Tissue and Vascular Contributions to Diffusion fMRI in Rat Inferior Colliculus Using Quadratic Exponential Kurtosis Model

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Target Audience: Researchers and clinicians with interest in the neurophysiological source of fMRI

Purpose: Diffusion fMRI has been used to alternate the fMRI signal composition of vasculature and tissue. It is reported that signal from high b-value regime is more weighted with tissue water diffusion changes, while signal from low b-value regime or non-diffusion weighted is dominant by vascular changes [1, 2, 3]. It is known that distribution of diffusion displacement in brain tissue is non-Gaussian [4], and the mono-exponential free/non-restricted diffusion assumption in most diffusion fMRI studies may be prone to errors/ may be invalid. In this study, kurtosis model is used to study the non-Gaussian diffusion changes in inferior colliculus (IC) during an auditory fMRI experiment.

Methods: ***Animal Preparation:*** Eight Sprague-Dawley rats were anesthetized with a mixture of air and isoflurane (3% for induction and 1% for maintenance) and mechanically ventilated (60rep/min). ***MRI Protocols:*** All fMRI scans were performed using single shot SE-EPI sequence in a 7T Bruker scanner. One non-diffusion weighted (b-values = 0ms/μm^2) and four diffusion weighted (b-values = 0.5, 1.0, 1.5, 2.2ms/μm^2) images were acquired consecutively. This cycle run 140 times and synchronized with block design auditory stimulation in each afMRI section. Diffusion gradient was applied along phase encoding direction. Imaging parameters: TR/TE= 1000/32.8ms, δ/Δ= 5/18ms, FOV= 4.8x4.8cm^2, acquisition matrix= 64x64, slice thickness= 1.4mm. ***Auditory Stimulation:*** Simulation during fMRI was transmitted from a high frequency speaker (MF1, TDT) and through a custom-built tube to the animal's left ear. Bandlimited noise was presented for 50s with 100s resting in a block design manner (4 blocks) [7]. ***Data Analysis:*** The registration, realignment, slice timing procedures and boxcar function fMRI fitting were performed using SPM8. Five b value data were fitted into quadratic exponential kurtosis model to compute dynamic kurtosis (K) and apparent diffusion coefficient (D) (Figure 2a). B values = 1.0, 1.5, 2.2ms/μm^2 were jointly fitted in a mono-exponential decay curve to compute dynamic D (hig b value diffusion model) and pseudo tissue fraction which is the y-axis intercept indicated in Figure 2a.

Results: Non-diffusion-weighted BOLD (at 0ms/μm^2) and diffusion-weighted (DW) BOLD signal (at >0ms/μm^2) increased during activation (Figure 1 top row). % non-diffusion-weighted BOLD change during activation is the highest among all fMRI signals. There was no significant difference in % DW BOLD change among non-zero b values. (Figure 2c and 3a) D from kurtosis model, kurtosis and pseudo blood fraction increased during activation. (Figure 1 bottom row, 3a and 3b) Meanwhile, D from high b value diffusion model remains unchanged. (Figure 3b)

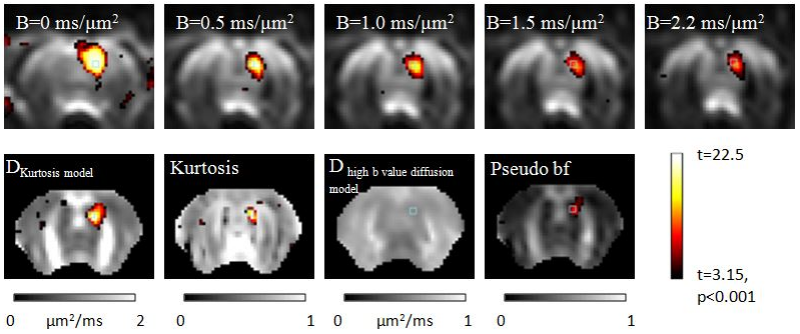


Figure 1. Typical activation maps (p<0.001) of auditory fMRI experiments at the level of inferior colliculus (IC) at multiple b-values, D (from kurtosis model and high b value diffusion model), kurtosis and pseudo blood fraction (bf) measurement. 2 by 2 pixels ROI is drawn at the center of IC in blue.

