to reach for the target as rapidly and precisely as possible without any conscious corrections. The participants were familiarized with the task

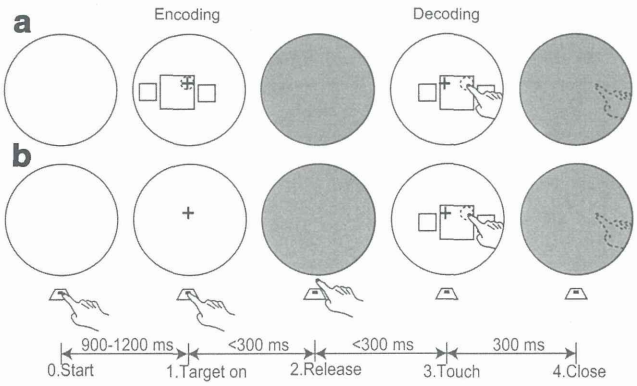

Figure 2. Task procedures. Each column schematically shows the status of the visual field (oval shape) and the position of the hand relative to the button and the screen. The shutters opened at 0 (Start) when the participant pressed the button. A target and background figures appeared after a random delay (900–1200 ms) at 1. Vision was blocked from 2 (Release) to 3 (Touch) and allowed again for 300 ms. The background figures were presented both before (encoding) and after (decoding) the reach in experiments 1–3 (***a***); they were presented only after the reach in experiment 4 (***b***).

procedure beforehand until they had little difficulty in generating the task movement within the required time period. Each participant sat for one or two sessions per day. When there were two sessions, the participants rested for 10–20 min between sessions. Thirty trials without visual displacement were added to ensure washout of any aftereffects before and after each session.

Experiment 1: effects of ipsilateral and contralateral shifts of the background. Six participants completed this experiment. Triple squares, a center square (80 mm, 13°) between two smaller squares (40 mm, 6.3°), were presented as a background both before (encoding period) and after (decoding period) the blank (Fig. 2*a*). There were two × three conditions depending on the direction of visual displacement (left or right) and the direction of the background shift (ipsilateral, contralateral, and no background shift conditions; Fig. 1*b*). Each participant completed six sessions, one for each of the two × three conditions. The order of the conditions was counterbalanced across the participants.

Experiment 2: effects of the size of background (see Fig. 4). Six participants completed this experiment. The size of background (triple squares) was altered in five steps with the background always shifted in the ipsilateral direction. There were two × five conditions: two directions of visual displacement (left or right) by five sizes of background (0, 8, 40, 80, and 120 mm width of the center square; 0, 1.3, 6.3, 13, 18° width; see Fig. 4*a*). Each participant completed 10 sessions, one for each of the two × five conditions. The orders of conditions were counterbalanced within and across the participants.

Experiment 3: effects of the complexity of background (see Fig. 5). Twelve participants completed this experiment. The complexity of the background was altered in six steps (no background, single line, parallel lines, single square, triple squares, and multiple squares; see Fig. 5*a*), with the background always shifted in the ipsilateral direction. The length of the line and the width of the center square were fixed at 80 mm. For the single line condition, one of the four sides of the center square was assigned for each participant (three participants for each side). For the parallel line condition, one of two pairs (vertical or horizontal pairs) was assigned for each participant (six participants for each). For each participant, the direction of visual displacement was fixed either to the right (six participants) or to the left (six participants). Each participant completed six sessions, one for each complexity. The order of the conditions was counterbalanced across the participants.

Experiment 4: necessity of the background during the encoding phase. Six participants completed this experiment. The triple-square background (center square, 40 mm, 6.3° in width) was presented in three ways: (1) the background was not presented (no background condition); (2) the background was presented both before and after the blank period with an ipsilateral shift (ipsilateral shift condition); and (3) the background was presented only after the blank (post-presentation condition). Each participant sat for the experiment in each of the six conditions (2 directions of prisms × 3 background conditions). The order of the conditions was counterbalanced across the participants.

