Neurovascular coupling and uncoupling in negative fMRI response

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Introduction

Understanding neurovascular coupling and uncoupling is the foundation of interpreting fMRI signals correctly. Neurovascular coupling indicates what the signals represent whereas neurovascular uncoupling signifies an fMRI response dissociated with brain activity and thus should be cautioned. Among the various types of fMRI responses, sustained negative fMRI signals are not very well understood. Their neurovascular coupling and uncoupling is especially intriguing. Afferent input and its local processing is recognized as the activity source coupled to fMRI signals. This concept, though not yet proved in negative fMRI signals, may shed some light on our issue. Afferent input and the local processing tend to be referred to as a conception in positive fMRI signals, but they are indeed two neuronal components with a causal relationship. They are activated concordantly with positive fMRI responses. But negative fMRI responses are more complicated, afferents and local processing may have discordant roles in the neurovascular coupling and uncoupling with respect to neuronal activity. To address the issue, the present study characterized a negative fMRI response that occurred in the striatum triggered by nociceptive stimulation. The effects of lesioning the input to the striatum on the negative CBV response were first assessed. The negative response was then evaluated in the circumstance in which local striatal activity was inhibited, which allowed us to identify whether the dopaminergic input was the only source of this activity. The last experiment explored the changes in the input activity to the striatum associated with the negative CBV signals using manganese-enhanced MRI (MEMRI). The experiments unraveled the intermingling relationship between afferents and local processing in the neurovascular coupling and uncoupling of the negative fMRI response.

Materials and Methods

Experiment 1: The right SN was lesioned by infusing 6-OHDA at 30 ug/kg and validated by the rotational test with ipsilateral turns of more than 6 per minute. On the experiment day, anesthesia was initiated with 3–5% isofluorane in O_2 flowing at 3–5 L/min. A PE-20 catheter was inserted into the right femoral vein for subsequent anesthesia, induced by α-chloralose (70 mg/kg). For the CBV-weighted fMRI study, SPIO nanoparticles (Resovist, Schering, Berlin, Germany) were administered as a contrast agent, also via the femoral vein at a dose of 30 mg Fe/kg. The negative CBV response of the striatum to noxious stimuli was induced by the application of noxious, nociceptive electrical stimulation to the rat forepaw. Stimulation adhered to an off–on–off paradigm, which would be correlated pixel-by-pixel with the corresponding image signals to generate the CBV correlation maps. fMRI images were acquired using a 4.7-T spectrometer (Biospec 47/40, Bruker, Germany) with a 72 mm volume coil as the RF transmitter and a quadrature surface coil placed on the head as the receiver. Images were acquired using a FLASH (Fast / Low Angle SHot) sequence with a repetition time of 150 ms, echo time of 15 ms, flip angle of 22.5°, field of view of 2.56 cm by 2.56 cm, slice thickness of 1.5 mm, 1 excitation, acquisition matrix of 128 by 64 (zero-filled to 128 by 128), and temporal resolution of 9.6 s. A series of 60 images were acquired during each stimulation paradigm. The first, middle, and last 20 time points corresponded to the off, on, and off statuses of the stimulation paradigm, respectively. Images were analyzed using a custom-built ISPMER data processing system. Correlation maps were generated by plotting the correlation coefficient (CC) between the image signals and the off–on–off stimulation paradigm on a pixel-by-pixel basis. Experiment 2: Eticlopride (Sigma-Aldrich, E101), a dopamine D2/D3 receptor antagonist, was used to antagonize activation of the D2/D3 receptors. CBV-weighted fMRI was first acquired in five rats that received electrical stimulation at the left forepaw, at an intensity of 10 mA. Eticlopride was then administered intravenously at 1 mg/kg. No significant alteration of the physiological condition was observed following the eticlopride administration. After allowing 10 minutes for the eticlopride to take effect via circulation, identical imaging protocols were performed with the same stimulation parameters described above. Processing and analysis of the results was similar to that in Experiment 1. Experiment 3: Before the nociceptive electrical stimulation, 3 ul of saline, 0.3% bupivacaine, or 0.75% bupivacaine was manually infused into the striatum, over the course of 5 minutes. A volume of 3 ul was found to be sufficient to spread over the majority of the striatum. Following infusion, 10 mins were allowed for the solution to diffuse to the adjacent area. Experiment 4: In this experiment, the activity of the nigrostriatal system was investigated by CBV-weighted fMRI combined with MEMRI, carried out in the same subject. On the experimental day, 0.15 ul of 100 mM Mn^{2+} was microinjected into the left SN. T1WI was acquired as the baseline of MEMRI with a FLASH sequence, with a repetition time of 150 ms, echo time of 4 ms, flip angle of 60, field of view of 2.56 cm x 2.56 cm, slice thickness of 1.5 mm, 46 excitations, and an acquisition matrix of 256 by 256. The total time for each scan was 30 minutes. At 5 hr post-Mn^{2+} infusion, T1WI was again acquired every 30 minutes to establish the signal-to-time curve.

