Differentiating BOLD and non-BOLD signals in 11.7 Tesla Rat Resting State fMRI

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Background The rat is an exciting model system for study with resting state fMRI (rs-fMRI) because it is well suited to many neuropharmacological and lesioning studies. Recent ultra high field (11.7T) animal MR systems now enable rat fMRI at higher spatial resolution and temporal signal to noise ratio than has been attainable in the past. However, as rat rs-fMRI is novel methodology [1,2], its capabilities and limits are not yet well understood. The spatial and temporal properties of spontaneous BOLD signals are not well characterized, nor are the nature and extent of motion and physiological artifact in ultra-high field fMRI. A means of distinguishing neuronally-related BOLD signals from non-BOLD artifact in rat rs-fMRI is thus an important methodological step. In this study we present an approach involving acquisition of multi-echo (ME) fMRI and analysis of TE-dependence using an emerging method called multi-echo independent components analysis (ME-ICA). Here we address the feasibility of ME-ICA for rodent rs-fMRI and present preliminary results regarding the effect of fMRI sequence choice. **Methods** Resting state fMRI data from 3 healthy Sprague Dawley rats (of 250-350g body weight) are presented here. Animals were anesthetized with a continuous intravenous infusion of medetomidine hydrochloride (200ug/kg/hr) throughout the duration of the fMRI data acquisition. Rs-fMRI data were acquired using a Bruker BioSpec 11.7T small animal MRI scanner (Bruker Instruments, Inc., Billerica, MA) equipped with a 72mm-diameter resonator used for emission and a 4-channel phased-array surface coil used for reception. Four ME-fMRI sequences were piloted, including 2D and 3D sequences, detailed in the caption of Table 1. Data were analyzed using ME-ICA in the same configuration as for human data [3]. Slices and volumes were first realigned. PCA decomposition followed, followed by TE-dependence analysis to find a high dimensional principal subspace of components with high variance, BOLD (high κ), or non-BOLD weights (high ρ). Dimensionally reduced data were decomposed with FastICA [4], and TE-dependence analysis separated BOLD components (high-κ) from non-BOLD (low-κ) components. **Results** ME-ICA of all scans yielded BOLD components representing functional areas, as listed in Table 1. κ values reflecting TE-dependence (distributed as F(1,2)) identified BOLD components ranged 60-200, consistent with findings from human rs-fMRI. Component maps are shown in Figure 1. Functional localization shown in components is remarkably consistent with known rat neuroanatomy. Noteworthy components show distinct dorsal and ventral striatum (from Sequence#1, 5 minute scan), and separate amygdala-insula and frontal cortex components (from Sequence/Rat#2,3 20 minute scans). Since these findings were made from single scans of individual anesthetized rats and did not require manual component selection, the proposed approach appears to be sensitive and robust. **Conclusions** ME-ICA of 11.7T rat fMRI can produce consistent components showing clear localization of functionally and neuropharmacologically interesting areas of rat brain. Further study involves systematic assessment of fMRI sequences to identify optimal configuration, and analysis of denoised time courses to assess temporal properties of rat endogenous oscillations.

	M1	S1	Frontal	Amyg. Insula	Cing./ DMN	Dors. Stria.	Vent. Stria.
R1/S1	Y	Y			Y	Y	Y
R2/S2	Y	Y	Y	Y	Y		
R3/S3	Y	Y	Y	Y	Y	Y	
R3/S4				Y	Y		

Table 1 Anatomical regions represented in spatial independent components (marked 'Y') from data acquired from 3 rats (R#) with four sequences (S#) as follows. *Sequence#1*: 2D Echo planar imaging (EPI) voxel size 0.3x0.3x1.2mm ; 16 coronal slices with 0.2mm gap; TR=3sec, FA=90; 3 TEs=8.5,27.0,45.5ms; BW/Pixel=4081Hz; 110 repetitions. *Sequence#2*: 2D EPI voxel size 0.4x0.4x0.6mm; 32 coronal slices with 0.2mm gap; TR=3sec, FA=77, 3 TEs=7.6,19.6,31.6ms; BW/Pixel=4688Hz; 500 repetitions. *Sequence#3*: EPI voxel size 0.5mm isotropic; 40 coronal slices; TR=3sec, FA=77, 3 TEs=7.6,19.6,31.6ms; BW/Pixel=4688Hz; 400 repetitions. Sequence #4: 3D Echo planar imaging (EPI); 0.5mm3 isotropic voxel size; 40 coronal slices; TR=0.075sec; FA=14.5, 3 TEs=8.25 20.25 32.25 ms; BW/Pixel=6250Hz; 400 repetitions.

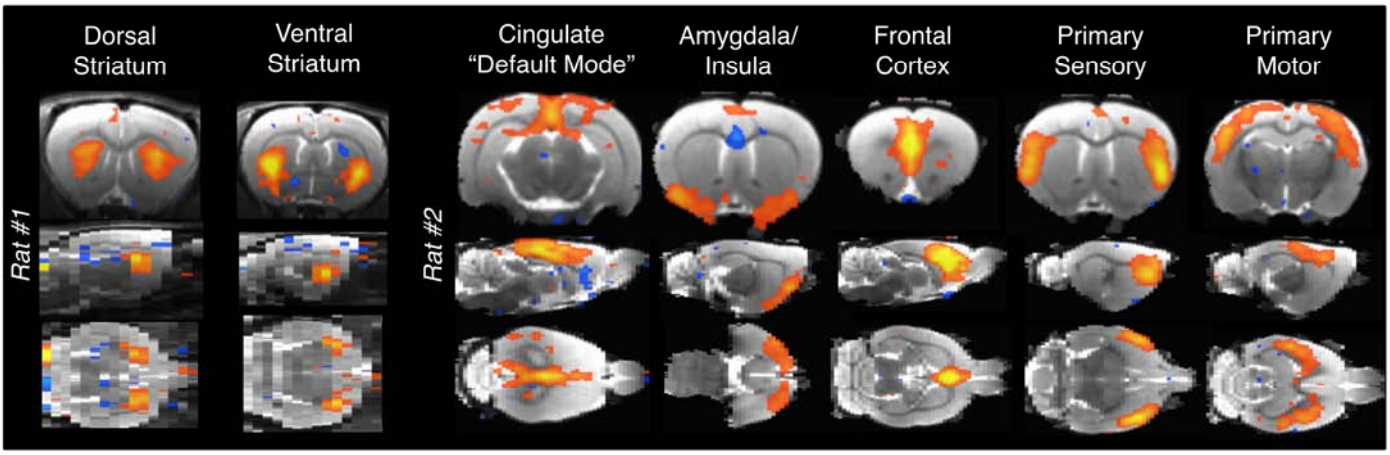

Figure 1 Example components (thresholded z[spatial]>3) extracted from multi-echo rat fMRI data using ME-ICA, displayed as overlay on high-resolution T_2 anatomical. High quality localization of neuroanatomical areas is evident. Primary motor, sensory, dorsal/ventral striatum, and amygdala-insula have symmetric, bilateral localization. Cingulate (i.e. default mode) and frontal cortex components have medial localization.

References [1] Pawela et al, Resting-state functional connectivity of the rat brain, MRM, 2008. [2] Liang et al, Uncovering intrinsic connectional architecture of functional networks in awake rat brain, Journal of Neuroscience, 2011 [3] Kundu et. al, Differentiating BOLD and non-BOLD signals in fMRI time series using multi-echo EPI, NeuroImage, 2012. [4] Hyvarinen et al, Independent component analysis: algorithms and applications, Neural Networks, 2000.