Data analyses. The horizontal errors in success trials (30 trials for each period) were analyzed. The mean horizontal error during the pretest period was regarded as a bias and was subtracted from the horizontal errors obtained during the exposure and posttest periods. The bias-free horizontal errors were then used for estimating the asymptote in the exposure period and the size of the aftereffect in the posttest period using a discrete model formulated as follows:

$$h(n) = h(n-1) - k(\bar{h}(n-1) - \alpha),$$

where $h(n)$, $\bar{h}(n)$, k, and α denote, respectively, the estimated horizontal error in the nth trial, the observed horizontal error in the nth trial, a constant rate at which the error is assumed to decrease, and an asymptote to which the error is assumed to converge. The model defines a learning algorithm in which the error decreases by an amount proportional to the error observed in the preceding trial to an asymptote. Except for the introduction of the asymptote, the model was the same as that used in our previous studies (Kitazawa et al., 1995; Kitazawa and Yin, 2002). The MATLAB optimization toolbox was used for least-squares estimation of $h(1)$, k, and α. The estimated asymptote (α) during the exposure period and the estimated initial error, $h(1)$, during the posttest period (aftereffect) were further compared across conditions using one-way repeated-measures ANOVA and a *post hoc* analysis (Ryan's method; Day and Quinn, 1989).

Results

Effects of ipsilateral and contralateral shifts of the background (experiment 1)

The results we obtained generally agreed with the predictions from our hypothesis. In the ipsilateral shift condition, the prism adaptation of a participant was almost completely cancelled (Fig. 3*a*); the error during the exposure period persisted at ~20 mm (3.2°), as large as the size of the visual displacement, and little aftereffect was observed (−2.4 mm). Conversely, in the contralateral shift condition, prism adaptation was enhanced (Fig. 3*c*) compared with the no-shift condition (Fig. 3*b*); in this case, the error during the exposure period decreased from 20 mm beyond the zero level and converged to −3.9 mm, and the estimated size of the aftereffect was 23 mm, larger than the visual displacement.

The results were basically similar when the data obtained from six participants were pooled (Fig. 3*d–f*, 12 sessions). The plateau during the exposure period decreased in the following order: 12 mm in the ipsilateral shift condition, 4.1 mm in the no-shift condition, and −0.96 mm in the contralateral shift condition. Conversely, the aftereffect increased in the following order: ipsilateral (7.2 mm), no-shift (14 mm), and contralateral shift (19 mm) conditions. One-way repeated-measures ANOVA applied to the size of asymptotes estimated for each session showed that the main effect of the shift condition was significant ($F_{(2,22)} = 21$, $p < 0.0001$). *Post hoc* tests (Ryan's test) showed that the mean asymptote was significantly larger in the ipsilateral shift condition (10 ± 2.0 mm, mean ± SEM; $p = 0.0018$) and significantly smaller in the contralateral shift condition (−0.87 ± 0.93 mm, $p = 0.0077$) than in the no-shift condition (4.2 ± 0.81 mm; Fig. 3*g*). The main effect of the shift condition was significant for the size of the aftereffect as well ($F_{(2,22)} = 8.4$, $p = 0.0019$). The mean aftereffect was significantly smaller in the ipsilateral shift condition (7.5 ± 2.4 mm) than in the no-shift condition (14 ± 1.4 mm, $p = 0.029$) or in the contralateral shift condition (19 ± 2.2 mm, $p = 0.00049$, Fig. 3*h*). Although the difference between the aftereffects in the contralateral shift condition and the no-shift con-

