Functional MRI Demonstrates a Novel Role for Callosal Function to Protect Deprived Barrel Cortex from Adjacent Cortical Takeover by Plasiticy in Rodent Brain

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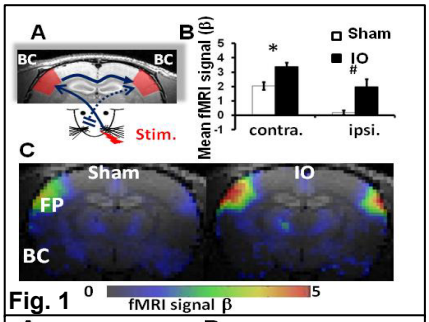
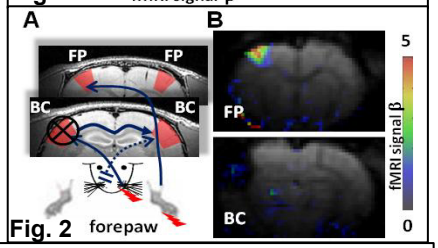
Introduction Following bilateral sensory deprivation, intracortical plasticity typically occurs in the deprived cortex, showing functional takeover by the adjacent cortices [1, 2]. Previously, plasticity associated with unilateral denervation of the infraorbital (IO) nerve was studied in the whisker barrel cortex of juvenile rats [3]. Unilateral IO denervation has been shown to lead to interhemispheric fMRI changes due to transcallosal mediated plasticity two weeks after denervation. This transcallosal plasticity was also shown in rats with unilateral denervation of forepaw and hindpaw [4]. Here, we studied the effects of this IO denervation-induced transcallosal plasticity on intracortical plasticity. In particular, whether area takeover of the deprived whisker barrel by neighboring regions is affected by transcallosal plasticity was analyzed. Mapping of the forpaw somatosensory cortex (FP S1) representation adjacent to the deprived barrel cortex demonstrated a significant expansion of the FP S1 into the deprived barrel cortex only when the interhemispheric callosal inputs were removed. This result indicated that homologous callosal inputs protect the functional identity of the deprived barrel cortex from takeover by adjacent FP S1 areas. This type of transcallosal plasticity could play a role in functional recovery after peripheral injuries.

Methods Three groups of Sprague-Dawley rats were used in this study: sham control (11 rats), unilateral IO denervation (13 rats), and unilateral IO deneveration + cortical ablation of the spared barrel cortex (11 rats). Surgeries were performed on rats at postnatal 4 weeks. BOLD fMRI were performed at postnatal 6-7 weeks allowing two weeks for plasticity to occur. BOLD-fMRI was performed on rats anesthetized with α-chloralose. Detailed procedures for imaging and animal preparation were described in the previous study [2]. All images were acquired with an 11.7T/31cm horizontal bore magnet (Magnex now Agilent), interfaced to an AVANCE III console (Bruker) and equipped with a 12 cm gradient set (Resonance Research). A custom-built, 9 cm diameter transmitter coil was used for transmit and a custom-built surface coil was used for receive employing a transmit/receive decoupling device. A single-shot 3D gradient-echo, EPI sequence was used for the fMRI studies (matrix 64 x 64 x 32, TE 16ms, TR 1.5s, isotropic resolution, 300μm). A sub-skin electrical stimulation with 2.5 mA, 300μs pulses at 3Hz was delivered to forepaw (FP) and whisker pads in a block design (15s on/ 30s off). AFNI software was used for fMRI image processing. For group analysis, custom C++ scripts were developed to register MRI images to rat the brain atlas to define brain ROIs. Student's t test (two-tail)/ one-way anova were used for statistical analysis.

