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学位論文題目	Asymmetric control mechanisms of bimanual coordination: an application of directed connectivity analysis to kinematic and functional MRI data
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The asymmetric control mechanisms of bimanual coordination were elucidated in the study. Significance of this study was to apply the directed connectivity analysis to kinematic and functional MRI data; the interaction between two hands and related neural foci, i.e., interhemispheric interaction, might not be depicted by the increment of the neural activity; it should be revealed by the connectivity analysis.

Bimanual movement in mirror-symmetrical mode in which homologous muscles are active simultaneously, is more stable than that in parallel mode, in which homologous muscles are engaged in an alternating fashion. This is well established at the kinematic level, however, neural substrates related the stability has not been revealed yet. She used functional MRI (fMRI) to evaluate the neural substrates of the stability of mirror-symmetrical bimanual movement.

As to the connectivity analysis, she adopted statistical time-series analysis of multivariate autoregressive (MAR) model; the MAR model represents a general statistical time-series model that propagates information from the past to the future. With regard to the causality analysis, the Akaike causality model was applied to both kinematic and fMRI time-series data; the Akaike noise-contribution ratio (NCR) quantifies the portion of the power-spectral density of an observed variable from the independent noise of the MAR, which becomes a measure of causality among variables. It allows interpretation of the causality from one hand to the other, or from the motor cortex of one hemisphere to the other. In her study, the noise-contribution ratio (NCR) was computed using a multivariate autoregressive model with latent variables, as a direct measure of the influence between both the two hands and the bilateral primary motor cortices (M1s). Thus, the influence of one hand to the other hand can be quantified by the causality that is represented by the NCR.

As for the task of bimanual coordination, she adapted the disk rotating task in continuous movement, instead of a discrete movement task, such as tapping, as continuous kinematic data are more easily handled by the multivariate autoregressive (MAR) model of time-series analysis. She hypothesized that kinematic stability is represented by the extent of neural the asymmetric NCR from the left M1 to the right M1, which, in turn, brings the asymmetric NCR from the right hand to the left hand during mirror-symmetrical movement more prominently than during parallel movement.

The standard deviation of the phase difference for the mirror mode was significantly smaller than that for the parallel mode, confirming that the former was more stable. The mode-by-direction interaction of the NCR was significant in both the kinematic and fMRI data. Furthermore, in both sets of data, the NCR from the right hand to the left was more prominent than vice versa during the mirror-symmetrical mode, whereas no difference was observed during parallel movement or rest. The asymmetric

interhemispheric interaction from the left M1 to the right M1 during symmetric bimanual movement might contribute to the stability of symmetric bimanual movements.

Previous physiological studies using paired transcranial magnetic stimulation (TMS) have provided evidence that the motor cortex has clear interhemispheric facilitatory effects and inhibitory effects, probably working via the corpus callosum. Whereas trans-callosal inhibition seems to play a crucial role in suppressing the mirror-symmetrical activation of the ipsilateral motor cortex during intended unilateral hand motor tasks, the functional significance of this facilitatory effect is unknown, particularly during bimanual movement. However, the present findings and the unstable bimanual coordination in callosotomy patients raise the possibility that cortico-cortical interference from the dominant hemisphere occurs in the non-dominant M1 during bimanual mirror-symmetrical movement.

In the model adapted in her study, the motor areas higher than M1 were not involved, and considering the low time resolution of fMRI data, the interhemispheric interaction between the right and left M1 regions during mirror-symmetrical movement might be mediated indirectly by areas involved in higher motor functions, such as the supplementary motor areas (SMA) and the dorsal premotor areas (PMd), in addition to the possible direct interaction between the bilateral M1s. The roles of direct and indirect pathways are still controversial. Previous studies adapting diffusion-tensor imaging (DTI) fiber-tracking procedure or TMS have provided the corroborative evidences of direct pathways. On the other hand, another study revealed significance of anterior portion of corpus callosum for coordination of symmetric bimanual movement. The evaluation of effective connectivity will contribute to the understanding of the mechanisms of bimanual coordination, in both normal and pathological conditions.

論文の審査結果の要旨

日常生活動作の多くは両手の協調を要する。この両手協調運動の基礎的な要素は両手周期運動を用いて調べられてきた。両手周期運動の基本的な運動モードとして、同名筋が同時に活動する対称運動と、拮抗筋が同時に活動する非対称運動が挙げられる。また、両手運動の基礎的要素として、対称運動は非対称運動に比べて位相の安定性が高いことが知られている。この位相安定性には、第一次運動野（M1）より上位の、皮質レベルの脳梁を介する半球間相互作用（higher cortical level crosstalk）及び、M1 より下位の皮質下レベルの相互作用（lower subcortical level crosstalk）による、鏡像反転した信号の伝達が関連していると考えられている（多段階 crosstalk 説）。後者に関して、皮質脊髄路を介して伝達される信号が、位相安定性に関連していることが実験で示されている。しかし、前者の大脳半球間の相互作用の関与に関しては未解明である。そこで、脳梁を介する半球間相互作用として、優位側から非優位側への影響度は、位相安定性の安定性に相関するという仮説に基づいて、17 人の健常被験者を対象に機能的 MRI を用いた実験を行った。

課題として両手周期運動である円運動(circle drawing)を用い、対称運動・非対称運動課題を設定した。影響度は、両手の軌跡、および機能的 MRI の信号の時系列データに対して、同じ多変量自己相関解析モデルを適用して解析を行った。なお、大脳半球間の相互作用は、皮質・皮質下レベル crosstalk の交点である両側 M1 の信号に焦点化して解析を行った。

今回の実験でも、対称運動時には、非対称運動に比べてより位相が安定していることが確認された。

両側の関連性に関しては、運動・機能的 MRI データともに、対称運動時に優位側から非優位側への影響度が大きくなることが観察され、非対称運動時には当差異は検出されなかった。位相安定性と優位側から非優位側への影響度とは、対称運動時の MRI データにのみ相関が観察された。

この実験の限界として、両側 M1 の信号のみを解析対象とした点が挙げられる。両手協調運動には M1 より上位の運動野、特に、補足運動野・右側運動前野が関連することが先行研究より示されている。そこで、補足運動野・運動前野を包含した解析をすることが今後の課題として残されていると考える。

以上より、今回の実験で両手協調運動時の対称運動の位相の安定性には、脳梁を介する優位側 M1 から非優位側 M1 への影響度が関連していることが示された。

学位論文の内容の一部は、既に申請者が第 1 著者としてまとめ、英文原著論文として発表した。研究内容は非常にすぐれており、国際的にも高いレベルであると、審査委員全員が判断した。