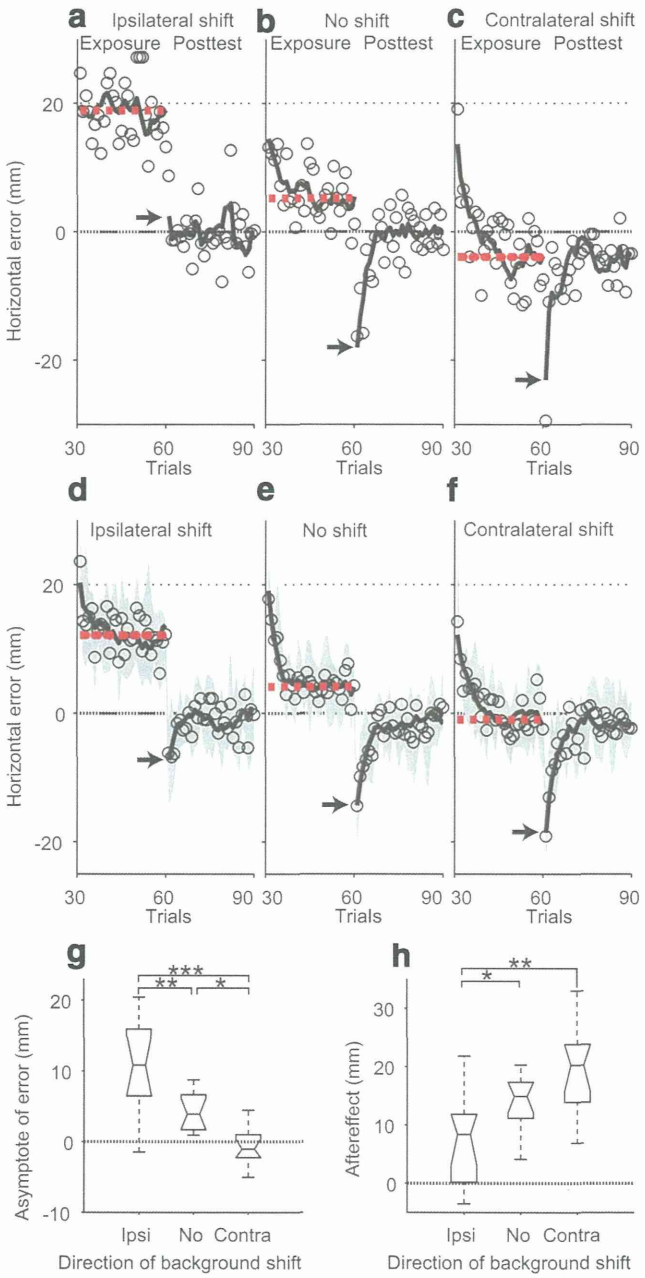

Figure 3. Effects of ipsilateral and contralateral shifts of the background (experiment 1). The data from an individual participant (***a–c***) and from all participants (***d–f***) are shown. Each circle represents the median of two (***a–c***) and 12 (***d–f***, 2 directions × 6 participants) responses plotted against trial sequence (abscissa). Errors in the direction of prism displacement (right or left) are indicated as positive. The thick black lines indicate the model predictions using model equation in Materials and Methods. Note the difference in the asymptotes during the exposure period (red dotted lines) and in the aftereffects (black arrows) across three conditions: ipsilateral shift (***a***, ***d***), no-shift (***b***, ***e***), and contralateral shift (***c***, ***f***). The gray shaded areas in ***d–f*** show the 25th and 75th percentiles. ***g***, ***h***, Distributions of the asymptotes during the exposure period (***g***) and aftereffects during the posttest period (***h***) estimated for each session ($n = 12$). Each box plot shows the 10th, 25th, 50th, 75th, and 90th percentiles. Brackets with asterisks indicate significant differences (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$) after corrections for multiple comparisons (Ryan's method after one-way repeated-measures ANOVA).

dition did not reach the level of significance, the results generally agreed with the predictions from our hypothesis: prism adaptation was attenuated in the ipsilateral shift condition and enhanced in the contralateral shift condition compared with the no-shift condition.

