Frequency distribution of the BOLD signal during resting-state and nicotine infusion in mice using a phased-array cryogenic coil at 9.4T

Joanes Grandjean[1], and Markus Rudin[1,2]

[1]*Institute for Biomedical Engineering, ETH and University, Zürich, Switzerland,* [2]*Institute of Pharmacology and Toxicology, University of Zürich, Switzerland*

Introduction: Resting-state fMRI (rs-fMRI) in humans has brought new insights into the functional organization of the human brain in both normal and diseased conditions. Analysis of the amplitude of low frequency fluctuations (ALFF) is one method used for analyzing human rs-fMRI data [1]. Studies with this method have shown that the ALFFs are topologically organized and that they can be used as a marker for studying pathological conditions [2]. The rs-fMRI field expansion has been more limited in rodents due to both the need to use anesthetics and the small voxel sizes in small animal fMRI, leading to a low signal-to-noise ratio. Yet, rodent rs-fMRI constitutes an attractive experimental platform for studying mechanistic aspects underlying the rs-fMRI signal. Moreover, rodent rs-fMRI may serve as translational platform to evaluate changes in brain activity state during a period of treatment rather than the response to an acute response to an intervention. To demonstrate the feasibility of this concept, we studied the effects of nicotine, which is of interest due to its high potential to create addiction and its role in attention and learning, on rs-fMRI responses in mice during slow infusion. The use of mice in rs-fMRI is attractive in view of the many transgenic mouse lines available for mechanistic studies. We used ALFF analysis to characterize effects of slow nicotine infusion on the frequency distribution in mouse brain.

Method: Female CB57/B6 mice were anaesthetized and maintained at 1% isoflurane and 0.5g/kg pancuronium was used as a muscle relaxant to reduce animal motion during measurements. Gradient-echo EPI images were recorded at a sampling rate of 0.5Hz, a resolution of 0.22mm x 0.25mm and a slice thickness of 0.5mm using a 2x2 phased-array cryogenic mouse head surface coil on a 9.4T Bruker system. Nicotine at 0.5g/kg/h was infused in the tail vein with a pump 10 min prior and during the EPI recording (16 min). Amplitude of Low Frequency Fluctuation was analyzed with the REST toolbox for matlab©. Frequency bands were selected as such: Low-frequency (LF) 0.01-0.05Hz, medium frequency 1 (MF1) 0.05-0.1Hz, medium frequency 2 (MF2) 0.1-0.15Hz, high frequency (HF) 0.15-0.2 Hz.

Results: The distribution of ALFFS, shown in figure 1, followed the topological organization of the mouse brain, with the major amplitudes found in the cortical region. Low frequencies (LF) were found distributed across frontal and posterior cortical regions, whereas MF2 and HF were more prominent in the frontal part of the cortical regions and reduced in the posterior regions. Sub-cortical regions showed little amplitudes for all frequency bands considered. Nicotine infusion led to a significant increase in LF and MF1 frequency amplitudes in the frontal cortex compared to control (figure 2, p=0.015 and 0.023 respectively), as well as an increase in LF and MF2 in the prelimbic cortex (figure 2, p=0.034 and p=0.049). Nicotine also led to an increased LF in the interpedencular nucleus; yet due to heterogeneity in the response (high, medium and low responders) the effect did not reach statistical significance (figure 2, p=0.15). MF1 and MF2 amplitudes were reduced in the sensory/motor cortex of the nicotine-infused group compared to control (figure 2, p=0.019 and 0.03 respectively).

