

The neural substrates of the warning effect: A functional magnetic resonance imaging study[☆]

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ABSTRACT

To test the hypothesis the warning effect is mediated by the top-down attentional modulation of the motor system, we conducted functional MRI using a Go/No-Go task with visual and auditory warning stimuli. For aurally-warned, visually-prompted trials, the auditory warning stimulus was presented for 1500 ms, during which visual cues were presented that prompted either Go or No-Go responses. The same format was used for visually-warned, aurally-prompted trials. Both auditory and visual warning cues shortened the reaction time for the Go trials. The warning cues activated the right-lateralized parieto-frontal top-down attentional network, and motor cortical areas including the pre-supplementary motor area (pre-SMA), the bilateral dorsal premotor cortex, and the left primary motor cortex (M1). The warning-related activation of the pre-SMA matched the difference between its activation by Go-with-warning and by Go-without-warning. Thus, the pre-SMA was primed by the warning cue. The same pre-SMA priming effect was observed for the No-Go cue-related activation, consistent with its role in movement preparation and selection. Similar but less prominent Go cue-related priming was observed in the M1. Thus, the warning effect represents the pre-potential of the motor control pathway by the top-down attentional system, from the selection and preparation of the movement to its execution.

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1. Introduction

Observers initiate motor responses to targets sooner if a preceding stimulus indicates that the target will appear shortly; this phenomenon is called the warning effect (Hackley and Valle-Inclan, 2003). The warning signal (WS) leads to the anticipation of the target response, and triggers motor-preparation processes during the period prior to movement (Fecteau and Munoz, 2007). Central components of response anticipation are achieving and maintaining the attentional state (Bertelson, 1967).

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The warning effect might therefore be explained by the phasic alertness that facilitates reflexive reactions, and the response anticipation that facilitates voluntary reactions (Hackley et al., 2009). A previous functional magnetic resonance imaging (fMRI) study showed that phasic alertness is related to the phasic activation of the midbrain–thalamus–anterior cingulate network and the pre-supplementary motor area (pre-SMA) (Yanaka et al., 2010). Response anticipation comprises the preparation and application of goal-directed selections for stimuli and responses; that is, the top-down attention processes that typically engage prefrontal and parietal cortices (Corbetta and Shulman, 2002; Foxe et al., 2005; Badler and Heinen, 2006). In electrophysiology, the warning effect is reflected in a cholinergic-dependent long-latency negative-polarity event-related potential (ERP) called the contingent negative variation (CNV) (Walter et al., 1967). Previous studies (Tecce, 1972; Ulrich et al., 1998; Fan et al., 2007) suggested that anticipatory attention and motor preparation are indexed by the CNV. Fan and colleagues used comparative electrophysiological (CNV) and fMRI to show that response anticipation

modulates overall activity in the executive control network, which deals with conflict monitoring and resolution (Fan et al., 2003, 2007). This executive control network is represented by the dorsal fronto-parietal network and the anterior cingulate cortex (ACC) extending to the pre-SMA. Fan and colleagues interpreted these findings as suggesting that the warning effect is brought about by the flexible control of a wide range of executive processes. Thus, the warning effect is related to both attention processes (such as alertness) and executive function (Raz and Buhle, 2006).

Electrophysiological studies have also shown that the warning effect is related to the excitability of the primary motor cortex (M1). According to the proposal by Näätänen (1971) (the motor action limit theory), preparation increases neural activation during the “foreperiod” (the period from the warning cue to the “go” cue). An overt response is triggered when the increase in preparatory neural activation surpasses an “action limit” threshold. The reaction time is a function of the difference between the motor action limit and the level of neural activation accumulated during the foreperiod. If this difference is large, the RT is long; if this difference is small, the RT is short. Response preparation is typically associated with an increase in cortical excitability (Tanji and Evarts, 1976; Trillenberg et al., 2000; Bastian et al., 2003; Sinclair and Hammond, 2008). However, the neural pathways that link the warning effect in the M1 with the attentional network remain unknown, as do the neural substrates of response anticipation and motor preparation.

Here we used fMRI to depict the neural substrates of the warning effect as an interaction of attentional and motor systems. Previous fMRI studies showed that the pre-SMA is related to the warning effect, and its activity is mediated by both phasic alertness (Yanaka et al., 2010) and executive control (Fan et al., 2007). Based on these findings, we hypothesized that the warning effect is mediated by top-down attentional processes, which potentiate the pre-SMA and other motor cortical areas, including the M1.

We used the following 12 types of trial in the experiment: visually-prompted Go, No-Go, and Rest trials, with or without an auditory warning cue (six possible trial types); and aurally-prompted Go, No-Go, and Rest trials, with or without a visual warning cue (six possible trial types). For aurally-warned visually-prompted trials, the auditory warning stimulus was presented for 1500 ms, during which there were either visual cues prompting Go or No-Go responses presented for 350 ms, or no visual cues. While subjects attended to the visual prompt cue, the auditory warning cue indicated the particular timing of the upcoming visual target cue. For visually-warned aurally-prompted trials, the same format was utilized. In this experimental setup, the presence of the warning stimulus allowed the subjects to anticipate the response timing, while the uncertainty of the response type (Go vs. No-Go) was kept constant (80:20). We expected that, irrespective of the sensory modality in which the cue was presented, the activity related to the warning cue would include the attention and the motor systems, because the warning cue prompted the prediction of the timing of the upcoming target cue.

2. Materials and methods

2.1. Subjects

Twenty-three healthy volunteers (11 male and 12 female) aged 18–33 years of age participated in the fMRI study. Four subjects were excluded because of either poor performance (two subjects, with <85% correct on Go trials in at least one of the four fMRI runs) or significant head motion (two subjects); thus, data from 19 subjects (nine male and 10 female; mean age $\pm$ standard deviation = 22.5 ± 4.2 years, range = 18–33 years) were analyzed. All of the subjects were right handed according to the Edinburgh handedness inventory (Oldfield, 1971). None of the subjects had a history

of neurological or psychiatric illness. The protocol was approved by the ethical committee of the National Institute for Physiological Sciences, and the study was conducted according to the Declaration of Helsinki. All subjects gave their written informed consent for participation.

