CBF DIFFERENCES BETWEEN HEALTHY AND SCHIZOPHRENIC BRAINS – A FBIRN PHASE 3 MULTISITE STUDY AT 3T USING CBFBIRN DATABASE AND ANALYSIS PIPELINE

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Introduction: Arterial spin labeling (ASL) is a MRI technique that provides a noninvasive and quantitative measure of cerebral blood flow (CBF). Most imaging studies of schizophrenia come from BOLD fMRI, SPECT, and PET [1] and to date there are only three ASL-based studies [2-4] in the literature. We used a pulsed ASL protocol to look at the whole-brain and regional changes in resting CBF between healthy and schizophrenic patients working with a larger sample size than the previous ASL studies. The data were acquired as a part of the multi-center Functional Biomedical Informatics Research Network (FBIRN) Phase III Study [5].

Methods: The study included 234 subjects (173 men vs. 61 women, 112 normal vs. 122 schizophrenic, 38.2 age ± 11.4) recruited from six different sites: Duke University, University of California, Irvine, University of California, San Francisco, University of Iowa, University of Minnesota, and the Mind Research Network. The control and patient groups did not differ significantly in gender ($\chi2 = 0.29$, dof = 1, p = 0.59), study sites ($\chi2 = 2.31$, dof = 5, p = 0.80), and age (t(232) = 1.81, p = 0.07). Imaging at each site was performed with a 3T whole body imaging system (GE Excite System at Duke, Siemens Trio with TIM at all other sites) using a multi-channel receive-only head coil (8-channel on GE system, 12 channel coil with TIM Trio). ASL was performed using a standardized 2D single shot FAIR protocol with presaturation pulses and QUIPSS II post-inversion saturation pulses [6, 7]. The ASL scan parameters were: TI1/TI2 = 600ms/1600ms, 10cm tag width, 1cm tag-slice gap, 220mm FOV, 24 slices (4mm thick, skip 1mm), TR 4 sec, 104 reps, spiral readout (TE = 3ms) for the GE system, partial Fourier EPI readout (TE = 12ms) for the Siemens system. Following the ASL scan, two 30-sec scans were acquired with the ASL module turned off to obtain an estimate of the equilibrium magnetization of cerebral spinal fluid [8] and to correct for transmit/receive coil inhomogeneities [9]. A high resolution anatomical image was acquired, which was registered to the ASL data to identify gray matter (GM) voxels and to warp the CBF map to standard Talairach space for subsequent group analysis. The raw image data and clinical assessments/demographics from all subjects were uploaded to the CBFBIRN Database & Analysis Pipeline (CBFDAP) [10], which was used to generate the individual CBF maps in physiological units of mL blood/100g tissue-min. Two types of group analysis were performed by the CBFDAP Group Analysis Pipeline: 1) a three-way ANOVA to assess the effect of site, gender, and diagnosis on the whole brain mean GM CBF; and 2) a voxelwise two-sample t-test to identify regions of significant group differences between controls vs. patients. For the second analysis, the CBFDAP warped individual CBF maps to standard Talairach space, resampling the maps to a 4x4x4mm resolution grid. Clusters of voxels with group differences were identified using an overall p-value significance threshold of 0.01 where the correction for multiple comparisons was performed using the 3dClustSim AFNI program.

Fig. 1

Fig. 2

Results: *Whole Brain Gray Matter Analysis:* There was a significant main effect of diagnosis (F(1,210) = 4.50, p = 0.035), gender (F(1,210) = 23.00, p = 0.011), and site (F(5, 210) = 3.04, p = 0.011) on the GM CBF but no significant interactions were found between factors, i.e. site did not interact with diagnosis/gender. Duke was found to have higher CBFs than the other sites. Fig. 1 shows the effect of gender and diagnosis on GM CBF, exhibiting lower CBF in schizophrenic patients relative to controls and higher CBF in women relative to men.

Fig. 3

Voxelwise Regional Analysis: CBF differences between controls and patients can be seen qualitatively from averaged CBF brains (Fig. 2). Voxel-level GM CBF comparisons identified 13 significant clusters (p<0.01, corrected) (Fig. 3). Excluding putamen, all regions were characterized by hypoperfusion in schizophrenia.

Fig. 4

Discussion & Conclusion: While the findings of this study are generally comparable to the other ASL studies [2-4], one notable difference is the detection of right insula as a region where CBF was lower in patients. Two separate clusters corresponding to anterior and posterior insula were found with 56 and 19 voxels, respectively (Fig. 4). Given that disruption of processing in insula can contribute to many of the sensory deficits found in schizophrenia [11], our finding may be clinically relevant. Another novel finding of this study is the reported difference in mean GM CBF between healthy controls and schizophrenic patients, likely attributed to increased statistical power from a larger sample size. The multi-site acquisition carried out in this work reflects multiple imaging setups and a relatively heterogeneous patient population, inherently adding to the generalizability of these findings. **References:** [1] Brown et al, Curr Top Behav Neurosci 4:181-214, 2010. [2] Horn et al, Br J Psychiatry 194:130-8, 2009. [3] Scheef et al, Radiology 256:253-60, 2010. [4] Pinkham et al, Psychiatry Res 194:64-72, 2011. [5] Glover et al, JMRI 36:39-54, 2012. [6] Kim et al, MRM 37:425-35, 1997. [7] Wong et al, MRM 39:702-08. [8] Wang et al, MRI 53:666-74, 2005. [9] Chalela et al, Stroke 31:680-7, 2000. [10] Shin et al, Abstract #4010, ISMRM, 2011. [11] Wylie et al, Schizophr Res 123: 93-104, 2010.