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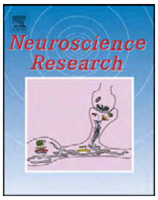

# Neural substrates of phasic alertness: A functional magnetic resonance imaging study

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ABSTRACT

The "warning effect" refers to the decrease in motor response reaction times to a target when its presentation is preceded by a stimulus indicating that the target will appear shortly. We hypothesized that cue presentation phasically enhances alertness, which in turn facilitates the preparation of a motor response. To test this hypothesis, we conducted functional magnetic resonance imaging during a Go/NoGo task with a warning stimulus. Fifteen subjects completed a visual Go/NoGo task, and 12 completed an analogous task in the auditory modality. After a warning stimulus was presented, a Go or NoGo stimulus was presented with equal probability. Both auditory and visual warning stimuli activated the midbrain, thalamus, and the anterior cingulate cortex (ACC) extending to the pre-supplementary motor area (pre-SMA). The warning-related activation in the pre-SMA and thalamus was greater when warnings were followed by Go events with faster reaction times than when followed by events with slower reaction times. The midbrain, thalamus, and ACC are known to be associated with vigilance or intrinsic alertness, and the pre-SMA is involved in movement selection and preparation. Thus, the warning effect may be partly mediated by the potentiation of the pre-SMA through the midbrain–thalamus–ACC alerting network.

## 1. Introduction

The presence of a cueing stimulus (warning stimulus) reduces reaction times (RTs) when individuals make motor responses towards a target. This reduction in RT is called the "warning effect". This effect is seen even if the warning stimulus conveys no information about the nature of the imperative stimulus or the required responses (Hackley and Valle-Inclán, 2003). The ability to increase and maintain response readiness in preparation for an impending stimulus is called alertness, and is considered a fundamental form of attention (Raz and Buhle, 2006). This ability can also be called vigilance and sustained attention (Raz and Buhle, 2006). Alertness can be broadly subdivided into two types, phasic alertness and intrinsic alertness (Sturm et al., 1999; Sturm and Willmes, 2001; Raz and Buhle, 2006). Phasic alertness is defined as alertness for a short period of time subsequent to an external cue or stimulus, whereas intrinsic alertness is defined as a state of general wakefulness (Sturm et al., 1999; Sturm and Willmes, 2001; Raz and Buhle, 2006). In general, RTs to trials lacking any warning stimulus provides a behavioral measure of intrinsic alertness, while the reduction in RTs produced by prior presentation of a warning stimulus is thought to be a measure of phasic alertness (Sturm et al., 1999; Coull et al., 2001). Thus, the warning effect is, at least in part, considered to be a result of increased phasic alertness triggered by the warning stimuli.

Previous imaging studies have suggested that the midbrain–thalamic–anterior cingulate cortex (ACC) system is part of the intrinsic alerting network (Kinomura et al., 1996; Sturm et al., 1999; Sturm and Willmes, 2001; Fan et al., 2005; Raz and Buhle, 2006). Kinomura et al. (1996) conducted a positron emission tomography (PET) study with an attention-demanding RT task using either visual or somatosensory cues. They found that, irrespective of the sensory modality of the cue, the midbrain reticular formation and thalamic intralaminar nuclei were activated when participants shifted from a relaxed and awake state to attention-demanding task trials. Using PET with $O^{15}$ water, Paus et al. (1997) showed that thalamic blood-flow responses to an auditory intrinsic alertness task covaried with those of the ponto-mesencephalic tegmentum and the ACC. During an audi-

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tory intrinsic alertness study, blood-flow responses in the ACC, thalamus, and mesencephalic reticular formation decreased at similar rates over a 50-min testing period; these changes occurred together with increases in response latencies and in the amount of electroencephalographic activity in the theta frequency range. These observations suggest that activation of the ACC is likely to be associated with intrinsic alertness.

In humans, the ACC is located in the medial wall of the cerebral hemisphere. The ventral (limbic) tier occupies the surface of the cingulate gyrus, corresponding to Brodmann's areas 24a and 24b, and the subcallosal area 25. The dorsal (paralimbic) tier is buried in the cingulate sulcus, corresponding to Brodmann's areas 24c and 32 (see Paus, 2001, for a review). The dorsal tier is known to be involved in motor control (Picard and Strick, 1996; Deiber et al., 1999). In the non-human primate, the ACC receives dense inputs from the midline thalamic nuclei (Barbas et al., 1991), which are involved in the regulation of cortical alertness (Montaron and Buser, 1988). Alertness-related modulation of the ACC might also arise from brainstem monoamine nuclei inputs, such as those from the mesocortical dopamine system originating in the ventral tegmental area, and norepinephrine inputs from the locus coeruleus (LC) (Barger, 1992; Crino et al., 1993). Thus we hypothesized that the ACC is a key neural substrate for the warning effect mediated via phasic alertness. This is consistent with the concept of an anterior alerting system proposed by Sturm and Willmes (2001).