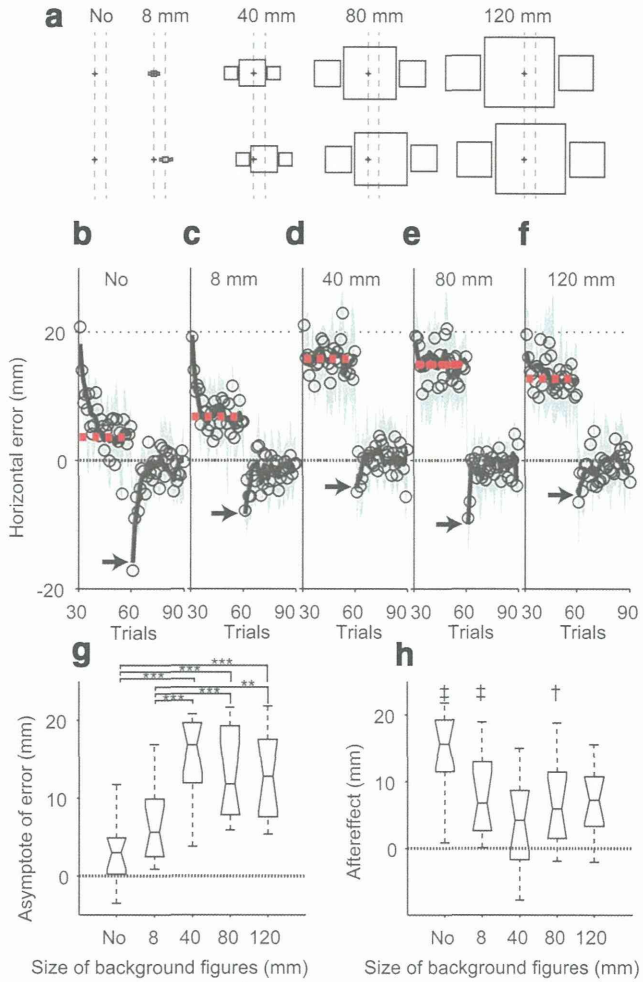

Figure 4. Effects of the size of the background (experiment 2) on cancelling. ***a***, Illustrations of background figures of different sizes. The size of the center square was 0 (no background), 8, 40, 80, or 120 mm. The top and bottom panels show the rightward shift of the background between the encoding (top) and decoding (bottom) phases. The vertical lines show the size of the shift (20 mm). ***b–f***, Prism adaptation with five different sizes of background. Note the maximal cancelling effects at 40 mm. Each circle represents the median of 12 responses (6 participants × 2 directions). ***g***, ***h***, Distributions of the asymptotes during the exposure period (***g***) and aftereffects during the posttest period (***h***). The daggers in ***h*** show that the mean aftereffect was significantly different from zero after correction for multiple comparisons ($^{\dagger}p < 0.05$; $^{\ddagger}p < 0.01$; *t* test, Bonferroni's correction). Other conventions are the same as in Figure 3.

Effects of the size of background (experiment 2)

In experiment 1, the size of the center square was fixed at 80 × 80 mm. In experiment 2, we examined the effect of background size under the ipsilateral shift condition (Fig. 4*a*). The asymptote during the exposure period, estimated from the data pooled across six participants, changed with the size of the square in an inverted U-shaped manner with a peak at 40 mm (Fig. 4*b–f*), as follows: 3.6 mm (no figure), 6.8 mm (square width, 8 mm), 16 mm (40 mm), 15 mm (80 mm), and 13 mm (120 mm). Accordingly, the size of the aftereffect changed in a U-shaped manner with a minimum at 40 mm: 16 mm (no figure), 8.3 mm (8 mm), 4.3 mm (40 mm), 10 mm (80 mm), and 5.3 mm (120 mm). One-way repeated-measures ANOVA applied to the size of the asymptotes estimated for each session ($n = 12$; Fig. 4*g*) showed that the main effect of the background size was significant ($F_{(4,44)} = 19$, $p < 0.0001$). The main effect of the size was also significant for the size of the aftereffect ($F_{(4,44)} = 2.6$, $p = 0.046$; Fig. 4*h*). *Post hoc* tests showed that the mean asymptote at 40 mm (15 ± 1.7 mm) was

significantly larger than the mean with no background (3.2 ± 1.2 mm, $p < 0.0001$) and the mean at 8 mm (6.6 ± 1.4 mm, $p < 0.0001$), although comparisons with the mean asymptote at 80 mm (14 ± 1.7 mm, $p = 0.38$) and 120 mm (13 ± 1.7 mm, $p = 0.24$) did not reach the level of significance (Fig. 4*g*, brackets). *Post hoc* comparisons of the mean aftereffect did not reach the level of significance for any of the combinations (Fig. 4*h*). However, when the mean aftereffect was compared with zero, the aftereffect was significantly larger than zero at 8 mm (8.1 ± 1.9 mm, $p = 0.0014$; Bonferroni's correction for multiple comparison) and 80 mm (6.8 ± 1.9 mm, $p = 0.0037$) but not at 40 mm (5.3 ± 2.9 mm, $p = 0.098$) or 120 mm (6.3 ± 2.1 mm, $p = 0.011$). These results show that the power of cancelling prism adaptation generally increased with the size of the square up to 40 mm but that it decreased or maintained a similar level with larger squares.

