Studying Functional Connectivity Strength between the Primary Motor Cortex (PMC) and the Supplementary Motor Area (SMA) in Brain Tumor Patients Using Resting State BOLD fMRI

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Introduction: Low frequency BOLD fMRI signal intensity during resting state has been used both in healthy (1) and clinical populations (2) to map functionally related regions of the brain. For example, resting state fMRI revealed a sensorimotor network in healthy controls (3) and in patients with brain tumors (4). We hypothesized that the connectivity between primary motor cortex (PMC) and supplementary motor area (SMA) can be affected by brain tumors. Such changes would include the connectivity pattern (3 and 4) and the connectivity stength. In the current study, for the first time, we present results of connectivity strength between PMC and SMA for patients with brain tumors.

Materials and Methods: 8 patients (3 glioblastoma multiform(GBM, grade 4), 2 metastases, 2 anaplastic astrocytoma (grade 3), and 1 oligodendroglioma (grade 2)) with a mean age of 50 years and standard deviation (SD) of 7.2 years, and 8 healthy volunteers (mean age 46 years and SD 5.2 years) participated in this study. All subjects were scanned using a 1.5 T or a 3.0 T General Electric (GE) scanner with a standard quadrature head coil. The protocol included high resolution T2 or T1-weighted spin echo images, followed by data acquisitions from no-task eyes-closed brain resting state and the BOLD fMRI with bilateral finger tapping using a gradient echo EPI with TR/TE =4000 (or 2000) /40 msec. The fMRI maps were generated from AFNI by using correlation coefficients to threshold the activation volumes of the PMCs and the SMA. Resting state functional connectivity analysis was performed on the resting data, which were first temporally band-pass filtered (0.01 Hz < f < 0.08Hz) to avoid the effects of the respiration and cardiac cycles. Two seed areas in the resting data were selected based on the activation volumes of the PMCs and SMAs identified by the bilateral finger tapping response of each subject. In each seed area, one mean time courses was generated and used as a reference vector, and then correlated with every voxel in the brain. The connectivity map was obtained from the correlation coefficients by selecting a threshold of r > 0.35 that corresponded to a significance level of p < 0.05. Relative connectivity strength between SMA and PMCs was calculated by the ratio SMA(mean signal change in the SMA)/PMC(mean signal change in the PMC). A paired two tailed t-test was used to compare the connectivity strength of the normal and the tumor groups. A $P < 0.05$ was set for the significant threshold of the fMRI and the t-test.

Results: Figures 1 and 2 show the fMRI maps from the bilateral finger tapping (a), the SMA and the PMC connectivity maps form the analysis by using the seed in the PMCs (b), the SMA and the PMC connectivity maps form the analysis by using the seed in the SMA (c) for a normal brain (Fig 1, the first row) and a brain with GBM in the right frontal lobe (Fig 2, the second row). The mean signal changes and the SDs for SMA, PMCs, and SMA/PMCs of the 8 healthy controls and the means and the SDs for SMA,PMC(T) (PMC in tumor side), PMC(NT) (PMC in non tumor side), SMA/ PMC(T), and SMA/ PMC(NT) of the 8 patients with the brain tumors by applying the PMC or the SMA seed were listed in the Table 1. The P values, dertemined by the t-test for the SMA/PMCs ratios of the healthy control and the patient groups, were also included in the table. Accordingly, the overall mean ratios for the SMAs and PMCs were 0.51 and 0.83 for the healthy controls and the patients, respectively.

Discussions: Resting state functional connectivity between PMC and SMA was observed in all of the subjects, both healthy and tumor patients. Representative images are shown in (b) and (c) of the figures 1 and 2, which means if a SMA or a PMCs seed was selected, the corresponding PMCs or the corresponding SMAs was found to be correlated (i.e., connected), respectively. Results from the brain tumor patients demonstrated that there was a connection between the PMC and SMA irrespective of tumor type and distance between the cortices to the tumor. One recent study (5) by using MEG found brain tumors induce a loss of functional connectivity that affects multiple brain regions, and that left side brain tumors have the more severe consequences in this respect. The overall means of the SMA /PMCs for the healthy and the tumor groups and the means of the PMCs and SMAs expose the tumors reduce the signals in the PMCs meanwhile increase the signals in the SMAs (Table 1). These P values in the table suggest the SMA/PMCs for the healthy are significantly smaller than the ratios for the patients with the brain tumors. As resting state connectivity of SMA and PMCs may result from the low frequency fluctuations of the local blood flow (3) and the respiratory-variation (6), the tumors seem to increase the amplitudes of these low frequency fluctuations in SMA while decreases the amplitiude of these fluctuations in PMCs, but may not change the frequencies of the fluctuations.

References: 1. Hampson, M, Hum brain Mapp, 2002, 15:247-262. 2. Greicius M, Curr Opin Neurol, 2008, 21:424-430. 3. Biswal, B, MRM, 1995, 34:537-541. 4. Quigley M, AJNR, 2001, 22:294-330. 5. Bartolomei F, Ann Neurol, 2006, 59:128-138. 6. Birn, RM, NeuroImage, 2006, 1536-1548.

a)   (b)   (c)
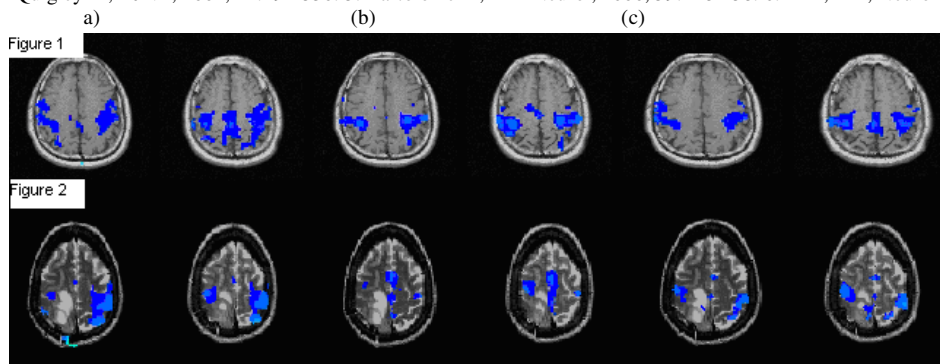
Figures 1 and 2: the fMRI maps (a), the SMA and the PMC connectivity maps from the seed in the PMCs (b), the SMA and the PMC connectivity maps form the seed in the SMA (c) for a normal brain (Fig 1, first row) and a brain with GBM (Fig 2, second row).

Table 1: means and SDs of the following parameters for the PMC or SMA seed in the brains of the healthy controls or the patients, & P (SMA/PMCs) for the groups.

	PMC seed			SMA seed		
Brains in healthy controls	PMCs	SMA	SMA/PMCs	PMCs	SMA	SMA/PMCs
mean±SD	2.47±0.67	1.18±0.30	0.48±0.08	1.77±0.44	0.94±0.27	0.53±0.10
Brains w/ tumors	PMC(T), PMC(NT)	SMA	SMA/PMC(T), SMA/PMC(NT)	PMC(T), PMC(NT)	SMA	SMA/PMC(T), SMA/PMC(NT)
mean±SD	1.60±0.38,1.92±0.54	1.31±0.33	0.81±0.16,0.68±0.11	1.49±0.35,1.62±0.41	1.43±0.32	0.96±0.20,0.88±0.18
P (Healthy: Patient)			0.02, 0.04			0.01, 0.02