2.2. fMRI experimental design and task procedure

2.2.1. Task

The subjects performed two Go/No-Go tasks inside the scanner: a visually-cued Go/No-Go task with and without auditory warning stimuli (AV task, Fig. 1a); and an aurally-cued Go/No-Go task with and without visual warning stimuli (VA task, Fig. 1b).

Throughout the AV task, subjects were instructed to fixate on a small white cross located centrally on the screen. Each trial was 5 s in duration. The start or end of each trial was not explicitly indicated to the participants. The warning Go/No-Go conditions started with 1500 ms of the auditory warning stimulus (frequency, 440 Hz; sampling rate, 44.1 kHz; stereo sound). The Go/No-Go cues appeared 400, 900, and 1400 ms after the onset of the trial, randomly and with equal probability. Having warning periods of variable duration allowed us to exclude factors related to specific predictions about the timing of the presentation of the Go/No-Go cue – in other words, temporal orienting (Coull et al., 2001) (Fig. 1). The visual Go/No-Go cue was a green or red square with a visual angle of $1.0^\circ \times 1.0^\circ$. The relationship between the cue colors (green/red) and the type of cued action (Go/No-Go) was counterbalanced across subjects. Subjects were required to press a button on a magnet-compatible optical button-box (Current Designs Inc., Philadelphia, PA) using their right thumbs as quickly as possible once a Go cue appeared, but not when the No-Go cue was shown. Responses were recorded for 1000 ms following the onset of the Go/No-Go cue. In the warning Rest condition, only the warning stimulus was presented, without a Go/No-Go cue. The no-warning Go/No-Go and Rest conditions were identical to the warning Go/No-Go and Rest conditions, except that no warning stimulus was presented. Each run consisted of 24 warning Go (wG), 24 no-warning Go (nwG), six warning No-Go (wNG), six no-warning No-Go (nwNG), six warning Rest (wR), and six no-warning Rest (nwR) trials. In total, there were 72 trials per run.

The VA task was identical to the AV task except that the modality of the warning stimuli and cue stimuli were swapped. A small yellow cross located centrally on the screen was presented as the warning stimulus (visual angle, $1.0^\circ \times 1.0^\circ$; 1500 ms). Either the lower pure tone (frequency, 330 Hz; sampling rate, 44.1 kHz; stereo sound; 350 ms) or the higher pure tone (frequency, 550 Hz; sampling rate, 44.1 kHz; stereo sound; 350 ms) was used as the Go/No-Go cue. In each task, the relationship between tone (lower/higher) and cue type (Go/No-Go) was counterbalanced across subjects. Each subject completed two runs of each task type, the order of which was counterbalanced across all subjects, giving a total of four runs. We adopted a rapid event-related design, the efficiency of which was optimized (Sadato et al., 2005; Saito et al., 2005; Morita et al., 2008).

A liquid crystal display projector (DLA-M200L; Victor, Yokohama, Japan), located outside and behind the scanner, projected stimuli through another waveguide to a translucent screen that the subjects viewed via a mirror attached to the head coil of the MRI scanner. The auditory stimuli were presented via MRI-compatible headphones (Hitachi, Yokohama, Japan). The volume was adjusted to about 100 dB. Presentation 12.2 software (Neurobehavioral Systems, Albany, CA, USA) was implemented on a personal computer (Dimension 9100; Dell Computer, Round Rock, TX) for the stimulus presentation and response time measurements.

The subjects received a detailed explanation of the task prior to fMRI scanning. In particular, to reinforce the task load,

