

Anatomical/Axonal Basis and Plasticity of Resting-state fMRI Connectivity in An Experimental Model of Corpus Callosum Transection

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INTRODUCTION Resting-state fMRI (rsfMRI) has been increasingly used in understanding brain functional organization and connectivity¹. However, the underlying mechanism of rsfMRI remains largely unexplained, hindering the specific interpretation of rsfMRI data in both normal and pathological states. Previous rsfMRI study reported the loss of interhemispheric rsfMRI connectivity in a single human subject after corpus callosum (CC) transection². Given the primary role of CC in interconnecting two hemispheres, we hypothesize that interhemispheric rsfMRI connectivity originates from the intrinsic neural communication mediated by axonal projections through CC. Manganese ion (Mn²⁺) as a calcium analog has been widely used to visualize functionally specific neuronal pathways *in vivo* due to the activity-dependent and axonal tract-tracing Mn²⁺ transport³. In this study, we investigated the role of anatomical/axonal connections in rsfMRI connectivity and the plasticity of rsfMRI connectivity. Animal models of complete and partial CC transection were examined by rsfMRI in conjunction with intracortical EEG recording and manganese-enhanced MRI (MEMRI) tracing of axonal connections.

METHODS Adult Sprague-Dawley rats (230–270g) underwent complete CC transection (N=10), posterior partial CC transection (N=10) and sham surgery (N=10), respectively. At day 7 and 28 after surgery, rsfMRI was conducted on rats under 1–1.5% isoflurane using a 7T Bruker scanner. rsfMRI data was acquired using single-shot GE-EPI with TR/TE=1000/18ms, FOV=32×32mm², 64×64 matrix and 9 contiguous 1-mm slices. All rsfMRI data was slice-timing corrected, co-registered, detrended and temporally band-pass filtered. rsfMRI connectivity of somatosensory cortex (S1) and visual cortex (VC) was examined using both independent component analysis (ICA) in GIFT and seed-based analysis. At day 30 after surgery, intracortical EEG recording was performed on 3–5 animals from each group under 1.2% isoflurane with electrodes placed bilaterally in both S1 (Bregma 0mm, lateral 3–3.5mm) and VC (Bregma -7.5mm, lateral 4mm). EEG signals were filtered at 0.1–100Hz and square rooted to obtain the power before correlation analysis. After EEG recording, MnCl₂ (100nL, 500mM) was injected intracortically to the right S1 and VC (where EEG recordings were made). MEMRI was performed 1 day later using T₁W MDEFT with TI/TR/TE=1100/12/4ms, isotropic resolution of 200μm, 4 segments and 4 averages.

RESULTS At post-surgery day 7, interhemispheric connectivity seen in S1 and VC of sham group (Fig.1c) was prominently absent in S1 and VC of complete transection group (Fig.1a) and in VC of posterior/partial transection group (Fig.1b). At day 28, the diminished interhemispheric connectivity was restored in partial transection (Fig.2b, right) but not in complete transection group (Fig.2a). Consistent findings were found using seed-based analysis (Fig.3). Persistent loss of interhemispheric connectivity after complete transection and restoration of VC connectivity after posterior partial transection were also observed in EEG recording (Fig.4). Moreover, increased intrahemispheric connectivity was found in both transection groups (Figs.2&4). Furthermore, the interhemispheric S1 and VC connections revealed by Mn²⁺ tracing in 3 groups at day 30 corresponded to the rsfMRI results (Fig.5).

DISCUSSION AND CONCLUSION CC is organized in a rostrocaudal topographical manner⁴. Primary callosal connections of S1 and VC were severed by complete CC transection while posterior partial transection disrupted callosal connections of VC. At day 7, interhemispheric rsfMRI connectivity significantly decreased in S1 and VC of complete and in VC of partial transection groups, indicating an indispensable role of anatomical/axonal connections via CC in rsfMRI connectivity. However, the disrupted connectivity in partial transection group was found to restore at day 28, which might result from the compensation that occurred in interhemispheric axonal pathways crossing the remaining intact CC since the restoration was not observed in complete transection group. These rsfMRI findings were also paralleled by the intracortical EEG results in this study. Similar to previous brain stroke study⁵, increased intrahemispheric connectivity was found after CC transection in this study, providing evidence for plasticity of resting-state networks. Moreover, interhemispheric transport of Mn²⁺ was not seen in areas exhibiting lost rsfMRI connectivity, but was observed in areas showing normal/restored connectivity, further pinpointing the primary role of axonal connections in resting-state connectivity. In conclusion, Our experimental findings here directly support that anatomical/axonal connections via CC play a primary and indispensable role in resting-state connectivity, and that anatomical connection based resting-state networks can be plastic.

