A Case for Correcting Attenuation of Correlation in Resting State fMRI

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Introduction: The correlation coefficient (CC) is commonly used in resting state fMRI analysis as a measure of neural connectivity between brain areas [1]. It is well established that noise sources may attenuate the temporal correlation between signals (e.g. [2,3]), an effect first described by Spearman in 1904 [2]. Here we suggest that this effect, attenuation of correlation, may be important for the interpretation of resting state fMRI, where non-neurogenic noise sources coexist with signals of interest. Properly determining neurogenic CC requires modeling and removal of nuisance effects. Physiologic noise (e.g. cardiac & respiratory-related) and motion are generally accounted for, but thermal noise often is not. We propose a procedure for determining functionally relevant CC based on estimates of the amplitude of thermal noise.

Methods: The level of random (thermal) noise var(n_i) in a regions *a* and *b* of the image can be estimated from a zero-flip angle measurement, data often already acquired in MRI, e.g. for optimal coil combining [4]. Based on this, the noise-corrected CC between two time series measurements (i.e. signal + noise) u_a and u_b in regions *a* and *b* can be calculated as follows:

$$CC_{corrected} = CC_{observed} \cdot \sqrt{\left(\frac{\mathrm{var}(u_a) \cdot \mathrm{var}(u_b)}{\left(\mathrm{var}(u_a) - \mathrm{var}(n_a)\right) \cdot \left(\mathrm{var}(u_b) - \mathrm{var}(u_b)\right)} \right)}$$

Monte-Carlo simulations were performed to illustrate the magnitude of this correction and its dependence on thermal noise levels. The effect of attenuation, and its correction, was evaluated on resting state fMRI data from an unpublished study (gradient-echo EPI at 7T; 2.5×2.5×2.0 mm^3 voxels; 2000 ms TR; 30 ms TE; 8 volunteers; 5-min eyes-closed rest). Here we specifically report on CC between bilateral lateral geniculate nuclei (LGN) on an ROI and voxel level.

Results: Fig 1 shows the observed, uncorrected CC as a function of the ratio of functional (neurogenic) signal fluctuation and thermal noise (fluctuation-to-noise-ratio, FNR) for 4 different actual signal correlation values. This simulation shows that, without correction, noise substantially decreases CC for FNR values of 5 or lower. It should be pointed out that additional sampling of the data, e.g. in the form of longer scanning, does not overcome this effect. This is shown by Fig 2, which displays the observed CC between two signals with a known actual CC of 0.5 for 4 different FNR levels as a function of the number of samples. The variance in the CC estimate, which is FNR dependent, can be observed to decrease with the number of samples, but the CC attenuation bias remains.

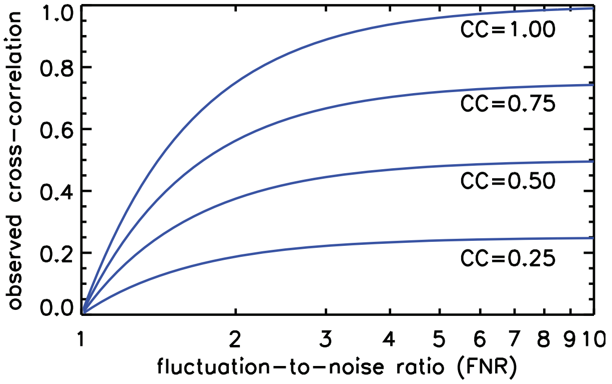

***Figure 1**: Plot of the correlation attenuation that is introduced by background noise. The observed correlation value is shown as a function of fluctuation-to-noise level for 4 different actual cross-correlation values.*

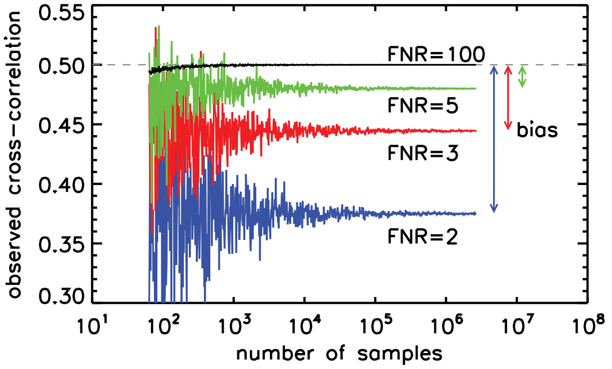

***Figure 2**: Observed correlation values as a function of the number of measurements for 4 different fluctuation-to-noise ratios, showing that additional sampling does not overcome the bias in the observed cross-correlation value. The actual signal correlation was 0.50.*

On experimental data, a total of 569 correlations were performed between pairs of voxels, one each from left and one from right LGN. The mean FNR was 2.41±0.58 (mean±SD), which led to an underestimation of CC of on average 21%. Attenuation even affects CC for small ROIs: Observed CC between bilateral LGN ROI-averaged time course signals (comprised of 7.3±1.8 and 7.8±1.7 voxels for left and right LGN) was 0.39±0.07 (mean±SE over volunteers), which after attenuation correction increased to 0.44±0.08.

Discussion: Temporal correlation between two fMRI signals is substantially underestimated if FNR levels drop below 5, a condition often encountered in practice: In resting state fMRI, the fluctuation amplitude in the voxel signal time courses is often at or below 10% of the baseline signal, whereas the noise level is on the order of 1% of the baseline signal (for image SNR=100), yielding FNR<10. A simple correction is proposed that is based on thermal noise estimates from readily available data. Note that this correction does not improve significance of the result but merely improves accuracy of the estimated CC.

Conclusion: This well documented and straightforward method can be used to correct for attenuation of the correlation coefficient, which can be substantial in a typical fMRI experiment. This is essential for correctly estimating CC in seed-based resting state fMRI.

References: [1] Biswal et al., Magn Reson Med, 1995; 34:537-541 | [2] Spearman, Am J Psychology, 1904; 15:72–101 | [3] Behsata et al., J Neurophysiol, 2009; 101:2186-2193 | [4] Pruessmann et al., Magn Reson Med, 1999; 42:952-962