Deafferentation Induced Cross-Hemispheric Brain Plasticity Detected by Resting-State Functional Connectivity Magnetic Resonance Imaging

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Purpose: To demonstrate resting-state functional connectivity magnetic resonance imaging (fcMRI) is capable of neuroplasticity detection. This was studied in a rat model that underwent a procedure to deafferent the right forelimb.

Introduction: Recently, resting-state fcMRI has gained acceptance in the study of brain disorders, including Alzheimer's disease (1) and children with ADHD (2). In this study, the investigators seek to develop an imaging methodology to detect changes in the resting brain brought about by changes in the peripheral nervous system (PNS). It has been demonstrated previously that damage to the PNS—such as removal of a finger—causes histological changes to the brain. Both intra- and inter-hemispheric expansion of the cortical representations of adjacent sensory organs (i.e., adjacent fingers) occur in the cortical space formally occupied by the deafferented digit (3,4). What is unknown is whether this expansion is beneficial or whether it can be manipulated through therapeutic means in a positive manner following peripheral nerve surgery (i.e., finger reattachment)? An animal model is introduced in this work to study this phenomenon and to demonstrate that fcMRI may have utility in studying subject populations, such as amputees, where task design may be problematic.

Methods: Twelve Sprague-Dawley rats (275-300 g) were used in this study and were split into two groups of six animals. One group was used as a healthy fMRI control, and the other group received a surgical protocol that cut the four major nerves of the rat brachial plexus (median, ulnar, musculocutaneous, and radial) on the right limb. The deafferented experimental group was allowed to recover for two weeks and then was scanned. A Bruker 9.4T AVANCE small-animal scanner was used. The rats were anesthetized with a constant infusion of 0.1 mg/kg/hr medetomidine and 2 mg/kg/hr pancurionium bromide during scanning. Resting-state echo planar imaging (EPI) scans were acquired prior to fMRI electrical stimulation experiments. An electrode was implanted on the left radial nerve prior to fMRI and fcMRI experimentation. EPI parameters were: TE=18.76 ms, TR=2 sec, FOV=3.5 cm, and 1 mm slice thickness; 110 images were acquired. The implanted electrode on the radial nerve was stimulated in a block design fMRI experiment to access any task-related changes in the blood oxygen level dependent (BOLD) signal.

Results: Figure 1 is a demonstration of cross-hemispheric brain reorganization following limb deafferentation using stimulation to the contralateral limb. Figs. 1A,B plot activation in response to stimulation of the left radial nerve in healthy control rats. Figs. 1C,D display activation following stimulation of the left healthy limb in right-limb deafferented rats. A p-value threshold of 0.005 was used for plotting, and the nerve was stimulated with 1 mA, 1 ms, and 5 Hz square-wave pulses. Notice the major changes in the task-activated network between experimental groups. This cross-hemispheric brain plasticity has been demonstrated previously using fMRI in humans (5) and rats (6). Figure 2 is a simplified flowchart demonstrating the intra- and inter-hemispheric connections of the sensorimotor system in the rat brain. This flowchart was used in conjunction with the Paxinos rat brain atlas (7) to develop regions of interest (ROIs) for resting-state functional connectivity analysis. Figure 3 tabulates the cross-hemispheric correlation coefficients for both the healthy and deafferented right-to-left cortical sensorimotor brain region connections. Principal component analysis was performed to generate this figure on the resting-state EPI images. An unpaired t-test revealed statistical significance for each of these values between the healthy and deafferented experimental groups.

Discussion: This study demonstrates that loss of afferent input (i.e., limb deafferentation) causes detectable changes in the resting-state cross-hemispheric connectivity between sensorimotor brain regions. These changes are also apparent in the task-activated fMRI experiments using direct electrical stimulation to the contralateral radial nerve. Here, we establish for the first time that lesional changes in the PNS cause changes in the baseline or resting brain. These changes can be indentified by fcMRI and used as a marker for neuroplasticity.

References: (1) Li, S.J., et al. Radiology 225:253-59, 2002. (2) Uddin, L.Q., et al. J Neurosci Meth 169:249-54, 2008. (3) Merzenich, M.M., et al. Neuroscience 8:33-55, 1983. (4) Calford, M.B., Tweedale, R. Science 249:805-07, 1990. (5) Hsieh, J.C., et al. Ann Neurol 51:381-85, 2002. (6) Pelled, G., et al. Neuroimage 37:262-73, 2007. (7) Paxinos, G. The Rat Brain in Stereotaxic Coordinates. Academic Press: 2005.

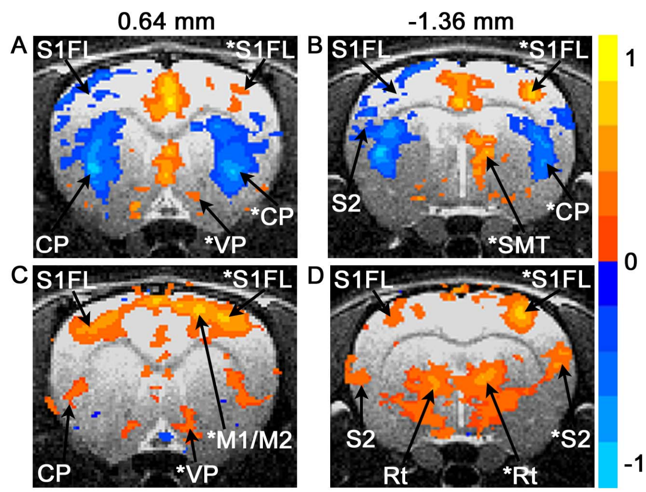

Figure 1: BOLD activation map following radial nerve stimulation.

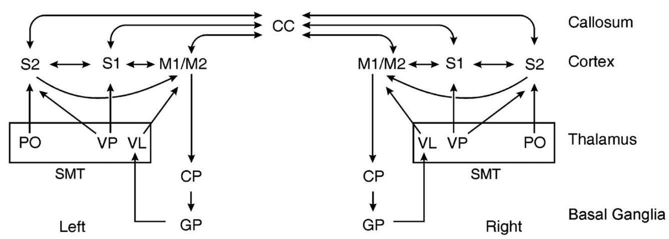

Figure 2: Flowchart of rat sensorimotor network.

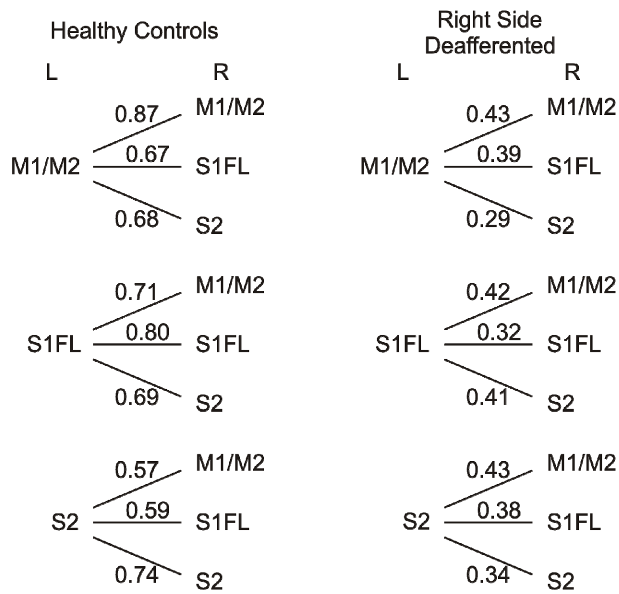

Figure 3: Sensorimotor resting-state cross-hemispheric connectivity.