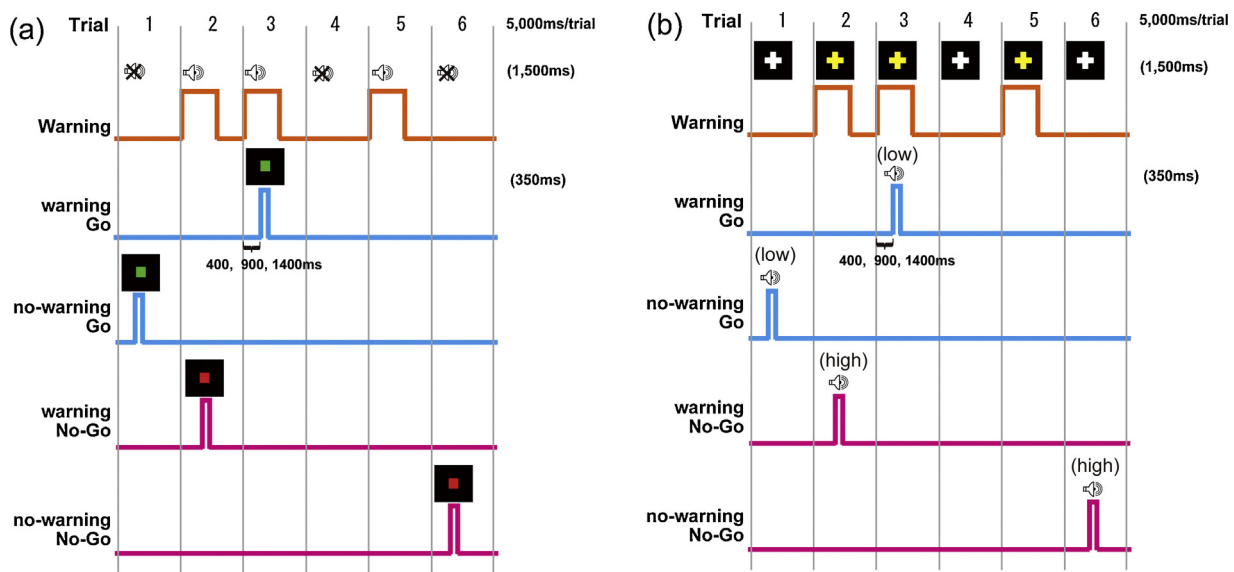


Fig. 1. Task design. (a) AV task run contains visually-prompted Go (blue), No-Go (magenta), and Rest trials, with or without the auditory warning stimulus (orange). The auditory warning stimulus was presented for 1500 ms, during which there was either a visual cue prompting Go or No-Go responses presented for 350 ms, or no visual cue. (b) VA task run contains aurally-prompted Go (blue, with low pitch), No-Go (magenta, with high pitch), and Rest trials, with or without the visual warning stimulus (orange, with yellow cross-hair). The visual warning stimulus was presented for 1500 ms, during which there was either an auditory cue prompting Go or No-Go responses presented for 350 ms, or no auditory cue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

the importance of response speed was stressed during task instruction.

2.2.2. MRI data acquisition

All images were acquired using a 3T MR scanner (Allegra; Siemens, Erlangen, Germany). Functional images were acquired using a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence. Each volume consisted of 39 slices, each 3.0 mm thick, without a gap, to cover the entire cerebrum and cerebellum (repetition time [TR], 2500 ms; echo time [TE], 30 ms; flip angle [FA], 77°; field of view [FOV], 192 mm; matrix size, 64 × 64; voxel dimensions, 3 mm × 3 mm × 3 mm; ascending; phase over sampling, 50%). Oblique scanning was used to exclude the eye-balls from the images. Each session consisted of a continuous series of 151 volume acquisitions with a total duration of 6 min 17.5 s. To acquire a high-resolution structural whole-head image, T1-weighted magnetization-prepared rapid-acquisition gradient-echo (MP-RAGE) images were also obtained (TR, 2500 ms; TE, 4.38 ms; FA, 8°; FOV, 230 mm; matrix size, 256 × 256; voxel dimensions, 0.9 mm × 0.9 mm × 1.0 mm).

2.3. Data analysis

2.3.1. Behavioral measures

For each subject, the accuracy of the Go and No-Go responses, and the mean reaction times (RTs) for the correct Go responses were calculated. Responses with a delay of longer than 1 s were classified as missed responses. Statistical analysis was carried out using SPSS version 10.0J software (SPSS Japan Inc., Tokyo, Japan). A three-way repeated measures analysis of variance (ANOVA) was performed to compare the mean percentage of correct responses, and a two-way repeated measures ANOVA was performed to compare the mean RTs. The results were considered statistically significant at $p < 0.05$.

2.4. fMRI data analysis

2.4.1. Preprocessing

Two volumes were automatically discarded by the MR scanner, and the first three volumes of each fMRI session were discarded

to allow for stabilization of the magnetization (in total, the first five volumes were discarded). The last trial was followed by 10 s (four volumes) of a baseline condition (144 volumes for trials + 4 volumes for baseline = 148 volumes per run). Therefore, in total, 592 volumes per subject for four runs were used for the individual analyses. The data were analyzed using statistical parametric mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Natick, MA, USA) (Friston, 2007). The Fourier phase-shift interpolation in SPM8 was used to perform slice-timing correction to the middle slice. After correcting for differences in slice timing within each image volume, all volumes were realigned for motion correction.

The high-resolution three-dimensional (3D) T1-weighted MP-RAGE image volume was co-registered with the realigned structural image volume. Subsequently, the co-registered high-resolution T1-weighted anatomical image was normalized to a standard T1 template image, as defined by the Montreal Neurological Institute (MNI), involving linear and nonlinear 3D transformations (Ashburner and Friston, 1999). The parameters from this normalization process were applied to each of the EPI images. Finally, the anatomically normalized EPI images were resampled to a voxel size of 2 mm × 2 mm × 2 mm and spatially smoothed using a Gaussian kernel with a full width at half maximum of 8 mm in the x, y, and z axes.

2.4.2. Statistical analysis

Statistical analysis of the functional imaging data was conducted at two levels. First, the individual task-related activation was evaluated with a general linear model. Second, to make population-level inferences, the summary data for each individual were incorporated into the second-level analysis using a random effects model (Holmes and Friston, 1998).

The signal time-course of each subject (592 time points) was modeled with five regressors of interest that accounted for each condition (W, wG, wNG, nwG, and nwNG), and another regressor for the “miss” trials. W is a columnar vector representing the onset of the warning stimuli with a duration of 1.5 s. The wG and wNG conditions represent the onset of the Go or No-Go cues with no duration following the warning stimuli. The nwG and nwNG

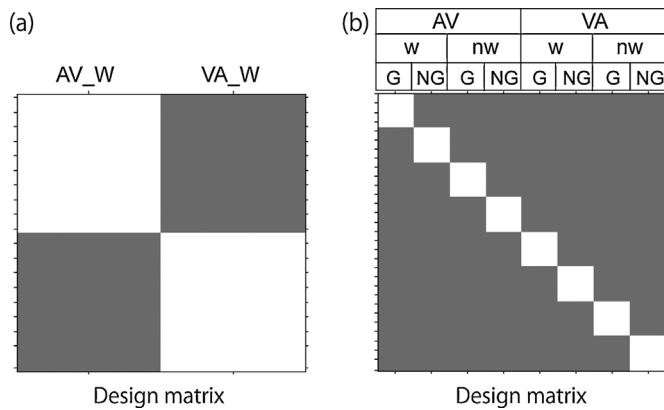


Fig. 2. Design matrices of (a) warning and (b) response for group analysis. (a) Design matrix containing the model vectors of the warning during AV run (AV.W) and during VA (VA.W), (b) design matrix containing the model vectors the Go (G) and NoGo (NG) responses with warning (w) and without warning (nw) during AV and VA task runs.

conditions represent the onset of the Go or No-Go cues with no duration that did not follow a warning stimulus. These regressors were convolved with a canonical hemodynamic-response function. A high-pass filter with a cut-off period of 128 s was applied to eliminate artifactual low-frequency trends. The serial autocorrelation was also corrected using the AR(1) model. To correct the global fluctuation between scans, global scaling was conducted.