Results and Summary :

By lesioning the distant nigrostriatal dopaminergic input, this negative response was abolished with spatial correspondence to dopaminergic denervation (Fig. 1). By further blocking the dopamine D2/D3 receptors with an antagonist, the remaining negative signals were diminished (Fig. 2). Interestingly, blocking local striatal activity did not affect the negative response (Fig. 3). The activity source was the activated nigrostriatal input, as revealed by manganese-enhanced MRI (Fig. 4). The negative fMRI response was uncoupled to the local neuronal activity yet coupled to afferents via neurotransmission.

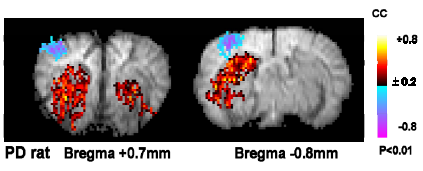

Figure1. The role of the nigrostriatal input pathway in the striatal negative CBV response. The CBV correlation maps at two axial positions of a rat with lesion to the SN in response to noxious electrical stimulation.

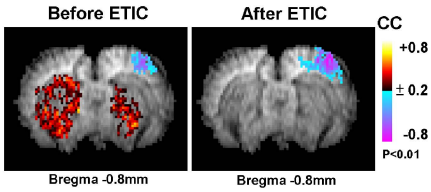

Figure2. The role of dopaminergic D2/D3 receptors in the striatal negative CBV response. (A) The CBV correlation maps before the eticlopride treatment. (B) The CBV correlation maps after the eticlopride treatment.

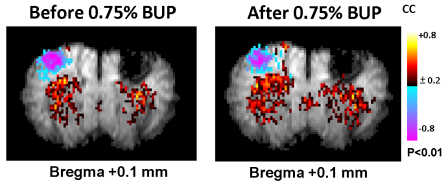

Figure3. The effects of striatal local anesthesia on the negative CBV signals. The CBV correlation maps of a case at bregma +0.1 mm before and after 0.75% bupivacaine.

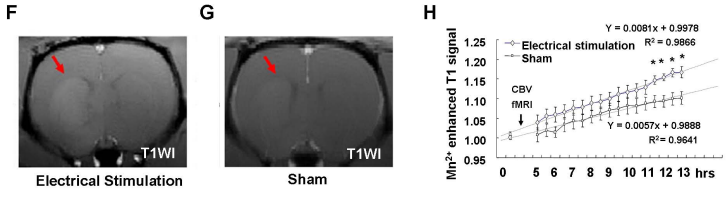

Figure4. The relationship between nigrostriatal input activity and negative striatal CBV signals. The T1WIs acquired from a stimulated rat and a sham-stimulated rat, respectively, following Mn^{2+} infusion into the SN. The Mn^{2+}-enhanced signal changes with time, for each of the two groups. Asterisks indicate significant differences between the sham and electrically stimulated groups (* denotes significance at $p < 0.05$).