Effects of the complexity of background (experiment 3)

We then sought to determine which part of the background figures was essential for cancelling prism adaptation by using six background figures with different complexities (experiment 3; Fig. 5*a*): (1) no figure; (2) single line; (3) parallel lines; and an 80 mm square with 0 (4), 2 (5), and many smaller squares (6). As the complexity of the background figures increased, the asymptote during the exposure period generally increased, whereas the size of the aftereffect decreased (Fig. 5*b–g*). As a result, the cancelling effect was most prominent with the multiple-square background (Fig. 5*g*). One-way repeated-measures ANOVA showed that the main effect of the complexity of background figures was significant for the size of the asymptote ($F_{(5,55)} = 8.7$, $p < 0.0001$; Fig. 5*h*) as well as the size of the aftereffect ($F_{(5,55)} = 4.2$, $p = 0.0027$; Fig. 5*i*). *Post hoc* tests (Ryan's test) showed that the mean asymptote became significantly larger than that in the no-figure condition (4.1 ± 0.89 mm) with two parallel lines (12 ± 2.8 mm, $p = 0.0013$) and with more complex figures: a single square (12 ± 2.3 mm, $p = 0.00035$), triple squares (13 ± 3.1 mm, $p = 0.00030$), and multiple squares (14 ± 2.1 mm, $p < 0.0001$). The mean aftereffect became significantly smaller than that in the no-figure condition (17 ± 1.8 mm) with a single square (7.6 ± 2.8 mm, $p = 0.0019$), triple squares (8.0 ± 3.1 mm, $p = 0.0027$), and multiple squares (5.9 ± 2.4 mm, $p = 0.00026$). Together, the results showed that the cancelling effect became significant with parallel lines and with more complicated figures, and the effect was most apparent with a square surrounded by many smaller squares (multiple squares).

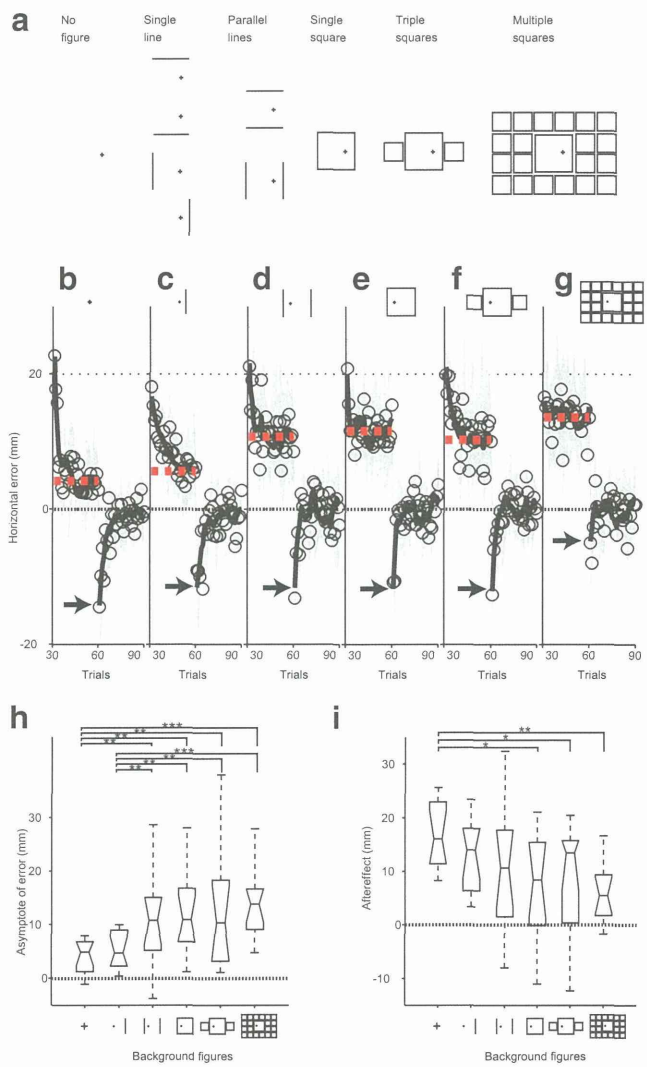

Figure 5. Effects of the complexity of the background on cancelling (experiment 3). ***a***, Illustrations of background figures with different complexities: no background, a single line, parallel lines, a single square, triple squares, and multiple squares. The size of the center figure was fixed at 80 mm. ***b–g***, Prism adaptation with background figures of different complexities. Note the maximal cancelling effects with multiple squares. Each circle represents the median of 12 responses (12 participants × 1 direction). ***h***, ***i***, Distributions of the asymptotes during the exposure period (***h***) and aftereffects during the posttest period (***i***). Other conventions are the same as in Figure 3.