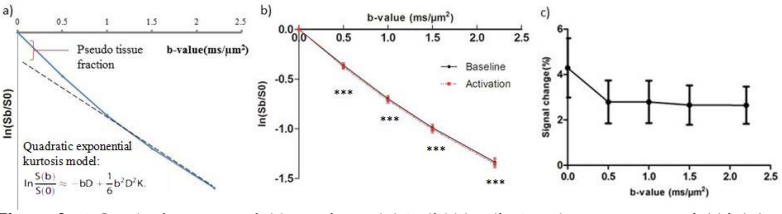
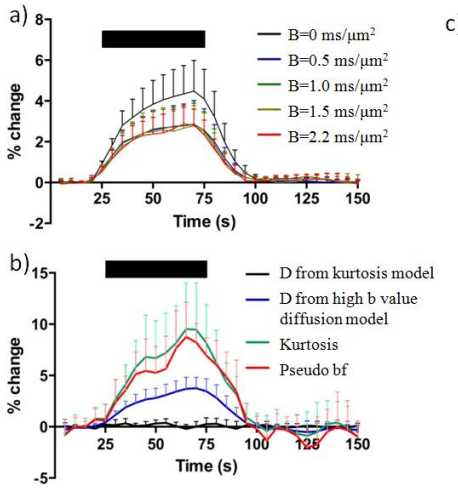


Figure 2. a) Quadratic exponential kurtosis model (solid blue line) and mono exponential high b value diffusion model (dashed line). b) Signal decay curve (Mean±SD) without stimulation(solid black) and with stimulation (dashed red) (two-tailed paired t-test between baseline and activation signal ***p<0.001) c) Signal (Mean±SD) change during activation



c)

	Baseline (Mean±SD)
D from kurtosis model (μm²/ms)	0.747±0.062
Kurtosis	0.65±0.111
Pseudo bf	0.153±0.031
D from high b value diffusion model (μm²/ms)	0.532±0.019
B=0 ms/μm²	3894±580
B=0.5 ms/μm²	2722±434
B=1.0 ms/μm²	1944±313
B=1.5 ms/μm²	1450±235
B=2.2 ms/μm²	1027±164

Figure 3. Temporal profile of a) multiple b-values, b) D (from kurtosis model and high b value diffusion model), kurtosis and pseudo blood fraction (bf) measurement during auditory fMRI experiments. The black bar indicates the duration of stimuli applied c) Table of baseline measurement (Mean±SD) of multiple b-values, D (from kurtosis model and high b value diffusion model), kurtosis and pseudo blood fraction (bf) measurement.

Discussion and Conclusion: Five b values were used in the quadratic exponential kurtosis model to study non-diffusion-weighted BOLD and DW BOLD signals during functional auditory activation of the rat inferior colliculus under isoflurane anaesthesia. With increasing high b values, activation hot cluster was more localized at the center of IC relative to non-diffusion-weighted BOLD fMRI activation. This may reflect more tissue water diffusion changes at the center of IC upon suppression of vasculature contribution by diffusion weighting during functional activation. D from kurtosis model and pseudo blood fraction increased due to blood flow increase during activation [2, 3]. However, D from high b value diffusion model remained unchanged. This could be due to the diffusion gradient coupling effect [5] which cancels out the increase fraction of restricted/hindered diffusion that occurs in osmotic cell swelling during neuronal activation [1, 6]. Kurtosis was found to increase during activation. Increase in kurtosis is commonly interrupted as more restricted diffusion in the tissue. The elevation of kurtosis, in this case, might not attribute to increase fraction of slow diffusion/cell swelling during neuronal activation, since there was no significant difference in %DW BOLD change among non-zero b values, instead the increase in kurtosis might be mainly contributed by the increase in blood flow during activation as indicated by the initial fast decay of diffusion signal.

In conclusion, without assuming mono-exponential free diffusion, kurtosis is found to increase which might be mainly contributed by the increase in blood flow. A caution is made to the interpretation of kurtosis in diffusion MRI when vasculature change is involved.

References: [1] Le Bihan D., PNAS 2009; [2] Jin T., Mag Res Med 2006; [3] Harshbarger T.B., Mag Res Med 2004 ; [4] Lu H., NMR Biomed, 2006; [5] Does M., Mag Res Med 1999. ; [6] Ransom BR., J Neurosci 1985.; [7] Cheung MM., Neuroimage, 2012