The weighted sum of the parameter estimates in the individual analyses constituted “contrast” images, which were used for the group analysis (Holmes and Friston, 1998). Contrast images obtained via the individual analyses represent the normalized task-related increment of the MR signal of each subject. The contrast images of W for each of the cueing modalities were incorporated into a two-sample *t*-test that modeled the cueing modality effect at the group level, in order to conduct conjunction analyses of the AV and VA W images (Fig. 2a). The contrast images of wG, wNG, nwG, and nwNG for each cueing modality were incorporated into a full factorial design that modeled the cueing modality effect and the different conditions (wG, wNG, nwG, and nwNG) at the group level

(Fig. 2b). All of the results we report in the group level are corrected using the variance component model, to account for the potential non-sphericity of repeated measures data. The resulting set of voxel values for each contrast constituted a statistical parametric map of the *t* statistic ($SPM\{t\}$). We delineated the common activation areas of the warning effect irrespective of the cue modality by conjunction analysis using a conjunction-null hypothesis (Nichols et al., 2005). Finally, to depict the warning effect in motor-related areas, we calculated the overlapping area of activation for the Warning and Go/No-Go images. Specifically, we searched the Go-related activation within the warning-related, irrespective of modality. The height threshold was set at $p < 0.001$ (uncorrected for multiple comparisons), and the cluster threshold was set at $p < 0.05$ (corrected for multiple comparisons). We converted the MNI coordinates to Talairach coordinates using an established formula (Brett et al., 2002) in order to label the activated foci according to the anatomical nomenclature of the Talairach and Tournoux atlas (Talairach and Tournoux, 1988). Additionally, the motor and premotor areas were labeled according to Hanakawa et al. (2002), and the cerebellar areas were labeled according to Diedrichsen et al. (2009).

3. Results

3.1. Behavioral results

Both auditory and visual warning cues shortened the reaction times for the Go trials (repeated measures ANOVA; $F_{(1,18)} = 217.94$, $p < 0.001$) (Fig. 3a). The main effect of modality was not significant ($F_{(1,18)} = 1.25$), and neither was the interaction between modality and warning condition ($F_{(1,18)} = 2.84$).

Fig. 3b shows the mean accuracy scores for each condition of the Go/No-Go task performed during the scan. A repeated measures ANOVA showed that the difference between Go and No-Go trials was statistically significant ($F_{(1,18)} = 30.78$, $p < 0.001$). The other main effect and interaction were not significant.

3.2. Imaging results

Conjunction analysis of the AV and VA W images (Fig. 2a) revealed that, irrespective of the presentation modality, the

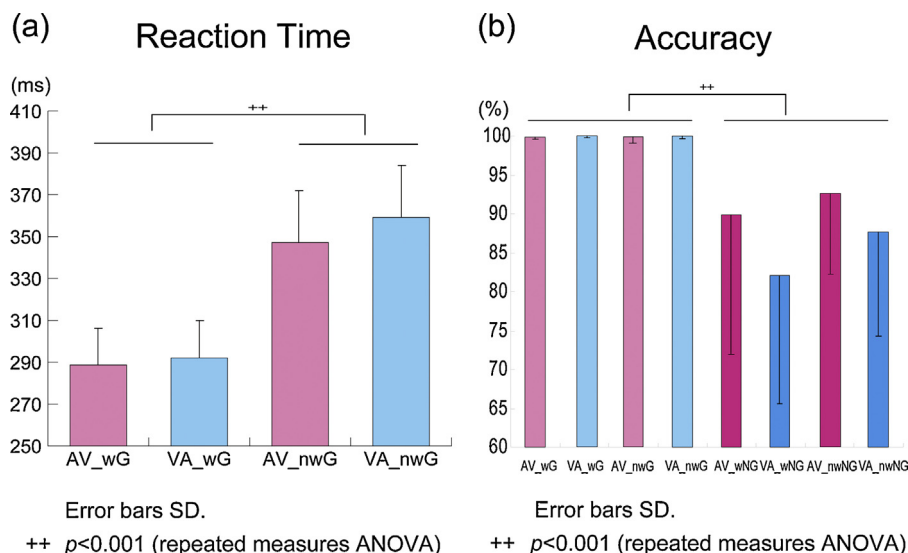


Fig. 3. Behavioral data. (a) Mean reaction time in ms for the Go response with warning (AV.wG) and without warning (AV.nwG) during AV task run (light magenta), and Go response with warning (VA.wG) and without warning (VA.nwG) during VA task run (light blue). (b) Accuracy (and SD) in % correct for the AV.wG and AV.nwG (light magenta), VA.wG and VA.nwG (light blue), No-Go response with warning (AV.wNG) and without warning (AV.nwNG) during AV task run (magenta), and No-Go response with warning (VA.wNG) and without warning (VA.nwNG) during VA task run (blue). Error bars indicate standard deviation. ** $p < 0.001$ (repeated measures ANOVA). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1
Modality-independent warning effect.