Although the warning effect is a well-replicated behavioral observation, it is unclear which aspects of cognitive or motor processing are facilitated by the presentation of a warning cue. Previous studies using event-related potentials suggest that the reduction of RT associated with the warning effect is caused neither by the facilitation of low-level motor processes nor by sensory-perceptual processing, but rather by non-specific motor "priming" within an early phase of response selection (Hackley and Valle-Inclán, 2003). This raises the possibility that the warning effect is mediated by the midbrain–thalamus–ACC network, which is thought to facilitate movement preparation in the premotor cortices. We conducted a functional magnetic resonance imaging (fMRI) study to test the hypothesis that warning stimuli activate the alerting system, including the midbrain reticular formation, thalamus, and frontal regions such as the ACC. To do this, we used visual and auditory Go/NoGo tasks with warning stimuli that had warning periods of variable duration. The application of both visual and auditory tasks allowed us to investigate modality-invariant effects, and the variable warning period allowed us to exclude factors related to temporal orienting attention, in which the task includes informative cues that predict with high probability the exact time interval when the target (Go or NoGo cues) will appear (Coull et al., 2001). In addition to these advantages, the Go/NoGo task allowed us to depict the activation related to motor execution by subtracting the NoGo from the Go condition (Go–NoGo contrast). Technically, the Go/NoGo task enabled us to dissociate the activation related to the warning signal from that related to the Go or NoGo task, because this design reduces the correlation between the expected activations during the Go or NoGo condition and the warning condition. Thus, the warning cue-related activation should represent the neural substrates of phasic alertness irrespective of the subsequent task cue (Go or NoGo). Specifically, we expected the warning stimuli to activate both the alerting system and those areas that are involved in the early stages of motor processing, such as movement preparation.

## 2. Materials and methods

### 2.1. Participants

In total, 51 right-handed healthy volunteers took part in the study. Twenty-four subjects participated in the preliminary psychological testing (12 males and 12 females; mean age, 27.9 ± 4.8 years). Twenty-seven healthy right-handed volunteers participated in the fMRI study. Fifteen of these (seven males and eight females; mean age, 24.1 ± 2.3 years) completed a visual Go/NoGo task, and the remaining 12 (seven males and five females; mean age, 22.8 ± 3.4 years) completed an auditory version of the Go/NoGo task. All subjects were right-handed according to the Edinburgh handedness inventory (Oldfield, 1971). None of the subjects had a history of psychiatric or neurological illness. The protocol was approved by the ethical committee of the National Institute for Physiological Sciences, Japan, and all subjects gave their written informed consent to participate.

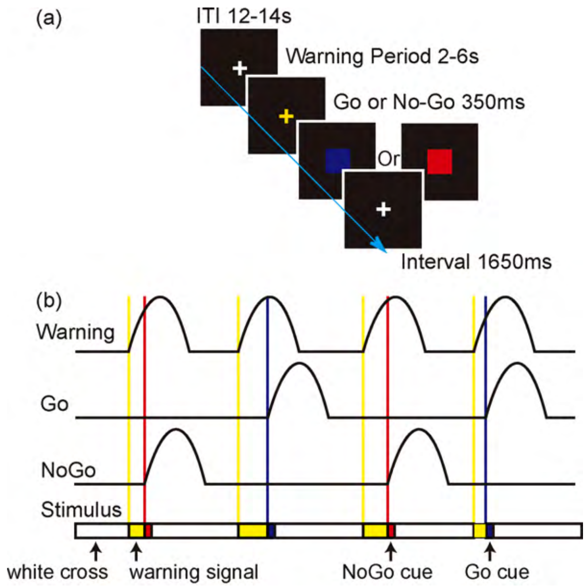

**Fig. 1.** (a) Schematic diagram of the visual Go/NoGo task. The subjects were initially presented with a central fixation cross. After a relatively long ITI of 12–14 s, the color of the fixation cross changed from white to yellow as a warning stimulus. Following a variable time period (2–6 s), a blue or red square was presented as the Go signal or NoGo signal, respectively. When the Go signal was presented, the subjects had to respond by pressing a button with their right thumb as quickly as possible. (b) Task design and models for analyses. The time course of the tasks is presented schematically at the bottom of the figure. The model of the expected blood oxygen level-dependent (BOLD) signal change is presented for the event-related paradigms (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.).

### 2.2. Tasks and preliminary psychological testing

We used Go/NoGo tasks with either auditory or visual cues. In the preliminary psychological testing, subjects completed four versions of the Go/NoGo task, differing in stimulus modality (visual or auditory) and the presence or absence of a warning stimulus as follows: visual warning (VW), visual no-warning (VN), auditory warning (AW), and auditory no-warning (AN) tasks. This was intended to confirm that the warning effect, as measured by a reduction in the RT, was not a modality-specific effect.

In the VW task (Fig. 1a), a trial began with the presentation of a central white cross-hair. The subjects were asked to fixate on the position of this white cross-hair during the run. Following this, the cross-hair turned yellow (the warning period). After a warning period of variable duration (2–6 s), the warning stimulus was replaced by either a blue square (Go cue) or a red square (NoGo cue) presented in the center of the display. The duration of the Go and NoGo cues was 350 ms. When a Go cue was presented, the subjects had to push a button with their right thumb as quickly as possible. When a NoGo cue was presented, the subjects were required not to push the button. Each visual stimulus was presented at a visual angle of $1.3^\circ \times 1.3^\circ$. After the cue disappeared, the white cross-hair was presented again, with an inter-trial interval (ITI) of 12–14 s, until the beginning of the next warning period. The VW task consisted of two successive experimental runs, which together comprised 10 Go trials and 10 NoGo trials. The trial order, the ITI, and the duration of the warning period were pseudorandomized across the two runs. The VN task was identical to the VW task except for the absence of warning stimuli. The AW task was identical to the VW task except for the task-related stimulus modality and the presentation of the white cross-hair, which was displayed throughout the run. In the AW task, the warning stimuli consisted of a pure-tone stimulus (frequency, 440 Hz; sampling rate, 44.1 kHz; stereo sound) presented for 2–6 s. A higher pitched pure tone (frequency, 480 Hz; sampling rate, 44.1 kHz; stereo sound) was used as the Go cue, and a lower pitched pure tone (frequency, 400 Hz; sampling rate, 44.1 kHz; stereo sound) was used as the NoGo cue. The AN task was identical to the AW task except for the absence of warning stimuli. Each subject completed two runs of each task type, the order of which was counterbalanced across all subjects, giving a total of eight runs, including 40 Go and 40 NoGo trials.

