Subtle physiologic rate differences affect group fMRI studies

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Introduction:
The present study addresses the effect of physiologic correction on a motor fMRI analysis in Multiple Sclerosis (MS) patients. fMRI analyses of the motor cortex are commonly assumed to be insensitive to physiologic noise, but the effect of group differences in this source of noise has not been evaluated by detailed study. A recent review of BOLD fMRI in the study of disease concludes there is a specific need for "***the recording of physiological parameters during scanning and subsequent correction of possible between-group differences***."[1]. Group population studies may be biased by differences in physiologic noise levels if the study population, such as patients with MS, differs significantly in physiology from healthy controls. The present study establishes that the effect of physiologic correction on activation volumes (i.e. the volume in un-corrected minus that in physiologic-corrected data) in MS patients is significantly different from the change in activation in controls. Although this did not change the overall findings of the study, this strongly suggests the need to correct for physiologic differences between groups to avoid biased results.

Methods:
34 subjects (13 male, age 41.9 ± 9.3 years), including 18 MS patients (7 male, age 41.1 ± 9.9 years) and 16 normal control subjects (6 male, age 42.8 ± 8.8 years) were scanned at 3T with 12-ch receive head coil: 1) anatomic whole-brain T1, 2) BOLD-weighted EPI, block-paradigm complex finger tapping fMRI for 156 volumes, 3) EPI, resting state fcMRI for 132 volumes. Both EPI scans were 128x128x31 matrix, 2x2x4mm voxels, TE/TR=29/2800. The EPI datasets were passed to the PESTICA tool [2] to obtain pulse and respiration estimators. Pulse and respiration was also recorded in parallel for scan 3, which was found to have identical periodicity as the estimators for every subject, which was used as validation of the PESTICA procedure for Scan 2. Scan 3 was not used for further analyses. Data was corrected for motion using 3dVolreg, physiologic noise using using PESTICA and RETROICOR [3], and spatially filtered to 4mm FWHM in-plane using a hamming filter.

Coupling Power vs Rate:
3dRetroicor was modified to store the coupling coefficients [see ref 2]. The total mean coupling power is compared with the mean physiologic rate (cardiac and respiratory separately) and linear correlation calculated.

Effect on Activation:
A second branch of data was created by skipping the physiologic noise correction step, to test the effect on the activation results. Both branches of activation data were analyzed using a least-squares fit of a boxcar reference function, representing the 45s off/45s on activation paradigm, to the timeseries data of each voxel [4]. The result is a whole-brain Student's *t* map that can be thresholded to determine regions of significant involvement in the three tapping tasks. Activation volume is calculated as the number of voxels significantly activated above a *t*-score threshold of 3.5 ($P < 0.001$, one-sided, uncorrected). Significance of all differences (Patient activation volume – control activation volume, and uncorrected-RETROICOR corrected) is determined using a two-sample t-test. **It is important to note that these groups are not matched for age or gender and the data was not controlled for subject performance**, as our hypothesis was simply that there will be a difference in the impact of physiologic noise.

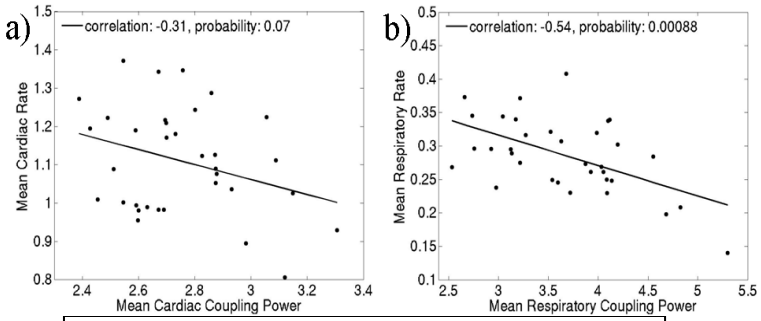

Fig 1: correlations and probabilities a) cardiac rate vs coupling power, b) respiratory rate vs coupling.

Activation Volume	Controls Mean	Controls Stddev	Patients Mean	Patients Stddev	t-test p-value	Difference Con-Pat
Act Vol – UNC	355.25	154.09	308.50	149.79	0.377	46.75
Act Vol - RET	313.63	130.53	299.78	154.53	0.781	13.85
ΔActVol(UNC,RET)	41.63	42.34	8.72	24.66	0.008	NA

Table 1: Activation volumes averaged over 16 controls, 18 MS patients, under uncorrected data and RETROICOR-corrected data. Note difference in activation volume is decreased when data is corrected. **Third row is subject-averaged difference in activation volume between uncorrected and corrected data.** Significant t-test of population difference indicated in yellow.

Results:
Fig 1 shows that physiologic rates have a strong effect on coupling power determined using RETROICOR, with higher rates corresponding to reduced physiologic noise coupling. The physiologic rates were not significantly different between populations, but they trended higher in the controls, with respiration having a greater difference between groups (respiration rate: $R_{patients}$=0.272Hz, $R_{controls}$=3.31Hz, t-test p=0.114). Mean coupling power was also not significantly different between groups (respiratory coupling power in arbitrary units: $P_r^{patients}$=3.826, $P_r^{controls}$=3.469, t-test p=0.117, and cardiac power: $P_c^{patients}$=2.787, $P_c^{controls}$=2.715). Table 1 shows the subject-averaged control and patient group activation volumes for corrected and uncorrected data on the first two rows and the change in activation going from uncorrected to corrected in the third row. The group activation volumes were not significantly different prior to correction or after correction. However, the third row shows physiologic correction produces a significantly different effect on activation volumes in MS patients than in controls. Furthermore, the difference in activation volumes between groups is smaller after correction with RETROICOR. This implies that observations of activation volume differences (or lack thereof) may be under- or over-reported if there are potential group physiologic rate differences and physiologic correction is not used.

Conclusions:
A common neuroimaging finding in MS is increased activation to motor tasks. This result demonstrates that the difference between controls and patients may not be as large as reported. Since coupling was lower in controls, the observation of a greater decrease in activation volume in controls may be surpising. However, this may be due to the unavoidable loss of signal as well as noise with any regression[5], with controls losing the same arbitrary signal but less noise since the noise is better-modeled with higher noise coupling power. This suggests that even in block-paradigm activation datasets, physiologic noise must be accounted for if there are any differences in population. **This indicates potential problems with the accepted practice of ignoring physiologic noise for group functional activation analyses where the populations differ in physiology.**

References:
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4) Lowe et al, J Comput Assist Tomogr 1999; 23:463-473, 5) Beall et al, J Neurosci Meth 2010;187:216-228.