BOLD fMRI investigation of trigeminal nerve stimulation at 9.4T

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Introduction: Rodents are characterized by the presence of vibrissae located on both sides of the muzzle. Each vibrissae sits in a follicle innervated by a deep vibrissal nerve arising from the infraorbital branch of the trigeminal nerve. During stimulation, the information travels along the trigeminal pathway and the signal enters the brain stem trigeminal nerve cells and progress through the trigeminal complex and thalamus to the barrel cortex. Because of the functional and morphological correlation between the vibrissae and the barrels, the vibrissae-barrel axis is an attractive model for studying structure, function, development and plasticity within the somatosensory cortex. The aim of the present study was to establish a reproducible paradigm to measure the BOLD-fMRI response to trigeminal nerve stimulation in the perspective of investigating the relationship between neural activity and BOLD activation, similar to previous studies using laser Doppler and neurophysiology (1,2).

Methods: All experiments were performed on an actively shielded 9.4T/31cm magnet (Magnex/Varian) with 12-cm gradients (400mT/m, in 120μs) with a quadrature T/R 17-mm surface coil. First and second order shims were adjusted using FASTMAP resulting in water linewidth of 15-17Hz for 216 ul volume.. The BOLD response was assessed using gradient echo EPI (TR/TE/nominal flip angle=2000/25ms/45°; FOV=25x25mm, 64x64, slice thickness= 1mm; 6-10 slices, BW=350KHz, 150 or 300 volumes). The echo alignment were adjusted using a reference scan.

5 SD rats (250-370g) were induced with 1-2% Isoflurane in O_2. The right femoral artery and vein were cannulated to monitor blood pressure (110-130mmHg) and blood gas measurements (PaCO2=40-50mmol/l) and administering α-chloralose (45mg/kg bolus followed by 5mg/kg/h) and Pancuronium Bromide, (1mg/kg i.v.) Rectal temperature was maintained at 37.5 ± 1°C by a temperature-controlled water-heating pad. The rat head was fixed with a homemade bite bar and ear bars to minimize motion artifacts during the fMRI experiment.

Trigeminal nerve Stimulation: The left trigeminal nerve was stimulated using percutaneously inserted stainless steel electrodes, whose cathode was positioned in the hiatus infraorbitalis and the anode was inserted in the masticatory muscles (1). The trigeminal nerve was stimulated using a stimulator with 100us constant current pulses applied every sec (WPI, Stevenage, UK) and 100μs long at 1Hz. 60s OFF was alternated with 60s ON periods. In order to establish the optimal protocol for trigeminal nerve stimulation, the current was varied from 1mA to 8mA.**Data analysis:** Analysis of the time series was performed using STIMULATE (University of Minnesota, Minneapolis, USA) .A correlation coefficient was calculated from cross-correlation of the motion corrected (SPM5, Matlab) and 3x3x3 smoothed Gaussian time series with a boxcar waveform representing the stimulation period. The activation threshold was set to 0.3 and only clusters comprising at least 4 pixels were considered significant.

Results and Discussion: Specific and reproducible activation of the barrel cortex was measured during trigeminal nerve stimulation (figure 1A (Cross-correlation map) and figure 1B (tmaps) overlaid on EPI-GRE images) more distally to the primary somatosensory cortex (SI) activated by forepaw stimulation (figure 1C) for a current intensity of 2mA in 5 rats The mean number of activated pixels at this intensity was 106±83 pixels. Figure2 shows the average time course BOLD % change from the barrel cortex for a rat stimulated at 2mA. The mean BOLD % change was 2.1± 0.8% for this rat but could rise up to 11.8 ±4%. In figure 3, a zoom over the activated region was performed for 4 rats stimulated at 2mA showing that the BOLD response is located both on the surface and deeper layers of the cortex. The current had to be increased above 1mA to elicit a reliable activated region, whereas at 2mA, a region encompassing 44 to 100 pixels was reproducibly activated. For one rat, the activated region extended to SI. Above 2mA, the effect of the intensity of current among rats becomes variable showing barrel cortex activation only to non-specific activation encompassing the primary and secondary somatosensory cortices or activation in the contralateral side of the rat brain. Above 2mA activation became highly variable in extent and magnitude which may reflect non-specific activation. The mean BOLD % change ranged between 5.5 and 12% at 3mA, 2.7 and 12.6% at 4mA and was above 15% above 5mA.

To our knowledge, this is the first BOLD fMRI study of direct trigeminal nerve stimulation. We conclude that with careful choice of stimulation parameters, highly reproducible activation of the barrel cortex can be detected using BOLD fMRI.

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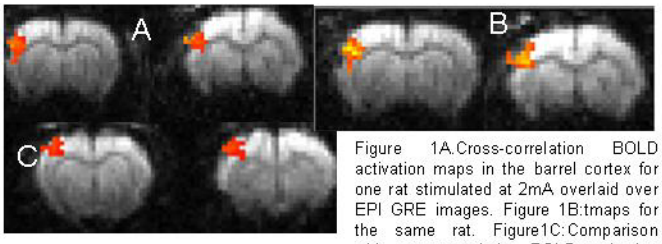

Figure 1A.Cross-correlation BOLD activation maps in the barrel cortex for one rat stimulated at 2mA overlaid over EPI GRE images. Figure 1B:tmaps for the same rat. Figure1C: Comparison with cross-correlation BOLD activation maps in SI after forepaw stimulation overlaid over EPI-GRE images.

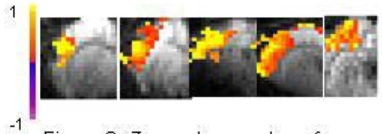

Figure 3. Zoomed examples of cross-correlation BOLD maps in the barrel cortex of 5 rats stimulated at 2mA . Clusters of pixels with high correlation coefficient (orange-yellow) extend to deeper cortical layers.

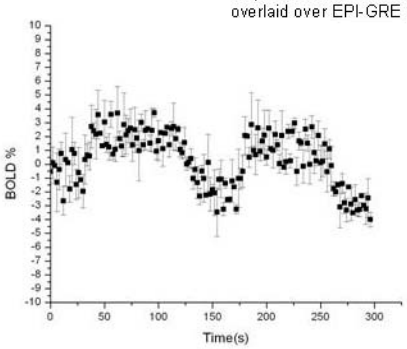

Figure 2: Average Time course from the barrel cortex for a stimulation at 2mA in one rat.

References : (1) : Nielsen and Lauritzen, J Physiology (2001), 773-785
(2) Enager et al, JCBF (2004), 713-719.