Cluster <i>p</i> -Value	Size	Z value	MNI coordinates (mm)			Side	Location
			x	y	z		
<0.001	1342	5.85	10	0	68	R	pre-SMA
		5.35	−6	−2	66	L	SMA
<0.001	636	5.11	−44	−8	46	L	PMd
		5.63	−36	−20	52	L	M1
0.002	317	4.61	56	−42	14	R	TPJ
<0.001	505	4.51	46	−2	36	R	PMv
		5.1	40	2	28	R	IFG (pars opercularis)
		4.34	42	−6	50	R	PMd
0.015	221	4.05	34	−58	48	R	IPS/SPL
0.002	320	4.03	−12	−74	−26	L	Cerebellar hemisphere (lobule VI)
		3.86	−34	−66	−26	L	Cerebellar hemisphere (lobule VIIa)

IFG, inferior frontal gyrus; IPS, intraparietal sulcus; M1, primary motor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; SPL, superior parietal lobule; TPJ, temporo-parietal junction. MNI, Montreal Neurological Institute; Size, number of voxels within the cluster; L, left; R, right. The statistical threshold was set at a height threshold of $p < 0.001$ (uncorrected for multiple comparisons) and a cluster threshold of $p < 0.05$ (corrected for multiple comparisons).

warning cue activated the pre-SMA extending to the SMA, the bilateral dorsal premotor cortex (PMd), the left M1, the cerebellum, and the right temporo-parietal junction (TPJ), the ventral premotor cortex (PMv), the pars opercularis in the inferior frontal gyrus, and the superior parietal lobule (SPL) including the intraparietal sulcus (IPS) (Table 1 and Fig. 4).

Within the warning-related areas, irrespective of the presentation modality, we also confirmed that the cluster in the left M1 overlapped with the areas that were involved in actual motor execution (i.e., Go–No–Go contrast, conjunction between VA and AV conditions) (Fig. 5), indicating that the presentation of the warning cue, which preceded the Go/No–Go cue, activated the motor system (warning effect).

Having identified the brain areas activated by the presentation of a warning cue, we next examined whether the degree of brain activity in response to Go–cue was modulated by the presence of the warning cue. We found that the presence of the warning cue resulted in significant reduction of Go-related activation, compared to the absence of it, in the pre-SMA (i.e., nwG–wG contrast, conjunction between VA and AV conditions) (Fig. 6). Thus these areas are the candidates for the interaction of the motor and attentional system. Finally, to test the hypothesis lead by motor action limit theory, we examined the relationship between the degree of activation induced by warning cue and reduction of Go responses (nwG–wG) in the left M1 and the pre-SMA. If the motor action limit theory is correct, individual differences in the degree of warning cue related activation should correlate with the degree of reduction in the Go–cue related activation. The results of this

analysis supported our hypothesis. Actually, a positive correlation between the warning related activation (W) and warning-related reduction in Go response (nwG–wG) was found in the left M1 ($r = 0.36$, $p = 0.007$, $F_{(1,17)} = 9.63$; Fig. 7a) and in the pre-SMA ($r = 0.82$, $p < 0.001$, $F_{(1,17)} = 75.98$; Fig. 7b).

4. Discussion

4.1. Warning engages attention

The present study showed that the warning cue activated the right-lateralized parieto-frontal areas, and the medial and lateral premotor cortices extending to the left M1. Previous fMRI studies suggested that attention tasks induce the following two types of task-related blood oxygen level-dependent (BOLD) signal: “source” signals, which provide information about the organization of attention systems; and “site” signals, which provide information about how motor, sensory, or cognitive systems are affected by attention (Corbetta, 1998). Considering that the WS engages attention, the right-lateralized parieto-frontal activation is likely to be related to the source effect, whereas the regions associated with the target response are related to the site effect of attention.

4.2. Source effect of the top-down attentional network

Irrespective of modality, the warning cues activated the right SPL, TPJ, PMd and PMv, and the left cerebellum.

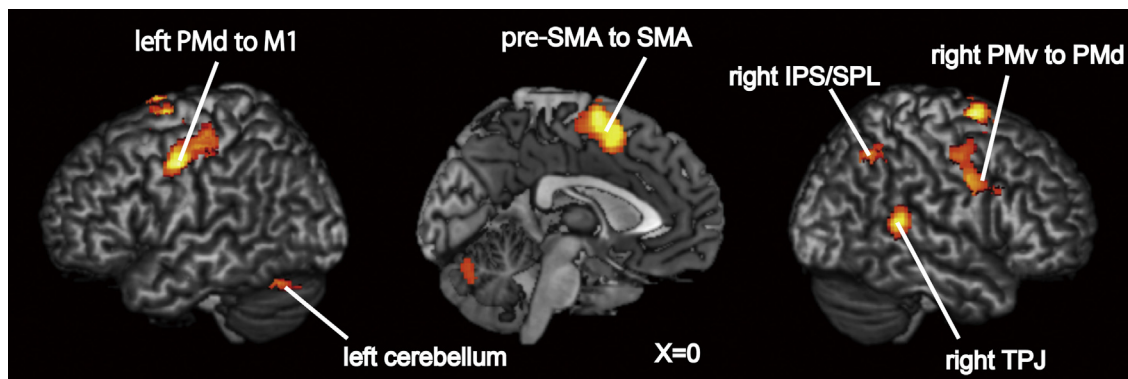


Fig. 4. Modality-independent warning effect. SPMs of the average neural activity by means of warning contrasts of the design matrix of warning (Fig. 2a) with conjunction across AV and VA tasks are superimposed on a surface rendered high-resolution MRI of left lateral, medial and right lateral view. The statistical threshold was $p < 0.05$, corrected for multiple comparisons at the cluster level.

