Laminar Specificity of fMRI Onset Times Distinguishes Top Down from Bottom Up Neural Inputs Mediating Cortical Plasiticty

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Target Audience This work will attract the attention of scientists working on human and animal brain mapping with fMRI.

Purpose Despite the increasing number of fMRI studies on brain plasticity, how fMRI signal can be interpreted to better understand the underlying synaptic mechanism of cortical reorganization remains challenging. This work focuses on analyzing the early phase fMRI signal to extract the underlying neural input to cortical areas. The early positive BOLD fMRI signal initiates in layers 4/5 of the somatosensory cortex of rats within 700ms at the capillary level after periphery stimulation[1,2], opening the possibility of detecting initial events. This observation is confirmed by a recent two-photon microscopy study[3], showing faster arteriole dilation onset in the deeper cortical layer. We recently showed that spatial specificity of fMRI signal highly relies on cerebral macro vessels of deep cortical layers even as early as 1s after stimulus onset[2]. The initial phase of fMRI signal before 1s showed higher neural specificity than the later phase, which was dominated by venules[2]. Together with the deep layer origin of neural activation through ascending pathways, the early fMRI signal may bear laminar specificity across cortical layers. Using a line-scanning fMRI method, we demonstrate that the layer-specific position of fMRI onset matches either bottom-up or top-down neural projection input layers into cortex. Thus, the laminar position of fMRI onset may bear specific neural projection information. This laminar specificity of fMRI onset to neural input activity allows us to directly analyze the underlying primary neural projection pattern of fMRI activation due to cortical plasticity. By examining the onset profile of ipsilateral fMRI activation in the deafferented cortex of rats with unilateral infraorbital denervation (IO)[4], we demonstrate that callosal projections may mediate interhemispheric plasticity in this rat model.

Methods BOLD fMRI studies were performed in Sprague-Dawley rats anesthetized with α-chloralose. Detailed IO surgical procedures and MRI scanner configuration (11.7T/31cm horizontal bore magnet) have been described previously[2]. BOLD functional maps were first acquired with 3D GE- EPI (TE 16ms, TR 1.5s, FA 12°, 300 micron isotropic). For the line scanning method, we modified a 2D FLASH sequence to get 1D spatial information from the surface of the cortex to the white matter (TE 10ms, TR, 50ms, slice thickness: 1.2mm for barrel cortex and forepaw S1, 1.0mm for the motor cortex, detail in Fig 1). Two saturation slices were set to circumvent 1.5mm width for the barrel cortex and forepaw S1 and 1 mm for the motor cortex. Electrical stimulation was delivered by an isolated stimulator (WPI, FL) (2.5mA, 300 μs pulses, 3Hz) to whisker pad and forepaw upon demand. IDL was used to fourier transform the k-space data to the line profile. Matlab was used to perform the group analysis and polynomial fitting. fMRI onset time was defined as the time point when fMRI percentage changes are higher than two times standard deviation of the noise before stimulus onset. The fMRI onset profile was fit with a high order polynomial function to calculate the earliest onset time and its cortical position.

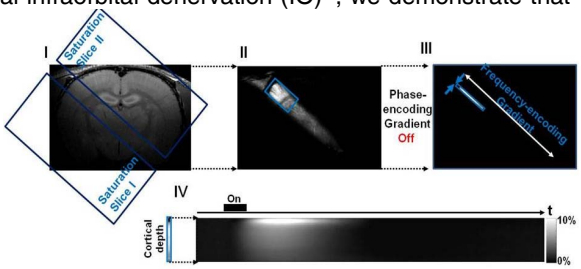

Fig. 1 I. Two saturation slices are aligned to set the borders for the cortex. II. MRI signal is acquired from the FOV (blue box) with the frequency encoding gradient perpendicular to the cortical layers. III. MRI line profile across cortical layers is acquired without the phase encoding gradient. IV. The line profile is acquired at every 50ms to record the hemodynamic response (HRF) as a function of time (grey-scale map for fMRI signal percentage changes; X axis: 1s off, 1s on, 13s off; Y axis: 2 mm cortex at 50μm resolution).

