# Validation of Resting State Interregional Connectivity Map via TMS/PET Map

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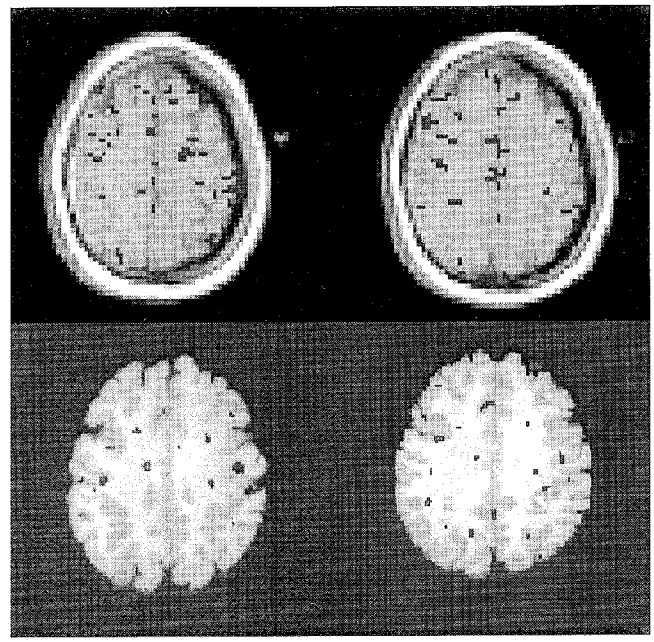
**Introduction:** Interregional connectivity within the human brain can be detected using covariance analysis of the resting-state MR images. The physiological basis of the detected co-activity is thought to be variation in the spontaneous firing of neurons during rest. Such neural firings will increase local blood flow, affect remotely located neurons in other brain areas, and result in BOLD signal fluctuations in an fMRI time course. By calculating the covariance of each voxel referenced to the time course of a selected brain region, the regions connected to the "seed" region can be detected. In this report, we made within-subject comparison of the interregional connectivity map revealed using covariance analysis of resting-state MR images to that using the combination of transcranial magnetic stimulation (TMS) and positron emission tomography (PET). TMS produces focal blood flow increases at the site of stimulation and at distant sites anatomically connected to the stimulated location. In the present validation, we compared the maps produced by each paradigm with respect to areas projecting to the supplementary motor area (SMA).

**Method**: Subjects participated in first in the fMRI study and then the TMS/PET experiments. In the fMRI study, a simple right hand movement task (i.e., the full opening and closing to a fist) was performed to define location of SMA. During rest, subjects were motionless, had their eyes closed, and were instructed to perform no cognitive/psychological task. MRI experiments were performed on an Elscint Prestige whole-body MRI scanner (Elscint Ltd., Haifa, Israel) operating at 1.9 T. Seven continuous 6 mm, fMRI slices were acquired in a transverse plane using a T2*-weighted gradient-echo EPI pulse sequence with TR / TE / flip-angle = 1000 ms / 45 ms / 70°. A total of 754 images per slice were acquired, with the first half of the images being acquired in the resting condition and the rest images being acquired in the task condition. The fMRI data were then analyzed with a clustered-pixels analysis procedure using both intensity and cluster size thresholds to detect significant activation using the images acquired at both the resting and task conditions. An ROI enclosing the region in SMA activated by the hand movement task was defined by a group t-test. The time course of the ROI for the resting condition was used as a reference function for cross-correlation analysis to reveal inter-regional connectivity, using only the images acquired at the resting state. Any cluster with correlation coefficient larger than 0.4 and cluster size larger than eight was considered significant ($P < 0.01$).

In the TMS/PET experiment, SMA was stimulated using TMS. The location of SMA for each subject was defined by the fMRI experiment. PET data were acquired during the resting state, both prior to TMS stimulation and immediately following TMS stimulation. PET images were acquired via a GE/Scanditronix 4096 camera simultaneously in 15 parallel slices with a center-center interslice distance of 6.5 mm and a transaxial field of view of 10.5 cm. Water labeled with oxygen-15 ($H_2{}^{15}O$, half-life 122 sec) was used as a blood-flow tracer. A group t-test ($P < 0.05$) was performed to detect the difference between the stimulated and non-stimulated states.

**Results:** The connectivity map of the covariance analysis of the resting state MR images was very similar to that of the TMS/PET. In the resting fMRI images, several areas covaried with activation in the ROI enclosing the left SMA (see upper panel). These cortical areas were primary motor, primary somatosensory, dorsolateral premotor, anterior cingulate, dorsolateral prefrontal areas (superior frontal gyrus, Brodmann Area 8), and superior parietal (precuneous, BA 7). The same set of areas were activated in the TMS/PET data with the stimulated left SMA (see lower panel).



**Discussion:** The inter-regional connectivity detected using the covariance analysis of the resting state MR images is very similar to that produced by TMS/PET. The connectivity produced by TMS/PET is assumed to be similar to that produced by direct cortical stimulation and is assumed to detect true connections of cortical regions. Resting state fMRI connectivity, like TMS/PET connectivity, is acquired without influence of a psychological task. Such task-free connectivity maps are more likely to give true anatomical connectivity as distinguished from "functional" or "effective" connectivity. Thus, these findings further confirm that covariance analysis of the resting state MR images is a useful tool for investigating the topographic organization and projections of cortical neurons.

1. Biswal et al. MRM 34: 537-541, 1995.
2. Xiong et al. Human Brain Mapping 3: 287-301, 1995
3. Xiong et al. ISMRM: 1480, 1998.
4. Fox et al. Neuroreport 8: 2787-2791, 1997.