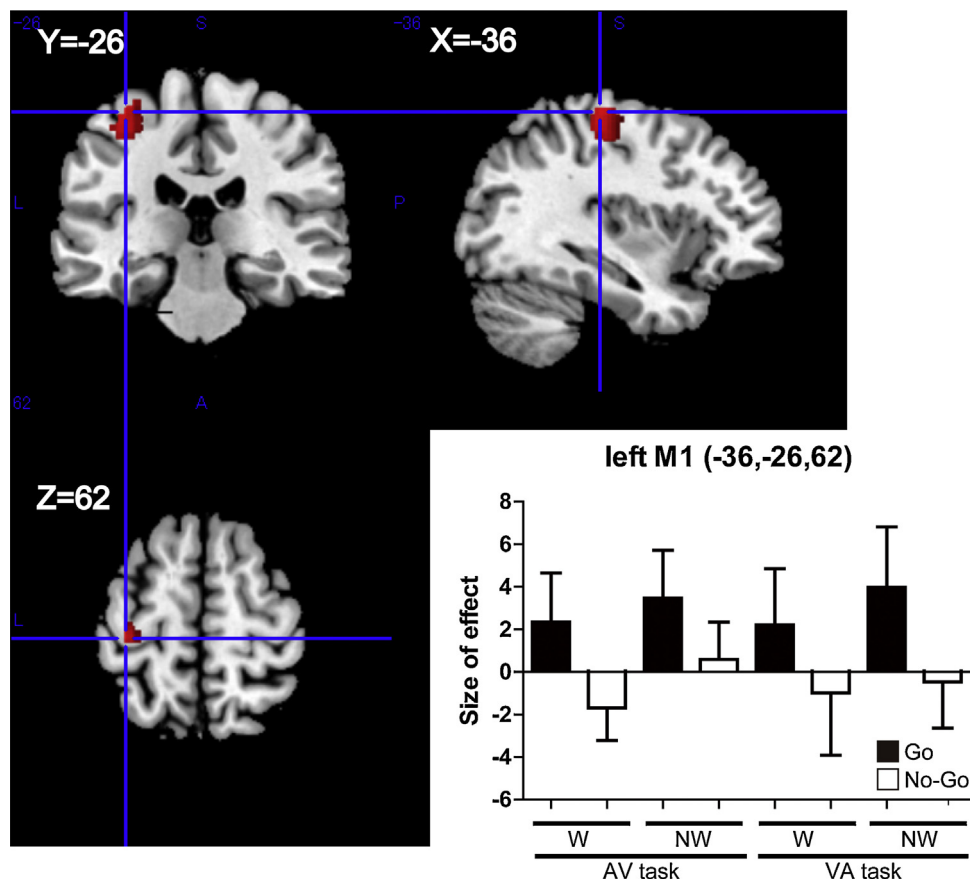


Fig. 5. Go-specific activation within the warning-related areas. SPMs of the average neural activity by means of Go–No-Go contrasts of the design matrix of response (Fig. 2b) with conjunction across AV and VA conditions are shown in standard anatomical space. The focus of activation on a pseudocolor fMRI superimposed on a high-resolution anatomical MRI in the sagittal (upper left), coronal (upper right) and transaxial (lower left) planes, as indicated by the blue lines that cross at (–36, –26, 62), corresponding to the left M1. The statistical threshold was $p < 0.05$, corrected for multiple comparisons at the cluster level. Lower right, size of effect (arbitrary unit) in the left M1 of Go (closed rectangle) and No-Go (open rectangle) with warning (W) or without warning (NW) during AV and VA tasks are plotted. Error bars indicate standard deviation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

4.2.1. SPL

The SPL is a part of a dorsal fronto-parietal network that controls the top-down distribution of visual attention (Corbetta et al., 2008), which generates attentional sets, or goal-directed stimulus–response mapping; this dorsal fronto-parietal network allows the selection of sensory stimuli based on internal goals or expectations (top-down attention) and links them to appropriate motor responses (Corbetta et al., 2008). In addition, the dorsal and ventral fronto-parietal networks are modulated by reorienting or oddball stimuli in different modalities (Corbetta et al., 2008).

4.2.2. TPJ

Recent studies have suggested that the right hemisphere, including the TPJ, is related to timing tasks (Lewis and Miall, 2003; Coull et al., 2004a, 2008; Coull and Nobre, 2008). The right TPJ is part of a right hemisphere-dominant ventral fronto-parietal network that detects salient and behaviorally relevant stimuli in the environment, especially when not attended to (stimulus-driven reorienting attention), which interrupts and resets ongoing activity (Corbetta et al., 2008). It has been suggested that the TPJ is strongly engaged by stimuli that are behaviorally relevant but require a change in the current task set. One of its key functions is to direct attention to behaviorally-relevant sensory stimuli that are outside the focus of processing. As the warning cue and the target cue were given in different modalities (visual vs. auditory, and vice versa) in the present study, the warning cue might have prompted the cross-modal re-direction of attention.

4.2.3. Right PMv and PMd

Our results showed that the WS activated the right PMv and PMd. The premotor cortices are reciprocally connected with ipsilateral (Lu et al., 1994; Wise et al., 1997; Dum and Strick, 2005) and contralateral (Marconi et al., 2003) cortical motor areas, most notably the M1, parietal cortex, and premotor cortex. The PMd and PMv, which have distinct evolutionary origins, constitute largely separate cortical networks that are interconnected by different regions of the prefrontal and parietal cortices (Hoshi and Tanji, 2007). The input from the dorsolateral prefrontal cortex (dlPFC) arises from different regions: the PMd receives inputs from the dorsal dlPFC, whereas the PMv receives inputs from the ventral dlPFC. Input sources from the parietal cortex also differ: the PMd receives its main inputs from the SPL, whereas the PMv receives inputs from the inferior parietal lobule (Hoshi and Tanji, 2007). Additionally, Salmi et al. (2009) observed activity in the premotor cortex during attention shifts triggered by bottom-up processing, as well as top-down, controlled attention shifts. These neuroanatomical considerations suggest that the PMv and PMd are involved in the ventral attention network and the dorsal attention network, respectively. Thus, these right-lateralized parieto-premotor areas are engaged by the task set related to the warning cue (Dosenbach et al., 2006).