Results Fig 1 demonstrated the increased bilateral fMRI responses to spared inputs in rats with unilateral IO denervation (IO rats). To examined whether the ipsilateral fMRI response was mediated through interhemispheric callosal connections. We ablated the non-deprived barrel cortex in the IO rats. Stimulation of the spared whisker pad and the forepaw elicited fMRI responses in the FP S1 area, but not in the deprived barrel cortex (Fig 2). This result is consistent with the model that the ipsilateral fMRI response in IO rats is transcallosally mediated. To examine the effect of transcallosal plasticity on intracortical plasticity, we mapped the FP S1 representation in three groups of rats (sham, IO, and IO+ablation). A significant expansion of FP S1 toward the deprived barrel cortex was observed only when the callosal inputs were removed. This result demonstrates a novel role of callosal inputs to protect the homologous deprived cortex from takeover by the adjacent cortices. The protection of homologous regions by callosal inputs has potential to play a role in functional recovery.

Ref:[1] Waite et al. Nature 274, 600-2 (1978) [2] Yu X. et al., NI, 49 :1667-76 (2010). [3] Yu et al. 5309 ISMRM (2010) [4] Pelled et al. PNAS, 106 :114-9 (2009)





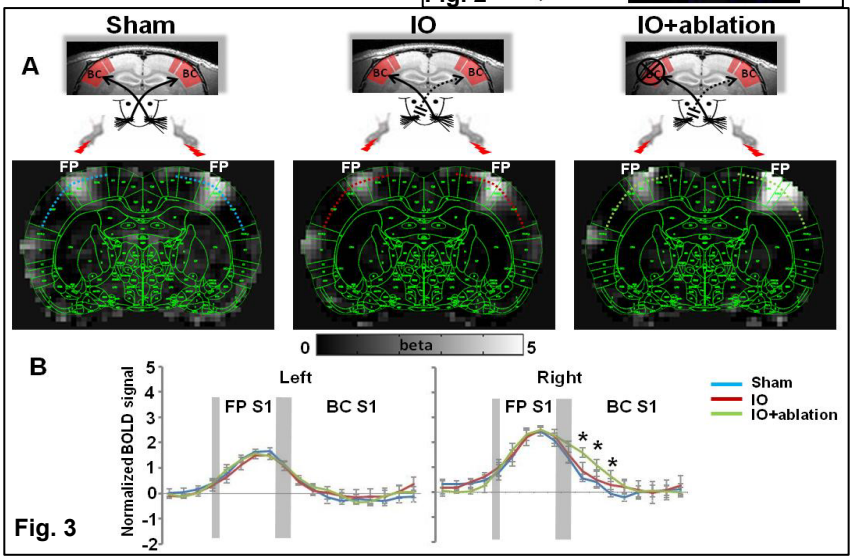


Fig 1. A. The diagram of the unilateral IO nerve resection with (red bolts) of the spared whisker pad. **B.** Analysis of fMRI signal changes from the barrel cortex (BC) (ROIs were defined as red contour in A; contra & ipsi to the stimulation side, $N_{(Sham)}$=9, $N_{(IO)}$=9; * p<0.01; # p<0.001). **C**. Averaged functional map to show fMRI signal in the BC.

Fig 2. A. The diagram of the unilateral IO nerve resection and cortical ablation of the ipsialteral barrel cortex (IO+ablation). Simultaneous stimulation of the forepaw (FP) and whisker pad. B. Averaged function maps to show fMRI responses in the FP and BC of IO+ablation rats (n=4; ablation was shown as signal drop in contra. BC).

Fig 3. A. Atlas-overlapped fMRI functional maps after bilateral forepaw stimulation (red bolts) in Sham, IO, and IO+ablation rats (upper panel). **B**. Line profile analysis of fMRI signals across L4 cortex in the two hemispheres (dotted lines in A: sham in blue; IO in red; IO+ablation in green). The FP and BC S1 locations (gray shadow) were defined by the brain atlas ($N_{(Sham)}$=11, $N_{(IO)}$=13; $N_{(IO+ablation)}$=11, * means P< 0.01).