The stimulus presentation and response collection were controlled by Presentation software (Neurobehavioral Systems, Albany, CA, USA) on a personal computer (Dimension 9100; Dell Computer Co., Round Rock, TX, USA). The visual stimuli were presented on a 19-in. liquid-crystal display (Diamond-crysta RDT197V; Mitsubishi Electric, Tokyo, Japan). The auditory stimuli were presented via a stereo-speaker system (SRS-A202; Sony, Tokyo, Japan). The responses were collected via an in-house button system that was made from a universal serial bus (USB)-connected numeric keypad (TNK-SUU211GY; LOAS Co., Ltd., Osaka, Japan) and a switch (Z-15GD; Omron, Kyoto, Japan).

For each subject, the accuracy of the Go and NoGo responses and the mean RTs for the correct Go responses were calculated. Responses with a delay of longer than 1 s were regarded as missed responses. Statistical analysis was carried out using SPSS version 10.0J software (SPSS Japan Inc., Tokyo, Japan). A two-way repeated measure analysis of variance (ANOVA) was performed to compare the mean percentage of correct responses and the mean RT. The results were considered statistically significant at $p < 0.05$. To examine the relationship between the duration of the warning stimuli and reaction times, we calculated the Pearson product–moment correlation coefficients in individuals, as well as the mean of these coefficients for all participants.

### 2.3. fMRI study

Prior to being scanned, each subject completed behavioral training. The training consisted of six tasks: three RT tasks and three Go/NoGo tasks. The time for response was gradually decreased until the performance reached a certain criterion (determined by RTs of each individual) level. During the scan, the subjects performed a visual or auditory Go/NoGo task (Fig. 1), which was similar to the VW and AW tasks, respectively, used for the preliminary psychological testing, differing only in the visual angle and the number of runs. In the visual task (Fig. 1a), each stimulus was presented at a visual angle of $1.9^\circ \times 1.9^\circ$, and the two successive runs were repeated four times giving a total of eight runs, including 40 Go trials and 40 NoGo trials. The accuracy and RTs in response to the Go cues were analyzed in the same way as the preliminary psychological data (described above).

For both stimulus modalities, the target stimuli in the Go/NoGo tasks were counterbalanced across subjects to control for possible stimulus-specific effects: in the visual task, the red square was used as the Go cue and the blue square was used as the NoGo cue for half of the participants, while this contingency was reversed for the remaining half of the participants. Similar counterbalancing was applied to the high-pitch and low-pitch tones used as cues in the auditory tasks.

Presentation 9.81 (Neurobehavioral Systems, Albany, CA) was implemented on a personal computer (Dimension 9100; Dell Computer, Round Rock, TX) for stimulus presentation and response collection. A liquid-crystal display projector (DLA-M200L; Victor, Yokohama, Japan), located outside and behind the scanner, projected stimuli through another waveguide onto a translucent screen, which the subjects viewed via a mirror attached to the MRI head coil. The auditory stimuli were presented via MRI-compatible headphones (Hitachi, Yokohama, Japan). The volume was adjusted to approximately 90 dB. Responses were collected via an optical button system (Current Design, Philadelphia, PA).

### 2.4. MRI data acquisition

All images were acquired using a 3 T MR scanner (Allegra; Siemens, Erlangen, Germany). Functional images were acquired using a T2*-weighted echo-planar imaging (EPI) sequence. Each volume consisted of 34 slices, each of which was 4.0-mm thick, with a gapless alignment to cover the entire cerebrum and cerebellum (repetition time [TR], 2000 ms; echo time [TE], 30 ms; flip angle [FA], 80°; field of view [FOV], 192 mm; 64 × 64 matrix; voxel dimensions, 3 mm × 3 mm × 4 mm). Oblique scanning was used to exclude the eyeballs from the images. The onset of each trial, relative to the preceding image acquisition, was jittered within 1 TR (2000 ms) (Dale, 1999). To acquire a fine structural whole-head image, T1-weighted magnetization-prepared rapid-acquisition gradient-echo (MP-RAGE) images were obtained (TR, 2500 ms; TE, 4.38 ms; FA, 8°; FOV, 230 mm; matrix size, 256 mm × 256 mm; voxel dimensions, 0.9 mm × 0.9 mm × 1.0 mm).

Each run consisted of a continuous series of 112 volumes acquired with a total duration of 3 min 44 s. To avoid subject fatigue, several breaks (of up to 5 min) were inserted between the eight runs. The total duration of the experiment was approximately 70 min, including the acquisition of the structural MR images.

### 2.5. fMRI data analysis

In addition to the first two volumes of each EPI sequence, which were discarded automatically by the MR scanner, the first three volumes of each fMRI run were removed from the analysis to allow for stabilization of the magnetization, and the remaining 109 volumes per run (a total of 872 volumes per subject for eight runs) were used in the analysis. The data were analyzed using statistical parametric mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, UK) implemented in Matlab (Mathworks, Sherborn, MA) (Friston et al., 1994, 1995, 2007). After correcting for differences in slice timing within each image volume, all volumes were realigned for motion correction. All EPI volumes were normalized to the Montréal Neurological Institute (MNI) EPI template using a nonlinear basis function. The functional images were spatially smoothed in three dimensions using an 8-mm full-width at half-maximum Gaussian kernel.

