氏　　名	谷中　久和
学位（専攻分野）	博士（理学）
学位記番号	総研大 1300 号
学位授与の日付	平成２１年９月３０日
学位授与の要件	生命科学研究科　生理科学専攻 学位規則第６条第１項該当
学位論文題目	Neural substrates of warning effect: a functional MRI study
論文審査委員	主　査　教授　伊佐　正 教授　南部　篤 教授　岡沢　秀彦（福井大学） 教授　定藤　規弘

論文内容の要旨

Introduction

Motor response reaction times towards a target decrease when presentation is preceded by a stimulus indicating that the target will appear shortly (warning stimulus). This decrement of reaction times is called as 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).

Previous behavioral, electrophysiological and neuroimaging studies have suggested that the warning effect triggers the phasic alertness and the facilitation of the early stage of motor processing (Hackley and Valle-Inclán, 2003; Raz and Buhle, 2006; Kinomura et al., 1996).

In terms of the alertness, previous imaging studies have suggested that tonic (intrinsic) alerting networks include the midbrain-thalamic-anterior cingulated cortex (ACC) system irrespective of stimulus modality (Kinomura et al., 1996; Paus et al., 1997). Previous studies have also implied that the phasic alerting network includes the midbrain-thalamic-ACC system (Fan et al., 2005), but it's unknown whether this system is active irrespective of stimulus modality in not only tonic but also phasic alertness.

To clarify this point, he used functional magnetic resonance imaging (fMRI) to depict the neural substrates of this warning effect during visual and auditory Go/NoGo tasks incorporating warning stimuli. He hypothesized that the warning stimuli activate the midbrain-thalamic-ACC alertness system irrespective of stimulus modality, and the areas which are related to early stage of motor processing such as pre-supplementary motor area (pre-SMA).

Methods

Fifteen subjects completed a visual Go/NoGo task, and 12 completed an analogous task in the auditory modality. After a variable-duration warning stimulus was presented, a Go or NoGo cue was presented with equal probability. When a Go cue was presented, subjects had to respond as rapidly as possible by pressing a button. When a NoGo cue was presented, subjects were required not to respond. All images were acquired using a 3T MR scanner and analyzed using statistic parametric mapping (SPM5). After the preprocessing of the data, he conducted following analyses: (1) the delineation of the areas that were related to the onset of the warning period, (2) the comparison of Go-NoGo, (3) the parametric modulation of warning condition using the reaction time of successive Go trial to obtain the warning related activation correlated with these reaction times (4) the comparison of divided warning conditions which were grouped by the reaction time of successive Go trials.

Because present fMRI experiments did not include a control condition without warning stimuli due to the time limitation, it is unclear whether the warning effect was exerted during the scan session. To confirm this point, additional 24 subjects of other group participated the preliminary psychological testing which examined the difference of reaction time between the task with warning stimuli and without warning stimuli. These tasks were identical to the Go/NoGo task during the fMRI scan session, except for the presence or absence of warning stimuli.

Results and Discussion

Preliminary psychological testing showed that the task with warning stimuli revealed faster reaction time than the task without warning stimuli. This confirms the warning effect was exerted during scan session.

For fMRI experiment, visual and auditory warning stimuli commonly activated the midbrain, thalamus and ACC. These areas are known to be activated by tonic alertness task (Kinomura et al., 1996; Paus et al., 1997) and unimodal phasic alertness task (Fan et al., 2005). Furthermore, ACC and thalamus revealed the activity which was negatively associated with reaction time of successive Go trial. This result also confirms the exertion of warning effects during fMRI experiment.

Visual and auditory warning stimuli also activated the pre-SMA which is associated with movement selection and preparation (Matsuzaka et al 1992). Additionally, the activation pattern was quite different warning condition from Go-NoGo comparison which indicates the activity of movement execution. These results are consistent with the view in which warning stimuli facilitate the early stage of motor processing (Hackley and Valle-Inclán, 2003). Thus present results support his hypothesis that the warning stimuli activate the midbrain-thalamic-ACC alertness system irrespective of stimulus modality, and the areas which are related to early stage of motor processing such as pre-supplementary motor area (pre-SMA).

Conclusion

Warning stimuli might potentiate pre-SMA activity related to movement selection and/or preparation, through the midbrain–thalamus–ACC alerting system.

References

Fan et al., (2005) Neuroimage 26: 471-479
Hackley and Valle-Inclán. (2003) Biol Psychol 64: 27-45.
Kinomura et al. (1996) Science 271: 512-515.
Matsuzaka et al., (1992) J Neurophysiol. 68: 653-662
Paus et al., (1997) J Cogn Neurosci. 9: 392-408
Raz and Buhle. (2006) Nat Rev Neurosci 4: 367-379.

博士論文の審査結果の要旨

課題においてあるターゲットに反応しなければならない時、ターゲットに先立った刺激（warning 刺激）がある時のほうがない時に比べて早く反応できる（warning 効果）。warning 効果は注意の基本的な形の１つである一過性 alertness と運動処理の初期段階の増進を引き起こすことが調べられてきた。しかし、warning 刺激に関連した活動が一過性 alertness による活動なのか感覚刺激に依存した活動なのか不明瞭なままである。

そこで出願者らは感覚刺激の種類に依存しない warning 効果の神経基盤について検討することを目的として、warning 刺激が感覚刺激の種類に依存せず中脳-視床-前帯状皮質 alertness システムと前補足運動野といった運動処理の初期段階に関連した領域を活動させるという仮説を立て、２７名の右利き健常成人を対象に機能的 MRI 実験を行った。

課題には Go/NoGo 課題と warning 刺激を組み合わせたものを用い、視覚性の課題と聴覚性の課題を導入した。本研究ではまず感覚刺激に依存しない warning 関連領域、運動実行（Go-NoGo コントラスト）に関連する領域を描出した。さらに、warning 関連領域内において、直後の Go 試行の反応時間が比較的短かった warning 条件と長かった warning 条件の比較を行った。

機能的 MRI 実験の結果では、視覚と聴覚の warning 刺激は共通して中脳、視床と前帯状皮質を活動させた。この結果は、一過性 alertness において感覚刺激に依存せずこれらの領域が活動することを示唆する。また、視床と前帯状皮質では直後の Go 試行の反応時間が比較的短かった warning 条件のほうが長かった warning 条件よりも大きな活動を示した。このことは warning 刺激が一過性 alertness のシステムを通じて反応時間を短くすることを示唆する。

また、視覚と聴覚の warning 刺激は前補足運動野を活動させた。さらに、今回活動した warning 関連領域と運動実行に関連する領域は異なったパターンの活動領域を示した。これらの結果は warning 刺激が運動処理の初期段階を増進するという知見に一致する。

従って、warning 刺激は中脳 - 視床 - 前帯状皮質の alertness system を通じて運動の準備のための前補足運動野を活動させる、と結論付けられた。

以上、本研究の結果は、視覚と聴覚の warning 効果の中枢神経機構を明らかにした画期的な研究成果である。実験方法は適切に考えられ、導かれている結論も妥当であり、それらは明快かつ平易な英語で記載されている。これらのことから本論文は、学位論文として十分にふさわしい内容であるものと結論された。