Does the interpretation of task-based BOLD activation in adolescent bipolar disorder require TRUST?

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Target audience. Those interested in physiological and functional neuroimaging in cardiovascular and/or psychiatric populations. ***Purpose.*** 1) To characterize and control for potential global cerebral physiological differences (i.e., base-rate oxygen availability) that may exist in groups with different levels of cardiovascular disease (CVD) in an fMRI study: Individuals with bipolar disorder (BD) have up to a five-fold increased risk of developing CVD over the course of their lifetime[1]. 2) To better understand how *cerebral venous oxygenation (Yv)* (indexed at the sagittal sinus) may interact with functional magnetic resonance (fMRI) signal when contrasting BDs with healthy controls (HC): fMRI contrasts rely on blood oxygenation level dependent (BOLD) T2* signal at a fixation or null-task baseline that is subtracted from BOLD signal after task-related brain recruitment increases oxygenation demands. ***Hypotheses.*** 1) Those with BD will have lower Yv (venous oxygenated hemoglobin) at resting baseline due to the same factors that eventually manifest as CVD. 2) Yv will be negatively correlated with BOLD task signal: Higher Yv will reduce the amount of contrast available after task recruitment. 3) Those with BD will show stronger negative Yv-correlations because the base-rate of Yv will allow for more signal change.

Methods. Thirty-eight adolescents (13-19 years of age; 21 with BD I, II, or NOS and 17 HC) completed the sustained attention to response task (SART). Magnetic resonance imaging (MRI) scans were collected with a 3 Tesla Philips Achieva MRI system using body coil transmission and an 8 channel head receive coil. Scans included: 1) T1-weighted high resolution fast-field echo imaging (TR/TE/TI = 9.5/2.3/1400, spatial resolution 0.94×1.2×1.2mm, 256×164×140 matrix, scan duration 8:38 min). 2) Gradient echo images with BOLD T2*-weighted contrast echo planar imaging (EPI) (TR/TE = 1500/30 ms; 230 volumes). 3) T2-Relaxation-Under-Spin-Tagging (TRUST) venous oxygenation sequence. The following imaging parameters were used for TRUST: a single oblique axial image parallel to anterior-commissure posterior-commissure line positioned a distance of 20mm above the sinus confluence, voxel size 3.44x3.44x5mm3, TR= 3000ms, inversion time=1022ms, labeling thickness=100mm, gap=22.5mm, effective TE=0, 40, 80 and 160ms and a scan duration of 1.2 minutes; see Figure 1 - left. Venous oxygenation (percent saturation, Yv) was estimated by a mono-exponential model in Matlab, by calculating the T2 relaxation of the venous blood [2]. Conventional statistics were analyzed with SPSS software. MRI and fMRI data were analyzed using the FMRIB software library (FSL, v.4.1.9, www.fmrib.ox.ac.uk/fsl) freeware package. T1-weighted scans were used to co-register individuals to a standard space reference brain. fMRI data processing was performed with fMRI Expert Analysis Tool (FEAT, v.5.98). Pre-processing included motion correction with MCFLIRT, brain extraction with BET, spatial smoothing (Gaussian kernel FWHM=5mm), and high-pass temporal filtering (114s). Covariate analysis included mean-centered (across groups) TRUST Yv levels in general linear model (GLM) testing for Group differences. Statistical thresholds were analyzed at alpha = .05 with corrections for multiple comparisons.

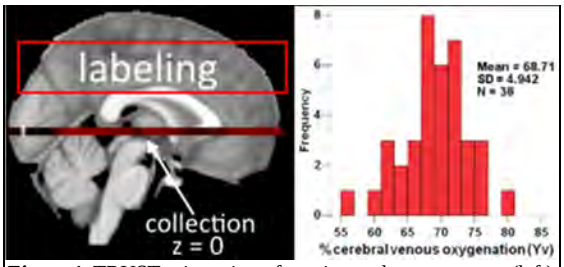

Figure 1. TRUST orientation of tagging and measurement (left). Distribution of Yv in the total sample (right).