Statistical analysis of the functional data was conducted at two levels. First, individual task-related activation was evaluated. Second, the summary data for each individual were incorporated into a second-level analysis using a random-effects model (Friston et al., 1999) to make inferences at the group level.

The signal was scaled proportionally by setting the mean value of the whole brain of all volumes to 100 arbitrary units. The signal time-course for each subject was analyzed with a general linear model, with condition and run effects as regressors, and high-pass filtering (128 s). To test our hypotheses about regionally specific condition effects, the model parameters were compared with linear contrasts. As we adopted a slow event-related design, the general linear model allowed us to estimate the amplitude of the activation for each condition relative to the implicit "rest" condition (the inter-trial interval). The slow event-related design consisted of the following three types of event condition: warning, Go, and NoGo (Fig. 1b). The design matrix ($X$) was created by convolving a set of three vectors with a hemodynamic response function ($h$) as follows,

$$X = [w, g, n] \otimes h$$

where $w$ corresponds to Warning, $g$ corresponds to Go, and $n$ corresponds to NoGo. We included trials for which the responses were correct. Initially, we delineated the areas that were related to the onset of the warning period. A Go–NoGo comparison was conducted to depict the neural substrates associated with the motor execution of hand movement.

The weighted sum of the parameter estimates in the individual analyses constituted "contrast" images which were used for the group analysis (Friston et al., 1999). Contrast images obtained by individual analyses represented the normalized task-related increment of the MR signal of each subject. The contrast images of Warning, Go, and NoGo for each cueing modality were incorporated into a flexible factorial design that modeled the subject effect, the cueing modality effect, and the different conditions (Warning, Go, and NoGo) at the group level. The resulting set of voxel values for each contrast constituted a statistical parametric map of the $t$ statistic (SPM$\{t\}$). We delineated the activation of the warning effect irrespective of the cue modality by masking images with the contrast of both the visual and auditory warning conditions at a statistical threshold of $p < 0.05$, family-wise error (FWE) corrected at the voxel level (Friston et al., 1996), with the cluster size set at >20 voxels. Similarly, we evaluated the execution effect as observed in the Go–NoGo comparison, irrespective of the cue modality.

Furthermore, to examine which regions were associated with the reduction of RTs, within the areas showing warning cue-related activation we examined the relationship between the activation related to the warning cue and the RTs of the following Go events. First, the correct Go trials in each run were divided into "faster Go" and "slower Go" trials based on their RTs, so that there were approximately equal numbers of events in each run. Then, we divided the warning events into three groups based on the faster Go, slower Go, and NoGo trials: warning events followed by faster Go (FWarning), by slower Go (SWarning), and by NoGo (NoGoWarning) trials. We reconstructed the design matrix using the following five types of events: FWarning, SWarning, NoGoWarning, Go, and NoGo. We conducted an FWarning–SWarning comparison to depict the warning-related areas which were associated with faster reaction times in the subsequent Go trials. The contrast images of the FWarning–SWarning comparison were tested at the group level using a one-sample $t$-test. The statistical threshold was set at $p < 0.05$, corrected for multiple comparisons at the cluster level within the search volume.

## 3. Results

### 3.1. Preliminary psychological testing

The mean (±standard deviation [SD]) percentages of correct responses on Go trials were 100.0 ± 0.0% for the AN task, 99.2 ± 2.8% for the AW task, 99.6 ± 2.0% for the VN task, and 99.6 ± 2.0% for the VW task. There were no statistically significant main effects on performance accuracy of the presence of warning (two-way repeated measures ANOVA; $F[1,23] = 2.09$; $p > 0.05$), modality (two-way repeated measures ANOVA; $F[1,23] = 0.00$; $p > 0.05$), or a significant interaction (two-way repeated measures ANOVA; $F[1,23] = 2.09$; $p > 0.05$). The false-alarm rates (±SD) were 7.5 ± 9.9% for the AN task, 3.8 ± 6.5% for the AW task, 4.2 ± 6.5% for the VN task, and 3.8 ± 6.5% for the VW task. Similarly, there were no statistically significant main effects of the presence of warning (two-way repeated measures ANOVA; $F[1,23] = 2.53$; $p > 0.05$), modality (two-way repeated measures ANOVA; $F[1,23] = 1.42$;

**Table 1**
Warning effect within the areas activated by both visual and auditory stimuli.

| Cluster | Voxel | | MNI coordinates | | | | Side | Location |
|---|---|---|---|---|---|---|---|---|
| P* | Size | P+ | *T* | *x* | *y* | *z* | | |
| <0.001 | 825 | <0.001 | 11.8 | −6 | 10 | 44 | L | ACG |
| | | <0.001 | 10.4 | 8 | 14 | 38 | R | ACG |
| | | <0.001 | 10.1 | 8 | 8 | 58 | R | Pre-SMA |
| <0.001 | 323 | <0.001 | 10.2 | 8 | −26 | −4 | R | Midbrain |
| | | <0.001 | 9.8 | 10 | −16 | 8 | R | Thalamus |
| <0.001 | 285 | <0.001 | 10.1 | −10 | −26 | −8 | L | Midbrain |
| | | <0.001 | 9.2 | −10 | −16 | 10 | L | Thalamus |
| 0.007 | 43 | <0.001 | 9 | 36 | 20 | 4 | R | Insula |
| 0.003 | 72 | <0.001 | 9 | 52 | 2 | 48 | R | PMd |
| 0.013 | 24 | <0.001 | 8.9 | −34 | 22 | 6 | L | Insula |

MNI, Montréal Neurological Institute; ACG, anterior cingulate gyrus; PMd, dorsal premotor coetex; pre-SMA, pre-supplementary motor area; L, left; R, right. P* corrected at cluster level, P+ FWE corrected. The areas were masked with the activated areas by both visual and auditory stimuli with $p < 0.05$ (FWE corrected at voxel level).