Necessity of the background during the encoding phase (experiment 4)

We hypothesized that the initial target position is encoded in terms of the background figures before the blank and decoded after the blank, again in terms of the background. However, a single presentation of a large frame offset to the left or right of an observer's midline is known to induce a shift of the subjective straight ahead, or the egocentric coordinate, toward the offset of the frame (Roelofs effect; Roelofs, 1935; Bridgeman and Klassen, 1983; Bridgeman et al., 1997; Dassonville and Bala, 2004; Dassonville et al., 2004). Thus, it may be argued that the effect of cancelling prism adaptation was not attributable to allocentric encoding and decoding of the target position but simply resulted from encoding and decoding in the egocentric coordinate, which was shifted toward the offset of the background after the blank. To test this possibility, we examined whether prism adaptation could be cancelled when the target was presented without any background (thus encoded in the egocentric coordinate) during the encoding phase, and the background was then presented after the blank in a position shifted in the direction of visual displacement (Fig. 2*b*).

When the background was presented exclusively after the blank (Fig. 6*b*, post-presentation condition), prism adaptation was little affected. This finding was in marked contrast to the apparent cancellation (a large asymptote and a small aftereffect) observed when the background was presented before and after the blank with a shift in the ipsilateral direction (Fig. 6*a*, ipsilateral shift condition). One-way repeated-measures ANOVA and *post hoc* tests confirmed these observations: the mean asymptote in the post-presentation condition (3.7 ± 1.1 mm) was not significantly different from the mean asymptote in the no-background condition (3.8 ± 0.70 mm, $p = 0.99$), but it was significantly smaller than the mean asymptote in the ipsilateral shift condition (13 ± 2.9 mm, $p = 0.0011$; Fig. 6*d*). The mean aftereffect in the post-presentation condition (14 ± 1.7 mm) was

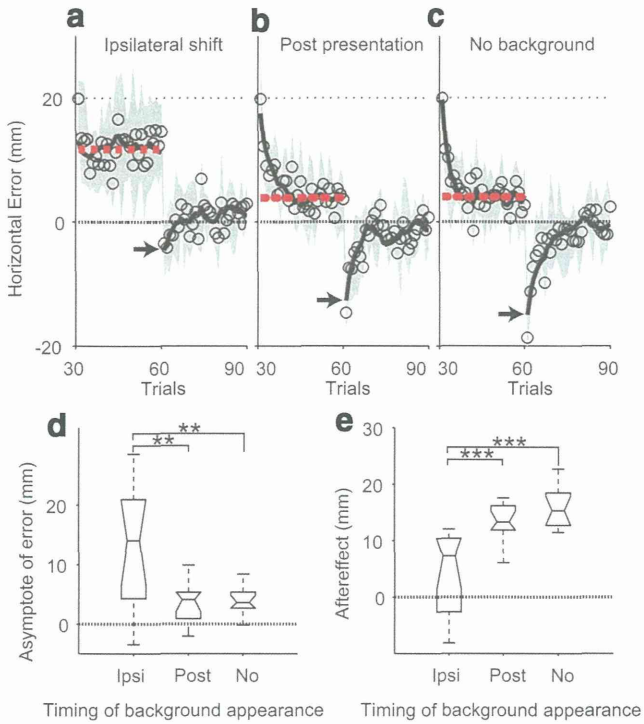

Figure 6. Necessity of the background during the encoding phase (experiment 4) for cancelling. ***a–c***, Prism adaptation in the ipsilateral shift (***a***), post-presentation (***b***), and no background conditions. Note the contrast between the ipsilateral shift condition and the post-presentation condition. Each circle represents the median of 12 responses (6 participants × 2 directions). ***d***, ***e***, Distributions of the asymptotes during the exposure period (***d***) and aftereffects during the post-test period (***e***). Other conventions are the same as in Figure 3.

as large as that in the no-background condition (15 ± 1.5 mm, $p = 0.51$) but significantly larger than in the ipsilateral shift condition (4.2 ± 2.1 mm, $p = 0.00020$; Fig. 6*e*). These results clearly show that presentation of the background was necessary not only during the decoding phase but also during the encoding phase to cancel prism adaptation; they exclude the possibility that the cancellation of prism adaptation was attributable to the shift of the egocentric coordinate resulting from the Roelofs effect.