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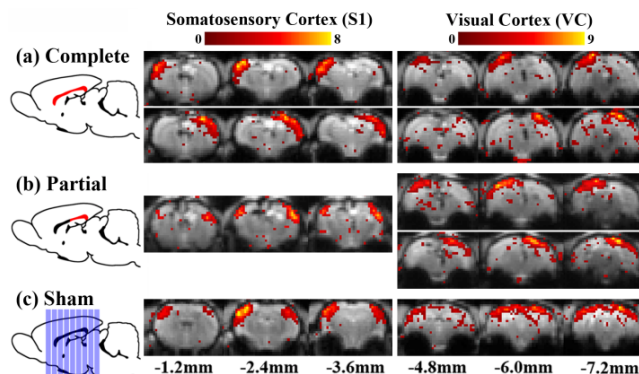


Fig. 1 Typical ICA maps from animals with complete (a), posterior partial (b) CC transection and sham surgery (c) at post-surgery day 7. Interhemispheric connectivity seen in S1 and VC of sham group was absent in S1 and VC of complete and in VC of posterior partial transection group after corresponding callosal connections were severed.

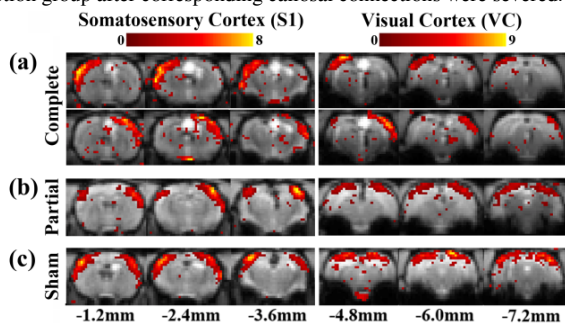


Fig. 2 Typical ICA maps from animals with complete (a), partial (b) CC transection and sham surgery (c) at post-surgery day 28. The diminished interhemispheric connectivity observed at post-surgery day 7 was restored in partial transection but not in complete transection group.

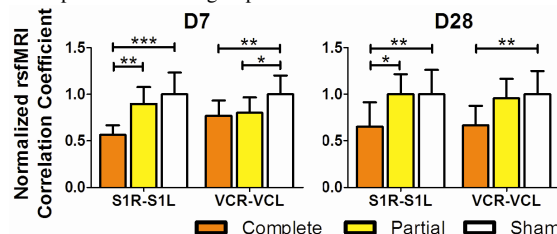


Fig. 3 Correlation coefficients of rsfMRI connectivity between right and left S1/VC (normalized to sham) at post-surgery day 7 and 28 from seed-based analysis showing consistent results with ICA findings. ANOVA, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$.

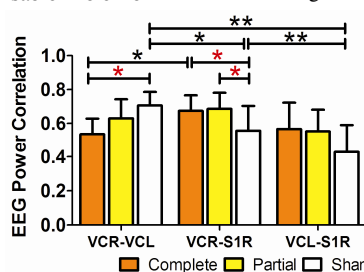


Fig. 4 Correlation analysis of wide-band power from intracortical EEG recording at post-surgery day 30. Interhemispheric correlation of VC (VCR-VCL) was significantly lower in complete transection group than that of sham. Increased intrahemispheric correlation (VCR-S1R) was found in both complete and partial transection groups. * $p < 0.05$, ** $p < 0.01$.

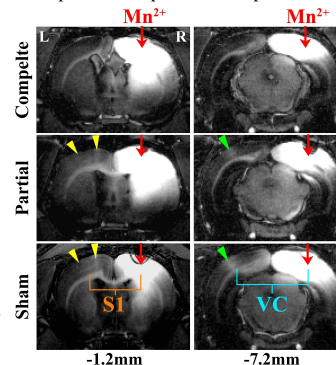


Fig. 5 Manganese-enhanced MRI at post-surgery day 30. Contralateral enhancement (arrowheads) indicated the normal/restored interhemispheric S1 and VC connections in sham and partial transection groups, and their absence in complete transection group.