Echo Time Dependence of Resting Signal Fluctuations in USPIO based Cerebral Blood Volume Imaging: Implications for Task-based and Resting State fMRI

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Introduction: Ultrasmall superparamagnetic iron oxide (USPIO), a strong T2* contrast agent with long blood plasma half-life, can be used for fMRI scans and is primarily sensitive to CBV changes. Previous work [1] in humans has shown that this method, termed ICE-BVI (Iron oxide Contrast Enhanced-Blood Volume Imaging) has 2-3 times higher contrast than BOLD in task-based fMRI. However, the increase in T statistics was not proportional due increases in the noise level in ICE-BVI. The components of the noise are believed to include system noise and physiological noises including respiration, cardiac pulsation, and fluctuations from spontaneous neural activities. For BOLD this noise was found to demonstrate echo time and signal intensity dependence [2]. It is therefore intriguing to characterize the noise behaviour with ICE-BVI and how it would affect the selection of optimal echo time and image resolution that optimizes temporal contrast to noise ratio. In this study, we performed experimental measurements and numerical simulation of the noise in ICE-BVI under different echo times and signal intensities. The results were interpreted with respect to optimal TE selection as well as their implications for ICE-BVI based resting state fMRI for studying functional connectivity.

Theory: According to [2], the temporal noise σ of BOLD signal can be modelled to include three components:

$$\sigma = \sqrt{\sigma_0^2 + \sigma_B^2 + \sigma_{NB}^2}$$

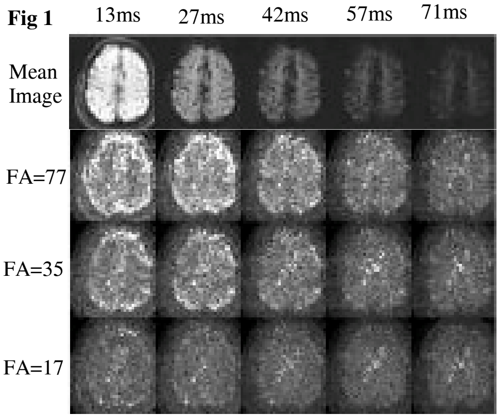
(Eq. 1), where σ_0 is thermal noise that does not depend on signal intensity, and σ_B is echo time dependent noise component that includes contribution from respiratory and cardiac induced ΔR_2^* changes, and σ_{NB} is noise component that depends on signal intensity but not on echo time, such as system gain instability, subjection motion, etc. Therefore the σ_B and σ_{NB} can be further formulated as

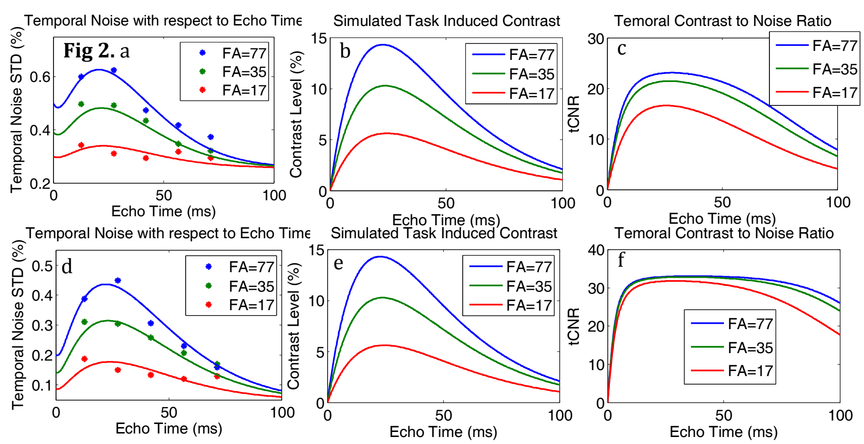
$\sigma_B = a*S*TE$, (Eq. 2). $\sigma_{NB} = b*S$, (Eq. 3)

where S is the signal intensity and TE is the echo time, and a, and b are the weighting coefficients. Static signal to noise ratio (SNR) is defined as the ratio between *S* and σ_0. In this study, we adopt this model for the study of the dependence of noise in post contrast ICE-BVI with echo time and signal intensity.