Discussion

In the present study, we proposed a novel use of the allocentric memory of target position in an immediate reach. We hypothesized that the initial position of the target is encoded in terms of the background figures when we plan a reaching movement and that the initial position is decoded in terms of the background to evaluate the motor error when the movement is completed. Assuming that this hypothesis is correct, we would be able to control the "motor error" in prism adaptation by shifting the background in flight of the reach while keeping the actual target position unchanged. Our results supported the hypothesis: we were able to cancel or enhance prism adaptation by shifting a background in flight of the reach in the direction of visual displacement (cancellation) or in the opposite direction (enhancement).

Was it really allocentric?

The results supported our hypothesis that the initial target position is encoded and decoded in terms of allocentric coordinates. However, it may still be argued that the error was encoded in the egocentric coordinate and decoded again in the egocentric coordinate that was shifted toward the offset of the background figures. This argument is reasonable because it is well known that the subjective midline, which forms the basis of the egocentric coordinate, is shifted toward the center of a large frame presented with an offset to the right or to the left (Roelofs effect; Roelofs, 1935; Bridgeman and Klassen, 1983). Accordingly, a target position is mislocalized in the opposite direction in such a way that a target presented in the actual midline is judged as localized to the left of the midline when a frame is presented with an offset to the right and vice versa (induced Roelofs effect; Bridgeman et al., 1997). The induced Roelofs effect is now generally accepted to result from the shift of the egocentric coordinate toward the offset of the large frame (Dassonville and Bala, 2004; Dassonville et al., 2004).

If the cancellation and enhancement observed in our experiments was caused by the shift of the egocentric coordinate resulting from the Roelofs effect, cancellation of prism adaptation should be observed simply by presenting a frame with an offset after the reaching was completed, without presenting any background at the time when the movement was planned (post-presentation condition). We tested this in experiment 4, and cancellation was not observed in the post-presentation condition. The results excluded the possibility that the cancellation was caused by the shift of egocentric coordinate resulting from the Roelofs effect.

Relationship with nonretinotopic exogenous attention

A recent study reported that reflexive, stimulus-driven exogenous attention operates not only in the retinotopic coordinates but also in allocentric coordinates (Boi et al., 2011). In the study, a cue was briefly presented in the first frame on a background that consisted of three squares, and then in the second frame, the background was shifted to the right or to the left. Exogenous attention was shown to be elevated in the second frame at a cued location in terms of the background as well as at a cued location in terms of the retinotopic coordinate. However, the exogenous attentional capture was transient. The effect peaked at 170 ms and disappeared before 300 ms after the cue onset. Thus, the nonretinotopic exogenous attention should have disappeared during the reaching movement, because the summation of the reaction time (150–300 ms) and the movement duration (~250 ms on average) was longer than 300 ms. However, it is still possible that encoding of the initial target position may share some resources with the nonretinotopic exogenous attention.

Merits of using the background coordinate

To generate motor commands that achieve an appropriate reaching movement toward a target, it is necessary to encode the target position in terms of an egocentric coordinate (Kawato et al., 1987; Soechting and Flanders, 1989; McIntyre et al., 1997; Henriques et al., 1998; Vetter et al., 1999; Blohm and Crawford, 2007; Chen et al., 2011; Tanaka and Sejnowski, 2013). The question then arises as to why the brain takes the trouble of using the allocentric coordinate instead of the egocentric coordinate for encoding and decoding the initial target position.

One possible reason for this can be suggested based on the lifespans of the allocentric and egocentric memories. Previous studies reported that the allocentric memory of target position survives longer than the egocentric memory in a delayed reaching task (McIntyre et al., 1998). It is thus possible that the brain had to rely on the allocentric memory because the egocentric memory faded during the 300 ms blank period. However, this is unlikely because the merit of allocentric memory in delayed reaching be-