Effects of 48hr Sleep Deprivation on Cerebral Blood Flow Measured with Arterial Spin Labeling MRI

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INTRODUCTION Changes in brain function and activity induced by sleep deprivation have negative effects on alertness and cognitive performance [1]. However, to-date, only few studies have investigated the degrading effects of sleep deprivation on normal volunteers [1]. These studies have mostly relied on FDG PET which, in addition to high cost and low availability, requires injection of exogenous radioactive tracers. Continuous Arterial Spin Labeling (CASL) is a non-invasive, feasible and cost-effective MRI technique that provides absolute quantification of CBF with reproducibility, resolution and contrast comparable to PET [2,3]. Furthermore, the long-term stability of ASL and its sensitivity to slow variation in brain function make it ideal for tracking functional changes such as those due to sleep deprivation in brain over several days [4]. The goal of this ongoing study is to quantify and characterize changes in baseline CBF caused by sleep deprivation. We have combined CASL with uni- and multi-variate statistical analysis for detection of CBF regions and network patterns involved in 48h sleep-deprivation. Although univariate methods are more commonly used in fMRI analysis, multivariate techniques can identify patterns that are not captured by the former. Uni-variate methods are based on a region-by-region (or voxel-by-voxel) analysis while in multivariate analysis the correlation/covariance of CBF variation across the brain is evaluated. Thus, the multivariate results can be more easily interpreted as a functional signature of neural networks [4].

METHODS *Subjects:* Here we present data from 19 healthy volunteers (age=26.7±2.5y.o.) with normal sleep patterns, no nicotine and low caffeine use. Subjects had no history of medical, psychiatric, neurological, or sleep disorder conditions. Each subject was scanned at two time-points, D1 and D2, separated by 48 hours of wakefulness which was monitored by staff and confirmed by Polysomnography. Written consent was obtained from all subjects as approved by the institutional IRB. *Imaging:* All images were acquired in a 1.5T scanner (Philips Medical Systems) using a standard transmit-receive head coil. Single shot SE- EPI images were acquired with: TR/TE=4s/36ms, θ=90º; FOV=220x198 mm^2; acq.matrix=64 x 58; 13 slices, thickness/gap = 8mm/1mm; post-label delay (PLD)=800ms; labeling duration =2.0s with the labeling plane positioned 100mm beneath the center of the imaging volume. Adiabatic inversion and correction for MT effects were achieved as described in [2]. For each subject a high resolution, 3D T1 (SPGR) image: TE/TR=3 ms/34 ms, θ=45°, 100 slices, thickness/gap=1.5mm/1mm, FOV=240x240mm^2, acq. matrix=256 x 256 was acquired. All EPI images were motion corrected, co-registered with subject's SPGR image, and spatially normalized to MNI standard brain space using SPM99. Each control-label pair yielded a percent change (Mcontrol-Mlabel/Mcontrol) image which was converted to a CBF [mL/100g•min] map using the formula derived by Alsop *et al.*[2]. For each acquisition slice, the effective PLD was calculated as PLD=[(acq. slice −1)• (64) + 800]ms thus accounting for the inter-slice time acquisition. The resulting CBF images were averaged within subject to yield a single average CBF image per subject per time point.

RESULTS *Voxel-wise analysis:* Fig.1 shows SPM{t} map for the voxel-wise group contrast, D1-D2, corresponding to the CBF difference at each voxel. The contrast showed areas of widespread CBF differences at the uncorrected false-positive rate, $\alpha_{uncorrected}$=0.001. Thalamus (Fig.1, left) and prefrontal cortex (Fig.1, right) were the areas that showed significant decrease in CBF from D1 to D2, in good agreement with involvement of these areas in alertness and high-order cognition [1]. *ROI analysis* Globally, there was a 10% decrease (P=.05) in gray matter (P[GM>.8) D2-CBF *vs* D1-CBF. In thalamus and prefrontal cortex ROIs, the average D2-CBF was 20% (P=.001) and 21% (P=.006) smaller than D1-CBF, respectively, comparing favorably with FDG-PET data [1]. *Covariance Analysis*: The same within-subjects average images that entered the voxel-wise analysis were subjected to covariance analysis. Fig.2 shows the discriminant pattern of the first 12 principal components whose subject expression distinguished D1 and D2 CBF (p=0.01). Fig.3 shows brain areas that were associated with the covariance pattern where red and green areas correspond to the positive and negative loads, respectively.

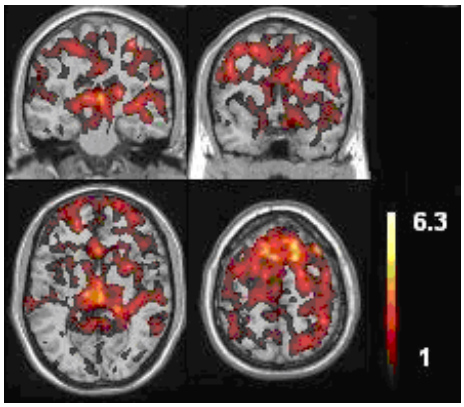

Fig. 1: The SPM{t} map of the D1-D2 contrast overlaid on a high resolution T1 template.

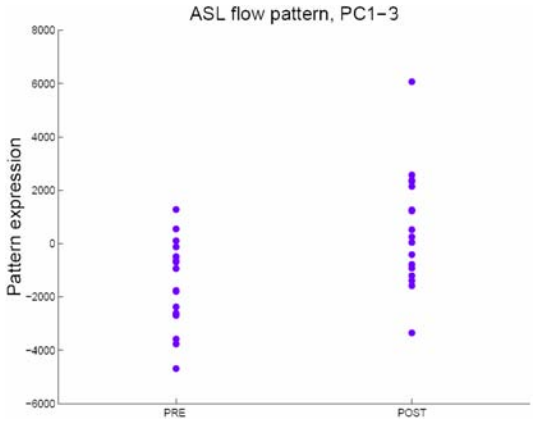

Fig.2: Subject expression values for the discriminant pattern constructed from the first principal components obtained from a covariance analysis using data from 19 subjects at two time points, D1 (pre) and D2 (post)

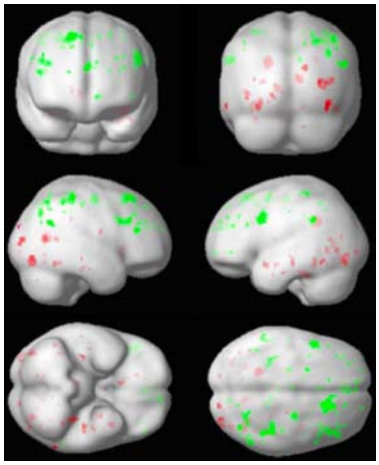

Fig.3: Areas associated with the discriminant pattern that show significantly decreased CBF (p<0.01) in D1 compared to the group discrimination. Red and green show areas with positive and negative loadings, respectively.

DISCUSSION To our knowledge, this is the first study showing CASL data detecting alteration in brain function over 48 hours of sleep deprivation. These results provide evidence that sleep deprivation produces global decreases in CBF, with larger reductions in the cortico-thalamic networks that are known to be involved in mediating attention and high-order cognitive processes. Globally, we found 10% decrease in CBF comparing favorably with 7.8% reported in FDG-PET literature [1]. Covariance analyses showed additional brain networks of deactivation associated with sleep deprivation. Future work is needed to assess the relationship between cognitive performance impairment due to sleep deprivation and CBF.

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