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Evaluation of the effective connectivity of the dominant primary motor cortex during bimanual movement using Granger causality

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ABSTRACT

Granger causality analysis of the whole brain, voxel-by-voxel, was applied to six right-handed subjects performing a classic bimanual movement, to describe the effective connectivity between the activated voxels in the left primary motor cortex (PMC) and other parts of the brain, by choosing the left PMC as a reference region. The results demonstrated that the left and right PMC interact during bimanual movement, and Granger causality mapping implied a possible cause–effect relationship. The supplementary motor area (SMA) and cerebellum were pre-activated during bimanual movement relative to the left PMC, confirming the prior qualitative results concerning the functions of the SMA and cerebellum in hand movements.

Functional MRI is widely used in neuroscience research to detect activated brain areas and the connectivity among these areas during cognitive tasks [9] have defined two types of functional integration of different brain areas: one is functional connectivity, which investigates the correlation between measured time courses; the other is effective connectivity, which is defined as the influence one neuronal system exerts over another. Effective connectivity research has become increasingly important, because it can provide information about the cause–effect relationships between different brain areas. Many methodological advances have been made that detect the effective connectivity between brain areas, such as covariance structural equation modeling [6], nonlinear system identification techniques [10], Bayesian estimation of deterministic state-space models [11], and time-invariant [13,23] and time-varying Granger causality mapping (GCM) [25].

Granger causality, which was brought forward and formalized by Granger [14,15], is an important approach to explore the dynamic causal relationships between two time series [29]. Granger's concept of causality has received a great deal of attention and has been applied widely in the econometrics literature [19]. With the assumption that the hemodynamic response function (HRF) is the same throughout the whole brain, it can also detect effective connectivity in the field of cognitive neuroscience by its predictive power. In recent years, Granger causality has begun to be used to detect the effective connectivity based on electroencephalography (EEG) or magnetoencephalography (MEG) data, because of their high temporal resolution [2,5,19]. Prior research has also focused on applying Granger causality analysis to fMRI data due to its high spatial resolution [23,29]. Using vector autoregressive modeling of fMRI time courses, Granger causality analysis linearly quantifies direct, indirect and instantaneous influences among a reference region and other brain regions [13,23]. According to whether the coefficients of the vector autoregressive model are time independent or time dependent, there are two different approaches for GCM, called time-invariant [13,23] and time-varying GCM [25]. Although there are different assumptions about information flow over time between the two methods (time-invariant GCM [13,23] provides only one connectivity structure for the entire experiment, whereas, time-varying GCM [25] provides different structures for each time point), the philosophies of time-invariant [13,23] and time-varying GCM [25] are similar, in that both approaches delineate the interregional connectivity in fMRI data and detect the direction of information flow between brain regions.

When considering hand movements, fMRI studies have so far quantitatively verified the results from prior neurophysiological studies, which considered the relationship between the primary motor cortex (PMC) and other parts of the brain in right-handed subjects. During self-paced finger tapping movements, the signal change in PMC was predicted by the previous changes in that signal itself, and was influenced by the supplementary motor area (SMA) and the anterior precuneus (ApC) [25]. Strong Granger causality between voxels of the left motor cortex and the SMA was also

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found in experiments using right-hand tapping movements [29]. However, the sub-cortical structures, which also have an important effect on hand movements, have not been studied together with the cortices so far.

In the present study, we used Granger causality analysis to explore effective connectivity during bimanual movements in six right-handed subjects to detect the cause–effect relationship of the dominant left PMC with other parts of the brain. To obtain an effective balance of complexity and interpretability, we used time-invariant GCM [13,23] to explore the effective connectivity. The reference region for the mapping was defined as the contralateral primary motor cortex corresponding to the dominant hand. Empirical probability density corresponding to an empirical null distribution was calculated from the resulting data to assess the statistical significance.

The present study was approved by the local ethical committees, and informed written consent was obtained from all subjects. Six right-handed subjects (three females) participated in the study. All subjects were healthy, with no history of psychiatric or neurological illness. Subjects age ranged from 18 to 26 years (mean age, 21 years). Handedness was evaluated by the Edinburgh Handedness Inventory (EHI) [22]. The average score on the Edinburgh inventory was 91.67, with a standard deviation of 7.53.

Functional image data were acquired on a 3.0-T GE scanner (EXCITE, General Electric, Milwaukee, USA) using a GRE-EPI sequence (TR = 2 s, TE = 30 ms, flip angle = 90°, field of view = 24 cm × 24 cm, matrix size = 64 × 64, voxel size = 3.75 mm × 3.75 mm × 5 mm).

The subjects were trained to grip their hands with a frequency of 1 Hz before the scan. In the scanner, visual stimuli were computer-generated by E-prime (www.pstnet.com/e-prime) [26], and projected onto an opaque screen located in front of the subject's head. The subjects viewed the screen through a 45° plane mirror with corrective lenses, if necessary. The current experiment followed a block designed paradigm. The subjects were instructed to grip both hands simultaneously by the presence of a stationary cross on the center of the screen throughout the task periods, and to remain still and fixate by the presence of a stationary asterisk throughout the resting periods. Each run consisted of 5.5 blocks of a gripping condition alternating with a resting period, starting with a resting period for scanner calibration and for the subjects to get used to the circumstances. The gripping condition and resting periods lasted 20 s each, and each consisted of 10 images.