Results The fMRI onset profile across cortical layers in the forepaw somatosensory cortex (FP-S1) showed an early fMRI onset at layer 4 (L4) corresponding to the ascending thalamocortical input layer (Fig 2). In contrast, fMRI activation in the motor cortex (MC) through corticocortical somatomotor connections had two peak onset loci at layer 2/3 (L2/3) and 5(L5), which is consistent with somatomotor projection into the MC layers (Fig 3 AB) [5]. These neuronal projection layers were determined by Manganese-tracing with MRI and matched the fMRI onset position across the different cortical layers (data not shown). This result indicates that fMRI onset coincides with the primary neural projection layers in the cortex. We applied this line-scanning method to examine the onset profile of bilateral fMRI activation in the barrel cortex (BC) of IO rats[4]. The fMRI onset shifted from L4 for the contralateral fMRI activation in the intact BC to L2/3 and L5 for the ipsilateral fMRI activation in the deafferented BC (Fig 3C). Given the corticocortical callosal projection to L2/3 and L5 of the deafferented cortex, it is probable that the callosal inputs mediate fMRI activation in the deafferented BC of IO rats.

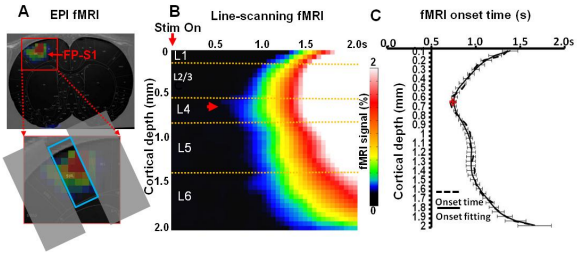

Fig 2. A. The EPI fMRI map of FP-S1 overlaps with the brain atlas. The center of activated FP-S1 (blue box) is scanned across the cortical layers. **B**. Line-scanning 2D color-map with early onset at L4 (red arrow). **C.** Polynomial fit to fMRI onset profile with earliest onset position (red circle, n=8, error bars mean ±SEM).

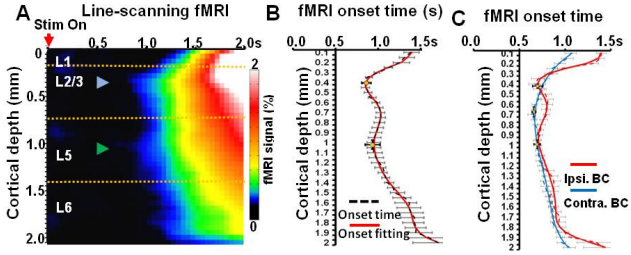

Fig 3. A. Line-scanning 2D color-map of the motor cortex (MC) with early onset at L2/3 and L5 (arrowheads). **B.** Polynomial fit to the fMRI onset profile in MC with earliest onset position (yellow circles, n=7,). C. Polynomial fit to the fMRI onset profile in both contralateral and ipsilateral barrel cortex (BC) with earliest onset position (yellow circles, n=6/8,). Error bars mean ±SEM

Conclusion We demonstrate that the laminar position of fMRI onset coincide with the neural projection into the cortex. The laminar specificity of fMRI onset to input activity lead us to identify that ipsilateral fMRI activation in the deafferented BC is not driven directly by the ascending thalamocortical inputs, but controlled by the corticocortical callosal connections. This work demonstrates the usefulness of the line-scanning fMRI method to characterize the neural circuit substrates of the bottom-up vs. top-down fMRI activation in the cortex.

Reference 1. Silva & Koretsky, *PNAS*, 99, 15182-87 (2002). 2. Yu et al. *NeuroImage* 59,1451-60 (2012). 3. Tian et al., *PNAS*, 107, 15246-51 (2010). 4. Yu et al., *Neuron*. 74, 731-42 (2012). 5. Sato et al. *JN*, 30, 4256-4260(2010).