Neuroscience Research 76 (2013) 230–239

Contents lists available at SciVerse ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

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

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ARTICLE INFO

Article history:
Received 19 April 2013
Received in revised form 19 May 2013
Accepted 29 May 2013
Available online 13 June 2013

Keywords:
Attention
Functional MRI
Pre-SMA
Temporal orienting
Warning effect

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-potentiation of the motor control pathway by the top-down attentional system, from the selection and preparation of the movement to its execution.

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).

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

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http://dx.doi.org/10.1016/j.neures.2013.05.008

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 ± 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,