Discussion: Frequency amplitude distribution found in the normal mouse brain compared well with the previously observed rs-fMRI signal analyzed with Independent Component Analysis, in which components were mostly found in the cortical regions [3]. Some discrepancies with the results were found in the amygdala and in the dorsal hippocampus, where we did not find significant amplitudes in the frequency bands considered, possibly due to different anesthetics used. Absence of activity in the thalamus is consistent with the effects of isoflurane, which is known to reduce thalamic activities [4]. Nicotine-induced response in the infralimbic cortex and the frontal cortex were reported in fMRI results in rats following bolus injection of the compound [5, 6]. It was suggested that α4β2 rather than α7 receptor subtypes are responsible for the response observed [6]. Furthermore, α4 and β2 mRNA showed an increased expression in the frontal areas compared to the rest of the cortex thereby providing a possible mechanistic explanation t for the changes in ALFF in these regions [7]. The present method failed to capture the activation of the sub cortical nuclei, possibly due to the lower doses of nicotine used in slow infusion compared to bolus injections in rats and the interaction with isoflurane. The results also fit with the observations in human fMRI, where frontal regions showed an increased BOLD signal following nicotine injection [8]. Nicotine also induced a reduced rs-fMRI signal in the default-mode network in humans [9] consistent with the reduction of MF1 and MF2 in the sensory/motor cortex in mice, while the frontal associative areas show an increase in LF and MF1.

References: [1] Baria M et al., JNEUROSCI.1296-11.2011 [2] Baliki M et al., JNEUROSCI.1984-11.2011 [3] Jonckers E et al. Plos One 6(4): e18876 [4] Ying SW et al. Neuropharmacology 56(2):438-4.2008 [5] Choi J et al., Synapse 60:152-157.2006 [6] Gozzi A et al., Neuropsychopharmacology 31:1690-1703.2006 [7] mouse.brain-map.org, November 2011 [8] Stein EA et al. Am J Psychiatry 155:8.1998 [9] Tanabe J et al. Psychopharmacology 216 :287-295.2011

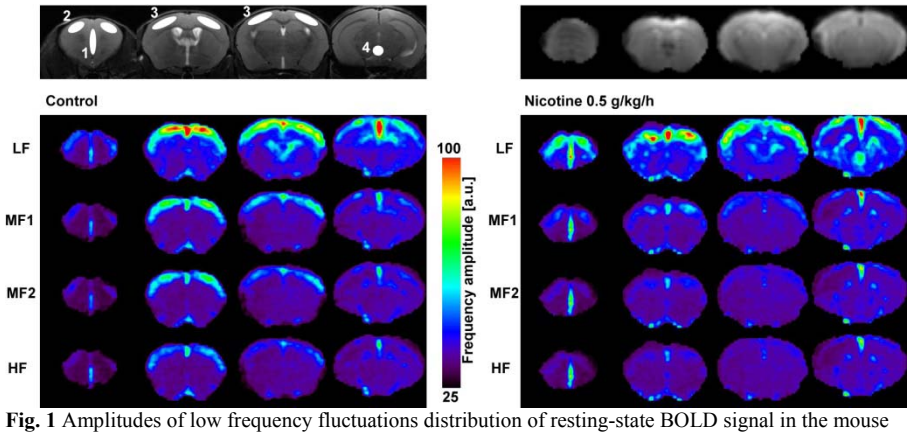

Fig. 1 Amplitudes of low frequency fluctuations distribution of resting-state BOLD signal in the mouse brain. Spin echo anatomical images and corresponding EPI images are shown on the top row. Areas shown on the anatomical images are: 1 prelimibic cortex, 2 frontal cortex, 3 sensory/motor cortex, 4 interpedencular nucleus. Bottom rows show the mean value across animals for low frequencies (LF 0.01-0.05 Hz), medium frequencies 1 and 2 (MF1 0.05-0.1 Hz, MF2 0.1-0.15 Hz) and high frequencies (HF 0.15-0.2 Hz) for control (n=8) and nicotine-infused (n=8) animals.

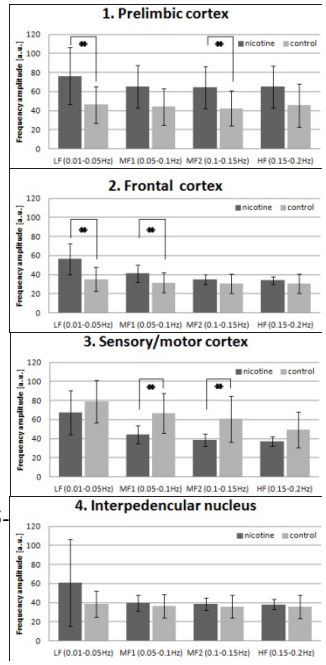

Fig. 2 Barplots showing the mean and standard deviation for the frequency amplitudes of the areas shown on the anatomical images of figure 1.