4.2.4. Cerebellar involvement

The cerebellum is known to be involved in attention (Allen et al., 1997; Allen and Courchesne, 2003), including the

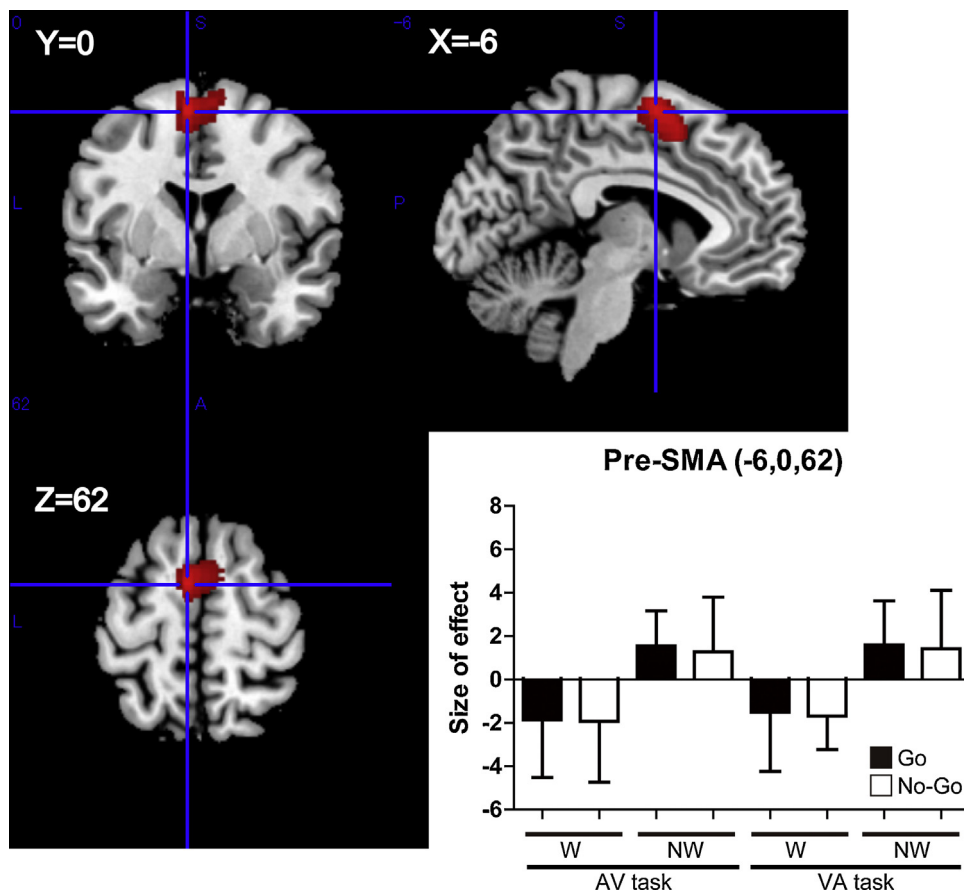


Fig. 6. Warning effect on the Go-related activation within the warning-related areas. SPMs of the average neural activity by means Go–No-Go contrasts with conjunction across AV and VA tasks are shown in standard anatomical space. The focus of activation on a pseudocolor fMRI superimposed on a high-resolution anatomical MRI in the sagittal (upper left), coronal (upper right) and transaxial (lower left) planes, as indicated by the blue lines that cross at $(-6, 0, 62)$, corresponding to the left pre-SMA. The statistical threshold was $p < 0.05$, corrected for multiple comparisons at the cluster level. Lower right, size of effect (arbitrary unit) in the left pre-SMA of Go (closed rectangle) and No-Go (open rectangle) with warning (W) or without warning (NW) during AV and VA tasks are plotted. Error bars indicate standard deviation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

anticipation/prediction of the internal conditions for a particular operation, and setting the specific conditions in preparation for that operation (Allen et al., 1997). Furthermore, the neural correlates of time perception also include the cerebellum (Ivry and Keele, 1989; Jueptner et al., 1995; Nichelli et al., 1996). It has been demonstrated frequently that the cerebellum plays an essential role in sensorimotor prediction (Blakemore and Sirigu, 2003), especially

for building predictions about the actual sensory consequences of an executed motor command. This prediction is mainly used in the early stages of movement execution in order to maintain accurate performance when there are sensory feedback delays (Wolpert and Kawato, 1998). By contrast, the cerebellum is involved in timing processes (Harrington and Haaland, 1999), which is supported by cerebellar lesion studies (Ivry, 1996, 1997). Thus, the WS-related

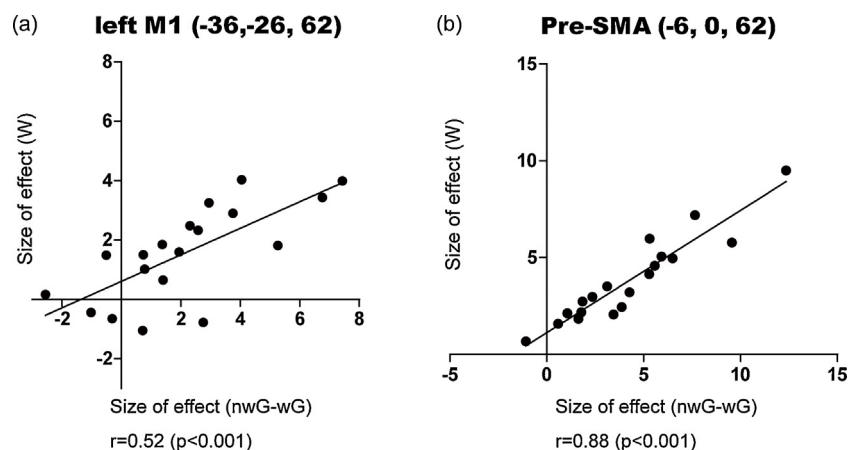


Fig. 7. The pre-potential by warning cue. The relationship between the warning-related activation (W) and the warning effect on the Go-related activation (nwG–wG) in the left M1 (a), and in the pre-SMA (b) are shown.

activation of the left cerebellum might be related to the temporal prediction cued by the WS.

4.3. The site effect in motor areas

4.3.1. Pre-SMA

The pre-SMA was active during the foreperiod when a WS was given. With the WS, the Go/No-Go cue-related activation was attenuated compared with when there was no WS, regardless of whether it indicated a Go or No-Go trial, and the degree of attenuation paralleled the WS-related activation. This is consistent with the motor action-limit theory: the WS primed the motor programming (Hackley and Valle-Inclan, 2003), and thus less activity was necessary to activate the primed programs.