The first 10 time points of the resting period were discarded before data processing, leaving five blocks of 100 time points for analysis. The functional image data were preprocessed, and analyzed using the SPM2 software package (www.fil.iom.ucl.uk/spm). All remaining images were realigned onto the first image in the series to correct for rotation and translation of the participant's head movements during the scanning session. Spatial normalization and smoothing were performed only before group analysis, allowing more precise localization on an individual basis.

Using the *t*-test statistical method ($p < 0.01$, corrected for the family-wise error of the SPM2 to test for the main effect of movement, the activated areas in the whole brain were highlighted. In this study, the region of interest (ROI) was defined as a sphere within the activated area located in the contralateral PMC corresponding to the dominant hand (right hand), centered at the voxel of the highest statistical value and with a radius of 10 mm. Then, the seed x was defined as the average signal of all activated voxels within such a ROI.

Time series x denotes the seed in reference region, and time series y denotes other voxels of the brain. Granger causality was used to describe the effective connectivity of the activated voxels. It can evaluate the three components: the linear direct influence of time series x on time series y ($F_{x\to y}$), the linear direct influence of time series y on time series x ($F_{y\to x}$), and the instantaneous indirect influence between time series x and time series y ($F_{x\cdot y}$).

Based on the methods of [13], the three components of Granger causality were calculated voxel-by-voxel separately for each subject. Subsequently, in order to extend the inference of individual statistical analyses to the general population from which the subjects were drawn, a group analysis was performed [17]. Spatially normalized into standard stereotaxic space at 2 mm × 2 mm × 2 mm; then spatially smoothed by Gaussian kernel (FWHM = 8 mm).

To assess the significance of Granger causality, at the group-level, we used empirical null distribution for non-parametric inference. The main steps were as follows: (1) the values of each of the three Granger causality components for each voxel of brain were pooled together and averaged across all subjects, to acquire the histogram of each component respectively, which are the reasonable empirical estimate under the assumption of large sample [27]. (2) The empirical null was estimated based on a normal kernel function [4]. Empirical null distribution is used because Granger methods are non-negative and we could not use theoretical null distributions such as one-sample *t*-test, which are based on a Gaussian distribution. The implicit exchangeability assumptions that underlie this procedure are that, under the null hypothesis, any voxel in the brain can be exchanged with any other. Although this is not strictly true (due to spatial dependencies in the data) it is a sufficient approximation for our purposes. (3) The thresholds for the three GCM maps were corrected by false discovery rate (FDR) [12] with $q = 0.05$, in light of previous studies [13,23].

The results of the activated area for one subject are shown in Fig. 1. The bilateral PMC, SMA, and cerebellum were activated during bimanual movement. An ROI in the left PMC (MNI coordinate: −36, −24 and 56) was chosen to accomplish effective connectivity assessment of the dominant PMC against the rest of the volume.

Granger causality maps for three components: $F_{x\to y}$, $F_{y\to x}$ and $F_{x\cdot y}$ were calculated by Matlab software (Mathworks, Inc., Natick, MA).

Fig. 2 depicts the histograms for $F_{x\to y}$, $F_{y\to x}$ and $F_{x\cdot y}$, along with the empirical probability density for each Granger causality component. The green marker in each image depicts the threshold of the statistical significance for each component.

Fig. 3 depicts the GCM of components $F_{x\to y}$, $F_{x\cdot y}$ and $F_{y\to x}$. The center of the ROI is shown by the red arrows in the glass brain picture (upper row, center). The left-most figure of the upper row demonstrates $F_{x\to y}$, in which a threshold value of 0.05 ($p < 0.002$) was selected. Statistically significantly interacting areas were obtained in the bilateral PMC. These results imply that the left PMC directly influences both itself and the right PMC. The right-most figure of the upper row demonstrates the GCM of component $F_{y\to x}$, which was created with a threshold of 0.08 ($p < 0.005$). The map of $F_{y\to x}$ shows the regions that directly influenced the reference region, namely, the ROI in the left PMC. Besides the bilateral PMC, it can be clearly observed that the SMA, vermis and cerebellum (9-R, 9-L) were statistically significant areas. In the SMA, most of the significantly interacting areas occurs on the left side. The lower row demonstrates the GCM of component $F_{x\cdot y}$, with a threshold of 0.1 ($p < 0.002$). The statistically significant area implied an instantaneous dependency relationship between the left PMC (the reference region) and the right PMC.

Table 1 shows a summary of the group analysis results for Granger causality. The coordinates of the center of the significantly interacting areas, along with the cluster size, are characterized in detail.

It is important to distinguish between Granger causality and true causality, particularly in the analysis of fMRI time-series [13,23].