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論文内容の要旨

INTRODUCTION

When observers initiate motor responses to targets, they do so sooner when a preceding stimulus indicates that the target will appear shortly. This phenomenon is called warning effect (Hackley and Valle-Inclan, 2003). The warning signal (WS) is supposed to lead the anticipation of the target response.

A central component of response anticipation is achieving and maintaining an alert state (Bertelson, 1967). Thus warning effect may be partly caused by the phasic alertness that facilitate reflexive reaction, and response anticipation that facilitate the voluntary reaction (Hackley et al., 2009). A previous study with functional MRI showed that phasic alertness is related to the phasic activation of the midbrain-thalamus-anterior cingulate network and the pre-SMA (Yanaka et al., 2010). Response anticipation has also been shown to include top–down processes of attention, which typically engage prefrontal and parietal cortices (Corbetta and Shulman, 2002; Liang et al., 2002; Foxe et al., 2005; Badler and Heinen, 2006). 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). Numerous studies (Tecce, 1972; Lang et al., 1988; Alexander and Crutcher, 1990; Ulrich et al., 1998; Lee et al., 1999; Leuthold and Jentzsch, 2001; Isomura et al., 2003; Paradiso et al., 2004) suggest that anticipatory attention, motivation, and motor preparation are indexed by the CNV. By conducting comparative electrophysiological (CNV) and fMRI study, Fan et al. (2007) showed that response anticipation modulates overall activity in the executive control network represented by a dorsal fronto-parietal network and the anterior cingulate cortex (ACC) extending to the pre-SMA. They interpreted that warning effect is brought by the flexible control of a wide range of executive processes. Thus warning effect is related to attention such as alertness, and executive function (Raz and Buhle, 2006).

Electrophysiological studies have shown the warning effect is related to the excitability of the primary motor cortex (M1). According to the proposal by Näätänen (1971) (motor action limit theory), time preparation increases neural activation during the foreperiod (the period from the warning cue to the go cue). When the increase in preparatory neural activation bypasses a threshold, termed "action limit", an overt response is triggered. Reaction time depends on the distance between the motor action limit and the level of neural activation attained during the foreperiod. If this distance is large, the RT is long, when the distance is short, the RT is short. "The CNV amplitude (Trillenberg et al. 2000) and single cell recording studies within primate M1 (Tanji and Evarts 1976; Bastian et al. 2003) suggest that response preparation is typically associated with an increase in cortical excitability." (Excerpt from Syclare et al. 2007). However, the neural pathways that link the warning effect in the M1 with the attentional network is not known, nor the neural substrates of response anticipation.

Here, to depict the neural substrates of warning effect as the interaction of attentional system and motor system, the author conducted functional MRI. Previous functional MRI studies showed that pre-SMA is related to warning effect mediated by both phasic alertness (Yanaka et al. 2010) and executive control (Fan et al. 2007).

These findings lead us to hypothesize that warning effect is mediated by the top-down attentional processes which potentiate the pre-SMA and other motor cortical areas including the M1.

METHODS

Nineteen healthy normal volunteers participated in the functional study using Go/NoGo task with visual and auditory warning stimuli. Rapid event-related task design was adopted to saturate the alertness. For aurally warned, visually prompted trials, auditory warning stimulus was presented for 1500 ms during which visual cues prompting Go or NoGo responses were presented for 350 ms, or no visual cue. For visually warned, aurally prompted trials, the same format was utilized. The regions with the effect of warning and Go cue were depicted with general lineal model.

RESULTS

Both auditory and visual warning cues shortened the reaction time in the Go trials. Irrespective of the modalities, warning cue activated the pre-SMA extending to the SMA, the bilateral dorsal premotor cortex (PMd), the left M1, the right temporo-parietal junction (TPJ), the right ventral premotor cortex (PMv), the right pars opercularis, the right superior parietal lobule (SPL), including intraparietal sulcus (IPS), and the left cerebellum. Within the warning-related areas, go related activation was observed in the left M1 extending to the PMd, indicating that warning cue activated the motor system including M1. Go-with-warning response was significantly less prominent than Go-without-warning in the pre-SMA, indicating that attentional and motor system are overlapped in the pre-SMA. The warning related activation of M1 and pre-SMA, and SMA proper was equivalent to the differences between the Go-with-warning response and Go-without-warning one, consistent with the motor action limit theory.

DISCUSSION

Present study showed that the warning cue activated the right lateralized attentional system and the premotor cortices extending to the left M1. Considering the previous electrophysiological studies (Davranche et al. 2007), this indicates that the latter is related to site effect, whereas the former to the source effect of the attention (Corbetta, 1998).

The SPL is a part of a dorsal frontoparietal network that controls the top-down distribution of visual attention (Corbetta and Shulman, 2008), that generate attentional sets, or goal-directed stimulus-response mapping. The right TPJ and right lateral frontal cortex form a ventral frontoparietal network important for stimulus-driven bottom-up shifts of attention. Thus these right lateralized areas are related to the warning cue related task-set (Dosenbach et al. 2006).