The SMA, which was previously regarded as a single motor area occupying the medial part of Brodmann's area 6, is now divided into two sub-regions: the anterior pre-SMA and the posterior SMA proper (Picard and Strick, 1996). In humans, the vertical anterior commissure (VAC) line, based on the stereotaxic coordinate system of Talairach and Tournoux (1988), serves as an anatomical landmark for the discrimination of the pre-SMA and the SMA proper (Hanakawa et al., 2002). The SMA proper, located immediately anterior to the foot representation of the M1, has somatotopically-organized movement representations, as shown in non-human primates (Luppino et al., 1991; Mitz et al., 1991; Matsuzaka et al., 1992; He et al., 1995) and humans (Fried et al., 1991; Yazawa et al., 1998). The SMA proper is tightly interconnected with M1 and the spinal cord (Luppino et al., 1993; He et al., 1995; Dum and Strick, 2005), and probably plays an important role in the preparation and execution of movements.

In macaque monkeys, the pre-SMA corresponds to the medial part of area 6, 6ab, or field F6 (Luppino et al., 1991, 1993; Matelli et al., 1991). Although the pre-SMA lacks direct connections with M1 and the spinal cord (Dum and Strick, 1991; Bates and Goldman-Rakic, 1993; Luppino et al., 1993; Lu et al., 1994; He et al., 1995), it receives major inputs from the prefrontal cortex (Bates and Goldman-Rakic, 1993; Luppino et al., 1993; Lu et al., 1994), as well as the rostral premotor and cingulate areas (Matsuzaka et al., 1992; Luppino et al., 1993). Thus, the pre-SMA likely plays a less direct role in the execution of movements. Supporting this, physiological evidence indicates that the pre-SMA might be involved in response selection, preparation (Matsuzaka et al., 1992), and planning (Hoshi and Tanji, 2004), rather than in motor execution itself. Recent studies have also provided evidence that the pre-SMA has a role in response inhibition (Isoda and Hikosaka, 2007).

Human functional neuroimaging studies also suggest that the pre-SMA might be specifically associated with the free selection of actions (Deiber et al., 1991; Lau et al., 2004a), the preparation of movements (Brass and von Cramon, 2002), and response inhibition (Aron and Poldrack, 2006; Mostofsky et al., 2003). Finally, attending to the intention to move accentuates activity in the pre-SMA (Lau et al., 2004b). Therefore, the warning-related activation of the pre-SMA in the present study might also reflect stimulus–response association – in other words, the preparation for both Go and No-Go responses.

The pre-SMA is also associated with the attention required during cognitively demanding tasks (Akkal et al., 2007). In human neuroimaging studies, the pre-SMA was activated during tasks requiring attention to time (Coull et al., 2004b; Macar et al., 2006). It has been suggested that the pre-SMA is part of a network associated with coordinating voluntary and stimulus-driven attention (Serences et al., 2005). Thus, the function of the pre-SMA appears to be related to some aspect of the attention required during cognitively demanding tasks. Consistent with this idea, the pre-SMA was active during the foreperiod when the warning cue was given. Furthermore, both Go and No-Go signals with preceding warning cues

elicited less activation than those without warning cues. In particular, the warning-related activation was equivalent to the reduction in the Go-related activation by the preceding warning. Therefore, the warning-related activation of the pre-SMA in the present study might represent the pre-potential of the motor selection and/or preparation processes through the top-down attentional system in the right hemisphere, resulting in the facilitation of motor processing.

4.3.2. Left M1

The left M1 extending to the PMd showed Go-specific activation that was potentiated by the warning cue. Similar to the pre-SMA, the warning-related activation was equivalent to the reduction in the Go-related activation. This is consistent with the motor action limit theory, in that the neutral WS decreases RT by lowering the threshold of response so that it can be reached more readily. This finding is also consistent with electrophysiological studies showing that the excitability of the M1 is enhanced by a neutral WS. Using single-pulse TMS of the motor cortex, Davranche et al. (2007) showed that the WS enhanced M1 excitability by shortening the silent period. They suggest that subjects attempt to adjust neural activation to be close to the motor action limit when they expect a stimulus (Davranche et al., 2007).

The pre-SMA might drive the specificity of the warning-related M1 activation during the Go condition. There are two major areas through which pre-SMA might influence M1: the basal ganglia, and the prefrontal/premotor cortex (Isoda and Hikosaka, 2007). A basal ganglia/subthalamic route might mediate important aspects of action inhibition (Isoda and Hikosaka, 2008; Aron and Poldrack, 2006). A pathway via lateral prefrontal cortex is also important for regulating changes in cognitive control (Kerns et al., 2004). An electrophysiological study of normal volunteers using paired pulse TMS showed that the pre-SMA influenced M1 motor evoked potentials at a short latency of 6 ms during action selection under conflict (Mars et al., 2009). Although the responsible pathway is unknown, the authors interpreted this finding as representing the process of action re-programming. Considering these previous findings, the No-Go related activation of the pre-SMA might represent the inhibitory process required to suppress the M1 response.

In summary, these findings indicate that the warning effect is represented by the top-down attentional modulation of the motor system, including the M1 and pre-SMA. The attentional and motor systems might be linked through movement preparation (the Go or No-Go decision). Thus, the warning effect is consistent with the motor action-limit theory, and involves the pre-potential of the motor control pathway, from the selection and preparation of the movement to its execution.

Authors' contributions

YY designed and conducted the experiments, analyzed the fMRI data, and wrote the manuscript. HCT and MJH participated in the experimental design and conducted the fMRI experiment. TK constructed the rapid event-related design. HK helped conduct the literature review and prepare the Discussion sections of the text. NS supervised the overall project and edited the manuscript.

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