$p > 0.05$), or their interaction (two-way repeated measures ANOVA; $F[1,23] = 1.56$; $p > 0.05$) on the false-alarm rate. The mean RTs (±SD) for each condition were 451.5 ± 126.1 ms for the AN task, 384.9 ± 70.9 ms for the AW task, 407.9 ± 65.0 ms for the VN task, and 380.9 ± 75.3 ms for the VW task. Significant main effects of the presence of a warning (two-way repeated measures ANOVA; $F[1,23] = 40.80$; $p < 0.05$) and the task modality (two-way repeated measures ANOVA; $F[1,23] = 5.73$; $p < 0.05$) were found on RTs, but there was no significant interaction between the presence of a warning and the modality of the warning signal (two-way repeated measures ANOVA; $F[1,23] = 3.78$; $p > 0.05$). The correlation analysis revealed a weak correlation between the duration of the warning stimuli and reaction times (mean $r = -0.12$; only 2 of 27 individuals showed a significant correlation ($p < 0.01$)). This suggests that the strength of the warning effect did not depend on the duration of the warning stimuli.

## 3.2. *fMRI study*

### 3.2.1. *Task performance*

The mean (±SD) percentages of correct responses were 98.2 ± 4.5% for the visual Go trials, 90.1 ± 5.9% for the visual NoGo trials, 98.3 ± 3.1% for the auditory Go trials, and 87.7 ± 10.0% for the auditory NoGo trials. There was a significant difference in performance accuracy between the Go and NoGo trials (repeated measures ANOVA; $F[1,25] = 29.077$; $p < 0.001$), but no effect of the cueing modality ($F[1,25] = 0.629$, $p = 0.435$) or significant interaction ($F[1,25] = 0.867$, $p = 0.361$). The RTs (± SD) of correct responses on Go trials were 351.1 ± 58.6 ms for the visual task and 333.2 ± 29.4 ms for the auditory task. There was no significant difference in RTs between the visual and auditory tasks (two-sample *t*-test; $p = 0.345$).

### 3.2.2. *Task-related activation*

Irrespective of the cue modality, at the population level neural activation related to the warning stimuli was identified bilaterally in the ACC, left pre-SMA, and right dorsal premotor area (PMd), as well as bilaterally in the insula and thalami extending into the midbrain, including the reticular formation, red nucleus and substantia nigra (Figs. 2 and 3, Table 1). The Go–NoGo contrast revealed activation in the left primary sensorimotor cortex and the right cerebellum (Table 2).

The ventral tier of the ACC (BA 24) is ventral to the cingulate sulcus, and the dorsal tier is buried in the cingulate sulcus (CS) (Paus, 2001). When the paracingulate sulcus (PCS) is present, BA 32 extends dorsally to the paracingulate gyrus (Paus et al., 1996; Paus, 2001). Thus, localizing the CS and PCS is important to precisely distinguish the ACC and pre-SMA. Using the anatomically normalized high resolution MRI of the participants of the fMRI study ($N = 27$), we measured the MNI coordinates of the CS and PCS, particularly the *z* coordinates (distance from the AC-PC plane) at $y = 14$, 10, and 8 mm (Table 3). Based on this, we differentiate the pre-SMA (8, 8, 58) and the ACC at (8, 14, 38) and (−6, 10, 44); the ACC coordinates were mainly located in the dorsal tier.

**Table 2**
Execution effect by Go–NoGo contrast irrespective of the cue modalities.

| Cluster | Voxel | | MNI coordinates | | | | Side | Location |
|---|---|---|---|---|---|---|---|---|
| P* | Size | P+ | *T* | *x* | *y* | *Z* | | |
| <0.001 | 740 | <0.001 | 9.7 | −38 | −22 | 66 | L | SMI |
| | | <0.001 | 9.7 | −52 | −20 | 52 | L | SMI |
| | | <0.001 | 8.2 | −36 | −22 | 52 | L | SMI |
| 0.001 | 158 | <0.001 | 9.2 | 26 | −54 | −26 | R | Cerebellum |
| 0.005 | 57 | <0.001 | 8.0 | 6 | −66 | −14 | R | Cerebellum |

MNI, Montréal Neurological Institute; SMI, primary sensorimotor cortex; L, left; R, right. P* corrected at cluster level, P+ FWE corrected. The areas were masked with the activated areas by Go–NoGo contrast of visual and auditory stimuli with $p < 0.05$ (FWE corrected at voxel level).

### 3.2.3. *Comparison of FWarning and SWarning trials*

Within the warning-related areas (Fig. 2, Table 1), the FWarning–SWarning contrast revealed activation in the left pre-SMA (−6, 12, 52) and bilateral thalamus (left: −12, −20, 10; right: 10, −12, 8) at the population level (Fig. 3). In contrast, the SWarning–FWarning contrast revealed no significantly activated regions.