Results. BOLD Task (*minus* Fixation) differences were observed in medial frontal cortex including anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) for BD>HC (Figure 2 A, *uncorrected & both*); there were no HC>BD differences. Although global cerebral venous oxygenation % (Yv) was not different between groups (BD = 69%, *SD* = 4.4; HC = 68%, *SD* = 5.6; $p > .5$; see Figure 1 - right), use of Yv as a covariate removed BD>HC activation differences in the left motor network and right dorsal caudate and anterior cingulate cortex regions of interest (ROI) for SART (*cf.* Figure 2 A). Across group, higher base rates of oxygenation were associated with increased Task activity in SART ROIs, left lateral prefrontal cortex (PFC) and bilateral medial ventral PFC (Figure 2 B -left). Lower oxygenation was associated with higher Task signal in a large and diffuse swath of the right hemisphere including subcortical, occipital, parietal, and motor regions (Figure 2 B - right). Critically, the two-group continuous covariate interaction testing for differential effects depending on diagnosis, found positive slope difference for BD>HC in medial PFC and PCC, with additional clusters in inferior parietal and lateral occipital cortex (Figure 3, yellow valence). Negative BD>HC slope differences were restricted to one frontal cluster reaching from left dorsal caudate to putamen toward insula (Figure 3, blue valence). Decomposing the interaction confirmed medial SART ROIs were positively correlated with Yv for the CVD at-risk group but not HCs. Left caudate and putamen activity flipped, with BDs showing negative correlation and HCs a non-significant positive trend.

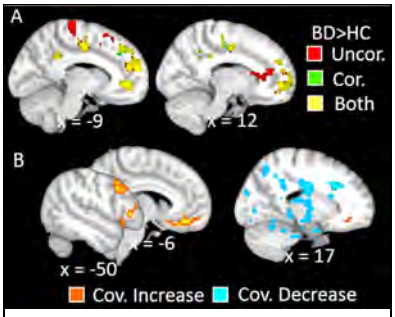

Figure 2. A) BD>HC activation contrasting the effect of correcting for resting cerebral venous oxygenation. B) Both groups combined, task regions for inhibition and attention where Yv positively correlated with BOLD (orange) and in blue, diffuse negative correlation throughout, contralateral.

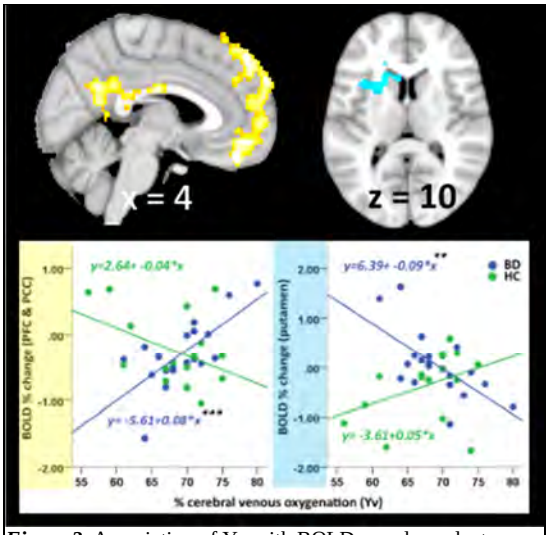

Figure 3. Association of Yv with BOLD was dependent on Group. For cingulate and medial PFC, positive slope difference BD>HC was observed. Post-hoc plot indicates positive association for BD with no significant relationship for HC (*yellow*). Negative slope difference observed for caudate and putamen, post-hoc plot indicates negative association for BD and none for HC (*blue*). ***p*=.002. ****p*<.001.

Discussion. In this adolescent psychiatry study, global cerebral venous oxygenation (Yv) was found to have both positive and negative associations with the BOLD % signal change. The findings indicate a more complex interplay between physiology and activation: 1) There were no group differences in cerebral venous oxygenation at baseline, Figure 1 - right. 2) Across both groups, the Yv relationship with SART activation was positive for regions most implicated in SART performance, Figure 2 B - left. 3) For non-task related regions, i.e. widely distributed, BOLD activity was inversely related to Yv, as predicted, Figure 2 B - right. 4) Much of the positive correlations between SART activity and base-rate oxygen availability in cingulate and medial PFC were driven by the BD group as evidenced by the interaction, Figure 3 - yellow. 5) Regions of covariate interaction were far more dependent on the CVD at-risk group than HC, Figure 3 - bottom.

Conclusion. Cerebral venous oxygenation (Yv) may be an important covariate of interest when comparing patient populations with cardiovascular disease risks above that of the normal population. TRUST is a good option relative to other physiological techniques, such as arterial spin labeling, because of shorter acquisition duration and good reliability [2,3]. Strikingly, differential Group effects of base-rate oxygen availability occurred in the absence of any difference in the estimated oxygenation rate between groups. Future work is needed to better understand how to interpret comparisons of corrected and uncorrected GLMs. For example, if effect differences in the corrected maps are due to meaningful recruitment differences or artefacts of downstream oxygenation demands.

References. **1)** Goldstein BI, Fagiolini et al. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord. 2009;11:657-662. **2)** Lu H, Ge Y. Quantitative evaluation of oxygenation in venous vessels using T2-Relaxation-Under-Spin-Tagging MRI. Magn. Reson. Med. 2008;60:357-6. **3)** Lu H, Xu F, Rodrigue KM, et al. Alterations in cerebral metabolic rate and blood supply across the adult lifespan. Cereb. Cortex 2011;21:1426-34.