Pre-SMA showed significant unwarning vs. warning signal related activation. This is related to some motor programming after onset of the response signals of unwarned trials (Hackley and Valle-Inclan 2003). The pre-SMA is not a typical motor area; its function is related to attention required during cognitively demanding tasks (Akkal et al. 2007). Concordant with this notion, the pre-SMA was active during foreperiod when warning cue was given. Furthermore, both Go and no go signals with preceding warning cue elicited less activation compared to those without warning. This is consistent with the role of the pre-SMA for preparation and selection of the movement that is influenced by the top-down attentional modulation.

On the other hand, left PMd and M1 showed Go specific activation that were potentiated by the warning cue. This is consistent with the motor action limit theory in that a neutral WS speeds up RT by lowering the threshold of response so that it can be reached more readily, and with the electrophysiological studies 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 warning signal enhanced excitability of the M1 by means of shortening of the silent period. They interpreted that the subjects attempted to adjust neural activation close to the motor action limit when they expect the stimulus (Davranche et al. 2007).

The Go-specificity of the warning related M1 activation may be related to the pre-SMA. The pre-SMA and M1 are known to be functionally connected during motor control. An electrophysiological study of normal volunteers using paired pulse TMS technique, Mars et al. (2009) showed that the pre-SMA influenced the MEP of the M1 at a short latency of 6 ms during action selection under conflict. The authors interpreted this finding representing a process of action re-programming. In the present study, with no-go signal, pre-SMA might suppress the response of M1.

These findings indicate that the warning effect is represented by the top-down attentional modulation on the motor systems that include the M1, SMA proper, and the pre-SMA, in last of which the linkage between attentional and motor systems may take place through movement preparation (decision of Go or noGo). Thus the warning effect is represented as the pre-potentiation of the pathway of motor control from the selection and preparation of the movement to its execution.

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博士論文の審査結果の要旨

ある刺激に反応する際、先行する刺激があると反応速度が増加する。この現象を予告効果(warning effect)と呼ぶ。予告効果にはTop-down attentionと呼ばれる、目的や予期に基づいて感覚刺激の選択を行って適切な運動反応へ結びつけることに関わる注意が関与している。一方、先行する予告刺激が一次運動野の興奮性を予め高めることにより、標的刺激に反応するための神経活動がより少なくすみ、その結果反応時間の短縮することが、電気生理学的実験から知られている(motor action limit theory)。しかしながら、注意がどの脳領域に影響を与えて反応時間短縮に関与しているのかは不明であった。

脳機能画像法を用いた先行研究では、Top-down attention の関係する脳領域には、注意の配分に係わる(source effect)領域と、その影響を受ける(site effect)領域が想定されており、前者は主に右半球に分布し、後者は遂行課題に依存することが知られている。このことから、出願者は、予告刺激が Top-down attention を惹起し、これが運動領域に site effect をもたらすとの仮説をたてて、機能的 MRI 実験を行った。被験者 19 名を対象に、予告がある条件とない条件の Go/NoGo 課題遂行中の脳活動を計測した。被験者には、Go を意味する標的刺激が現れた際にはできるだけ早く右手親指のボタンを押し、NoGo を意味する標的刺激が現れた際には、ボタンを押さないとように教示した。感覚入力のモダリティに依存しない予告効果に関わる神経基盤を特定するため、聴覚と視覚の 2 種類の刺激課題を同一の被験者に行ってもらった。即ち視覚性予告刺激に聴覚性標的刺激を組み合わせた条件と、その逆の条件を用意した。

感覚入力のモダリティに関わらず、予告刺激は反応時間を短縮した。予想どおりに、予告刺激によって、右頭頂間溝~上頭頂小葉、右側頭-頭頂接合部、右腹側~背側運動前野、左背側運動前野~一次運動野、前補足運動野に活動がみられた。一次運動野と前補足運動野における予告刺激による脳賦活は、予告刺激がなかった場合の Go 刺激による脳賦活とあった場合の脳賦活の差と強い正相関を示した。このことは一次運動野と前補足運動野が、motor action limit theory に適合する形で top-down attention の source effect を受けていることを示している。一次運動野は Go 特異的な反応をしめし、前補足運動野は Go, NoGo のいずれにも反応したことから、前者は運動の実行に関与しており、後者は運動選択に関与していると考えられる。以上の所見により、予告効果は、これらの運動関連領域が、予告刺激により、主に右大脳半球に分布する top-down attention システムを介して、事前に賦活されることで引き起こされると結論した。

上記の成果は、warning effect の神経機構について、その基盤となる知見を与えるものであり、新規性が高く、研究としての完成度も高い。従って本論文は学位に値すると認める。