**Table 3**
MNI coordinates in the *z* direction (mm) of the paracingulate and cingulate sulci.

| *y* (mm) | Left | | | Right | | |
|---|---|---|---|---|---|---|
| | 14 | 10 | 8 | 14 | 10 | 8 |
| Paracingulate sulcus | | | | | | |
| Mean | 48.5 | 50.8 | 52 | 50.1 | 50.3 | 50.6 |
| SD | 3.8 | 4.4 | 4.4 | 2.2 | 2.9 | 3.3 |
| *N* | 10 | 10 | 10 | 9 | 9 | 9 |
| Cingulate sulcus | | | | | | |
| Mean | 37.7 | 40.7 | 41.8 | 40.2 | 42.3 | 43.2 |
| SD | 3.8 | 3.8 | 4.2 | 3.8 | 4.7 | 5.2 |
| *N* | 27 | 27 | 27 | 27 | 27 | 27 |

*z* coordinates (mm) at the planes of $y = 14$, 10, and 8 mm are shown. MNI, Montréal Neurological Institute; *N*, number of subjects the sulci were identified; SD, standard deviation.

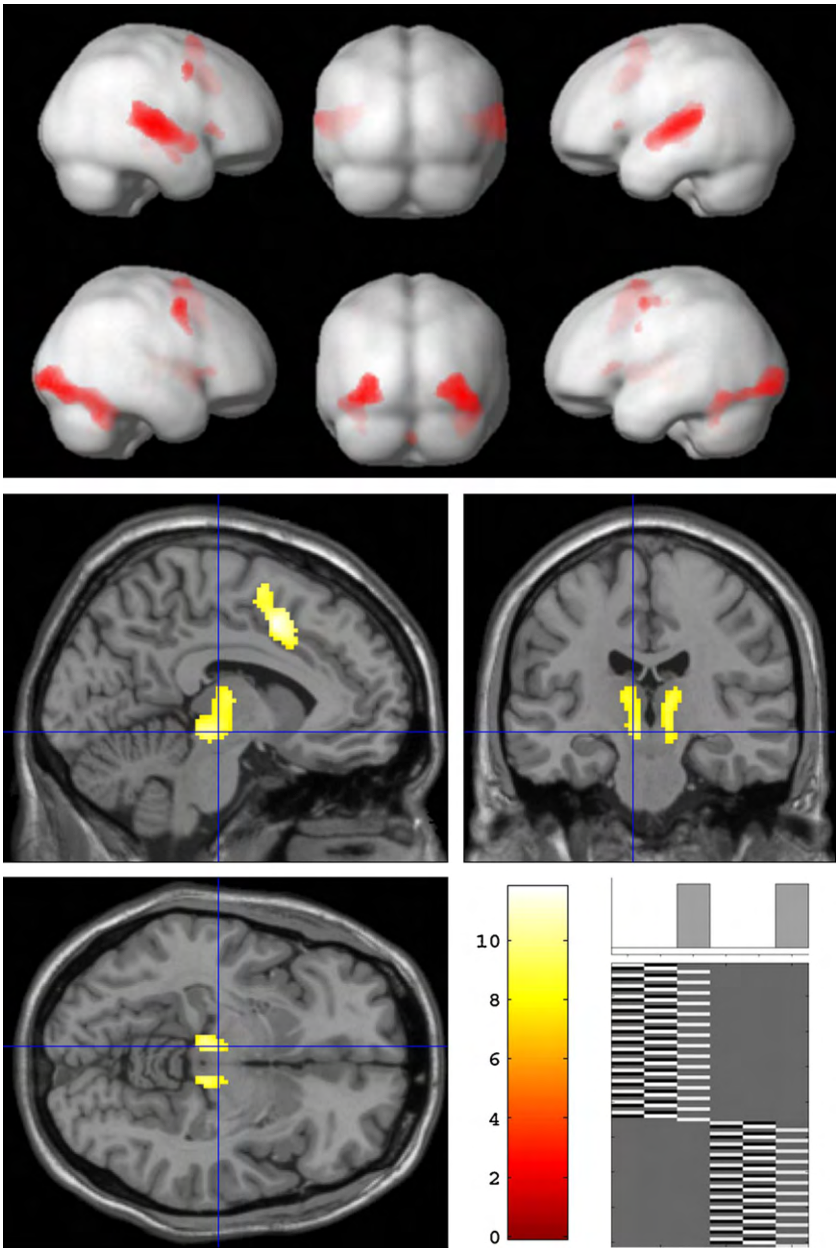

**Fig. 2.** (Top) Auditory (upper row) and visual warning effects at the population level superimposed on the three-dimensionally rendered average MRI. The statistical threshold was family wise error (FWE) corrected ($p < 0.05$ and cluster size >20 voxels). (Bottom) The warning effect irrespective of the modality of the warning cue superimposed on the high-resolution MRI in sagittal, coronal, and transaxial views at (−8, −20, −8). The activated areas were masked with those regions activated by both the auditory and visual warning effects, shown in the top panel. The statistical threshold was FWE-corrected ($p < 0.05$ and cluster size >20 voxels). The color scale indicates the magnitude of the *t*-value. (Bottom right) Design matrix of the flexible factorial design at the second level with the contrasts. From left to right, the vectors represent the visual Go, visual NoGo, visual warning, auditory Go, auditory NoGo, and auditory warning conditions.

## 4. Discussion

As expected, the warning stimuli activated both the alerting system and the areas for movement preparation.

### 4.1. *ACC and thalamus-midbrain*

Warning stimuli activated the ACC, midbrain regions including the reticular formation, red nucleus and substantia nigra, and the thalamus, regardless of the stimulus modality. As the activation in the midbrain did not extend to the level of the 4th ventricle, it was unlikely that the locus coeruleus was activated.