Materials and Methods: MR imaging was performed at 3T with an 8-channel head coil (MR750, GE Healthcare, Waukesha, WI) under IRB approval. This study is part of a larger ongoing project developing the application of USPIO for human imaging. Two subjects were included in the current study who had the following sequences performed: A 3D T1-weighted inversion recovery spoiled gradient echo (IR-SPGR) sequence covering the entire brain was acquired. After the injection of ferumoxytol (approx 7 mg Fe/kg), a multi-echo 2D EPI was acquired (FOV=24cm, Matrix = 64x64, slice thickness/gap = 4 mm/1mm, number of slices = 23, TR=2s, parallel imaging factor =2, 32 time frames, five echoes: TE = 12.7ms, 27.4ms, 42ms, 56.7ms and 71.4ms). The sequence was performed with different flip angle (FA) to give different signal intensity without changing TE,. Three FA were used including 77, 35 and 17 degrees; these FA were selected because 77 is approximately the Ernest angle of gray matter at TR of 2s and 35 and 17 degrees gives approximating 2/3 and 1/3 of the signal at 77 degree FA. A region of interest (ROI) with 3x3 voxels was placed in the posterior part of the brain. When measuring the noise level, two scenarios were considered including (1) single voxel noise statistics (2) statistics when smoothing is used. For single voxel statistics, the time series of the each voxel in the defined ROI was extracted and quadratically detrended and the temporal standard deviation was calculated and averaged for all the voxels in the ROI. To consider the scenario of spatial smoothing, the time series were first averaged over all the voxels in the ROI and quadratically detrended, and the standard deviation was then calculated. The two ways of processing are different since smoothing (or averaging) will have different effects on the three components of noise since thermal noise σ_0 is considered to be independent while physiological noises are likely to be correlated with neighbouring voxels. The measured noise values under different TE and FA were then used to fit the noise model given by equations 1-3. All values were normalized to the mean signal intensity of the first echo with FA of 77 degrees.

Fig 1





Results and Discussions: Figure 1 shows the mean images with FA of 77 at different echo times as well as temporal noise at different TE and FA (therefore static SNR). The dependence of the noise on TE and signal intensity can be observed. The top panel of Figure 2 (a-c) shows the (a) measured noises and model fit using Eq. 1-3, (b) simulated signal contrast with an ΔR_2^* change of $0.01ms^{-1}$ due to task, and (c) the estimated temporal contrast to noise ratio at different static SNR for single voxel statistics. The bottom panel of Figure 2 (d-f) shows corresponding measurement and simulation for the scenario of spatial smoothing. Fig 2 (a, d) shows that the noise model used in this study provides reasonable fit to the measured noise and that the noise level peaks at a TE around 23ms, which is approximately the T2* value of gray matter after contrast injection [1]. Fig 2c shows that temporal CNR is slowly varying around optimal TE, even slower than the contrast change as shown in Fig 2b. This suggests that TE can be chosen according to other factors such as signal dropout and slice coverage without significantly sacrificing sensitivity. This is more true when spatial smoothing/averaging is applied (Fig 2f). Also, when the static SNR is reduced by using the smaller FA, the reduction in CNR is not proportional (Fig 2c), suggesting increasing the spatial resolution (hence reducing static CNR) from what is currently used would not see a significant reduction in temporal CNR. It is estimated that the TE-dependent component of the noise σ_B accounts for about 75% of the noise at TE=23ms with FA=77. This component is believed to include physiological fluctuations including respiration, cardiac pulsation, and spontaneous neural activities. Our group is also exploring the application of post contrast ICE-BVI for studying resting state functional connectivity. The dominance of σ_B suggests that effective methods for reducing physiological noise, such as high-speed inverse imaging with spectral filtering, is required to increase the power of resting state ICE-BVI.

Conclusion: In this study, we characterize the noise behaviour of post-contrast ICE-BVI under different TE and static SNR. The result is useful in guiding study designs in task based and resting state ICE-BVI. It is suggested that higher resolution task based ICE-BVI can be achieved without significantly sacrificing sensitivity, and that effective methods for reducing physiological noises are important for resting state ICE-BVI studies of functional connectivity.

References: **[1]**Qiu D. 2012. Neuroimage. 62(3):1726-31. **[2]**Kruger G. 2001. MRM. 46:631-7. **Acknowledgments:** National Institute of Health (2RO1NS047607, 1R01NS066506, P41EB015891), Lucas Foundation, and Oak Foundation