ACC activity has been shown to be related to intrinsic alertness rather than modality-specific attentional processes (Paus et al., 1997). In the present study, the ACC was activated by the warning cue irrespective of its modality. The ACC might therefore be involved in phasic alertness as well. Similarly, the regions in the midbrain reticular formation and the thalamus (intralaminar domain) which showed an intrinsic alertness effect in Kinomura et al. (1996) are close to the areas activated by warning stimuli, irrespective of modality, in the present study. Therefore, intrinsic and phasic alertness could conceivably share neural substrates in the midbrain–thalamic system.

Although the present study failed to show any involvement of the locus coeruleus, recent studies have suggested that both phasic and intrinsic alerting processes are related to the LC–norepinephrine (NE) system (Aston-Jones and Cohen, 2005;

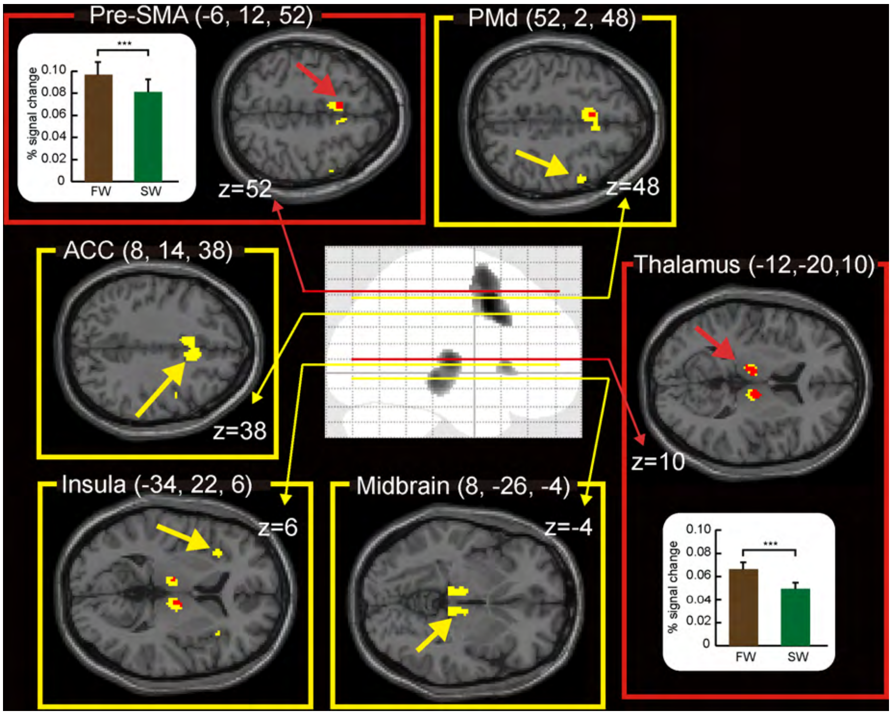

**Fig. 3.** The relationship between the RTs of the Go responses and the neural responses to the preceding warning cues. Within the warning-related areas (yellow), greater warning cue-related activation was followed by Go trials with faster RTs (FW) compared with Go trials with slower RTs (SW) at the population level (red). Activation patterns are superimposed on high-resolution transaxial MRI images. The statistical threshold was set at $p < 0.05$ corrected for multiple comparisons at the cluster level within the search volume. (Center) The statistic parametric map of the warning effect (as shown in Fig. 2) for the height reference. The three-dimensional information was collapsed into two-dimensional sagittal images. Error bars indicate the standard error of mean. $^{***}p < 0.001$, paired-$t$ test (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.).

Raz and Buhle, 2006). Given that the LC sends dense projections to the ACC (Neiuwenhuys et al., 1988), the involvement of the ACC in intrinsic alertness (Paus et al., 1997) and phasic alertness, as shown in the present study, might be partly explained by the bottom-up effects of the LC–NE system. However, the monkey LC also receives prominent direct input from the ACC (Aston-Jones and Cohen, 2005), which appears to exert a top-down effect on the LC. This connection may be the anatomical basis of the “anterior alerting system” proposed by Sturm and Willmes (2001). They suggest that the ACC intrinsically controls the brainstem NE activation system via the reticular nucleus of the thalamus, through which brain-stem activation can be directed to cortical areas for specific information processing (“thalamic gates”, Sturm and Willmes, 2001). Consistent with this proposal, we found that the thalamus was activated more prominently by warning stimuli that were followed by faster Go responses than by warning stimuli followed by slower Go responses, and thus the thalamus is activated in a RT-dependent manner (Fig. 3).

We reason that the imaging data can be linked to “alertness”, as judged from the RT data, because the variability of the RTs of the Go responses may reflect the variability of the warning effect: a stronger warning effect should lead to a shorter RT of the subsequent Go response. Therefore, the areas that showed more prominent activation by the warning events that were followed by faster Go trials (FWarning) compared to those followed by slower Go responses (SWarning) should represent the neural correlates of phasic alertness.

### 4.2. Pre-SMA

In the present study, the pre-SMA was also activated by the warning cues irrespective of modality in an RT-dependent manner. According Sturm and Willmes’ (2001) “thalamic gates” theory, this suggests that the pre-SMA is the target of the directed information from the brainstem via the thalamus.

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 subregions: the anterior part (pre-SMA) and the posterior part (the SMA proper) (Picard and Strick, 1996). The SMA proper, located immediately anterior to the foot representation of 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, which is tightly interconnected with the M1 and the spinal cord (Luppino et al., 1993), probably plays an important role in the preparation and execution of movements. The pre-SMA in macaque monkeys corresponds to the medial cortex of area 6, 6ab, or field F6 (Vogt and Vogt, 1919; Luppino et al., 1991; Matelli et al., 1991; Luppino et al., 1993). Although the pre-SMA lacks direct connections with area M1 and the spinal cord (see also 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 as well as the rostral premotor and cingulate areas (Matsuzaka et al., 1992; Luppino et al., 1993). Thus, the pre-SMA is likely to play a less direct role in the execution of movements. 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. 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., 2001). Functional neuroimaging studies suggest that the pre-SMA might be specifically associated with the free selection of actions (Deiber et al., 1996; Lau et al., 2004a) and the preparation of movements (Brass and von Cramon, 2002). Attention to the intention to move accentuates activity in the pre-SMA (Lau et al., 2004b).

These regions, along with the ACC, are places where information converges for motor control, homeostatic drive, emotion, cognition, and alertness (Paus, 2001). Because we found RT-dependent activity in the pre-SMA but not in the ACC, these medial regions may have a different functional role in the processes of phasic alertness. The ACC, together with the midbrain and thalamus, constitutes the anterior alerting system (Sturm and Willmes, 2001). As the pre-SMA is involved in response selection and/or preparation, the RT-dependent co-activation pattern found in the pre-SMA in the present study can be interpreted as acting to prime the motor selection and/or preparation processes in the pre-SMA via inputs from the anterior alerting system, resulting in the facilitation of motor processing.

Recent studies have also provided evidence that the pre-SMA has a role in response inhibition (Mostofsky et al., 2003; Aron and Poldrack, 2006; Isoda and Hikosaka, 2007). Therefore, warning-related activation, including that found in the pre-SMA in the present study, might also reflect the facilitation of NoGo processes. Further research is necessary to address this issue, using paradigms such as the stop-signal task, which can measure the index of covert inhibitory processes as the stop-signal reaction time (Rubia et al., 2001; Aron and Poldrack, 2006) following warning stimuli.

Previous functional MRI studies suggest that attention tasks induce two types of task-related blood oxygen level dependent (BOLD) signals. The first are “source” signals, that provide information about the organization of attention systems, and the second are “site” signals, which provide information on how motor, sensory or cognitive systems are affected by attention (Corbetta, 1998). If we consider the RT-dependent pre-SMA and thalamic activation patterns as site signals, the warning stimuli could potentiate the pre-SMA for movement initiation or inhibition via the midbrain alerting system through thalamic gating, which in turn is controlled by the ACC. In summary, we proposed that the warning effect is mediated by the interaction of the alerting system and the motor system.

### 4.3. Interaction of the anterior alerting system and other attentional systems

Previous investigations into a possible neural alerting system have shown that, in addition to the anterior alerting system, tasks requiring phasic alertness activate frontal and parietal regions (Sturm and Willmes, 2001; Fan et al., 2005). This has been explained as co-activation of the attention-orienting networks that are distributed in parietal and frontal areas (Fan et al., 2005). Although several behavioral studies employing tasks designed to recruit both networks demonstrated no correlation between the alerting and orienting scores, suggesting that they are functionally distinct (Fernandez-Duque and Posner, 1997; Fan et al., 2002, 2005; Rueda et al., 2004), interactions have been observed under some conditions (Callejas et al., 2004).

In the present study, there was no activation in the lateral parietal-frontal areas that are involved in the orientation of attention. This may be due to the task design: the warning stimulus contained no information about the nature of the imperative stimulus or the required responses, and thus might have eliminated the effects of cognitive components other than phasic alertness during the presentation of the warning cue.

### 4.4. Other areas of activation

We observed activity related to the warning cue in the PMd and insula. The PMd is known to be related to movement preparation in non-human primates (Weinrich et al., 1984) and in humans (Watanabe et al., 2002; Kansaku et al., 2005). The insula is a center for interoception and is associated with autonomic motor control (Craig, 2003). The contribution of the insula to motor function is thought to be related to the sense of “body ownership” of a movement rather than the production of the movement itself (Hallett, 2007). The insular activation observed in the present study might be the indirect result of movement preparation.

### 4.5. Limitations of the present study

The present fMRI experiment did not include a control condition without warning stimuli, due to the time constraints of a slow event-related fMRI design. Because of this, it was unclear whether the warning effect was present during the scan run. However, the RTs measured during the experiment were comparable to those reported by another group who performed identical tasks outside the MRI scanner and showed a clear warning cue effect. Thus, it is likely that the same warning effect was present during the fMRI experiment. Furthermore, to link the imaging data to “alertness”, as judged from the RT data, we examined the relationship between the RTs of the Go responses and the neural responses to the preceding warning cues. If the warning effect of the preceding warning cue is strong, the RT of the following Go response should be shorter. Concordant with this notion, the pre-SMA and thalamus showed RT-dependent warning cue-related activation. This suggests that the warning effect, as indicated by the shortening of the RT, is mediated by the interaction of the alerting system and the motor system.

The current study used a between-subjects design, in which different groups completed tasks with different stimulus modalities, making it difficult to compare effects between stimulus modalities. Again, this was due to time limitations. As our primary interest was to investigate whether the anterior alerting system is activated by cues of different modalities, rather than comparing the degree of activation between modalities, the present results are still valid. Future studies may adopt task designs that test both warning and modality effects for each individual.

## 5. Conclusion

We showed that warning stimuli activated neural circuits associated with a neural alerting system, as well as the pre-SMA, irrespective of stimulus modality. These findings suggest that the warning effect is mediated by the priming of the mesial motor structures, including the pre-SMA and ACC, for the self-initiation of movement through the midbrain–thalamic–ACC alerting system.

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