Brain Perfusion Differences in Autism Spectrum Disorders

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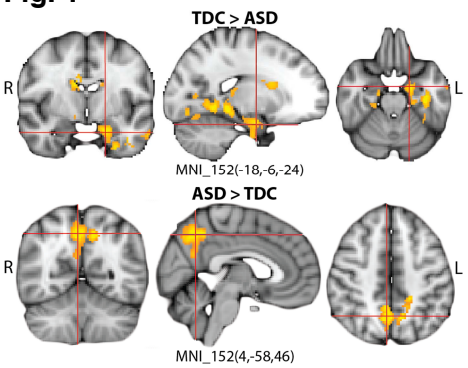
Target audience: Researchers interested in arterial spin labeling (ASL) methods, and applications of ASL to psychiatric populations.

Introduction and purpose: Functional imaging studies of autism spectrum disorders (ASD) have associated deficits in social perception with abnormalities in multiple portions of the temporal lobes – particularly the amygdala, fusiform gyrus, and superior temporal sulcus. Almost all imaging studies to date have relied on differences in blood-oxygenation level-dependent (BOLD) effects derived from experimental task manipulations – i.e., differences in the relative magnitude of BOLD signal changes between two conditions (usually social versus non-social information processing). However, temporal lobe deficit models of ASD suggest that alterations in brain function are a phenotypic trait that should also be present at rest. Arterial Spin Labeling (ASL) allows noninvasive quantification of cerebral blood flow (CBF), which is coupled to regional neural activity, and can be used as a measure of regional brain function at rest [1]. We used ASL to measure regional CBF within temporal lobe structures in ASD during a resting state passive viewing task.

Methods: *Participants:* 26 typically developing controls (TDC) and 33 children with ASD (mean ages = 14.9 years for both groups) viewed a six-minute video (The Discovery Channel's "Planet Earth") while pseudo-continuous ASL (pCASL) data were collected**.** Our goal in presenting the video was to provide some between-group consistency in the deployment of basic attentional orienting. The ASD group was diagnosed following CPEA (Collaborative Programs of Excellence in Autism) guidelines [2], which included diagnostic gold standards: Autism Diagnostic Observation Schedule – Generic (ADOS-G) and Autism Diagnostic Interview-Revised (ADI-R), by research reliable clinicians. The assessment battery included a variety of additional measures including the Behavior Rating Inventory of Executive Function (BRIEF), which includes eight subscales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor).

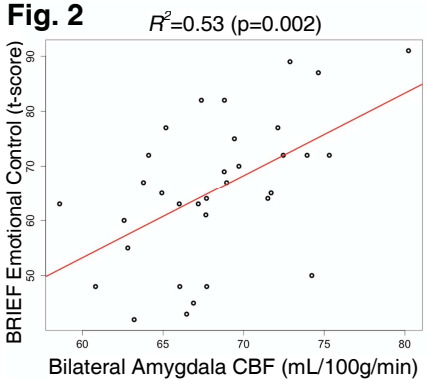
Scanning protocol: Scanning was carried out using a Siemens Verio 3T scanner with a 32-channel head coil. High-resolution structural MRI data (MPRAGE sequence, .9 x .8 x .8 mm, TR/TE=2000/3.3 ms) were collected for each participant in order to generate brain regions of interest (ROIs) and register ASL data into standard space. CBF was measured using pCASL with a 2D gradient-echo echo-planar sequence. The labeling and control RF duration was 1.5 sec with post-labeling delay of 1.2 sec. Multi-slice perfusion maps with 40 label/ control pairs were acquired (TR/TE=4000/17 ms, flip angle=90^0, bandwidth=3005 Hz/pixel, slice thickness=5mm, matrix size=64×64, FOV=220×220 mm^2 and slice number=20).

Fig. 1



Data preprocessing and analysis: ASL images were processed using a perfusion data processing toolbox, ASLtbx [3]. EPI data were first motion-corrected using a 6-parameter rigid body spatial transformation and coregistered to the MPRAGE images of the same session. Pairwise subtraction images were generated and images with signal spikes caused by motion artifacts were removed according to previously published criteria [3]. Averaged difference images were converted to mL/100 g/min using a single-compartment model [4]. Each subject's MPRAGE dataset was segmented into probabilistic gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) maps. A binary global mask was then created by adding together GM and WM masks. The global mask was used as an ROI to extract CBF for whole-brain area from the individual CBF map. Per-voxel CBF (rCBF) maps were then generated by normalizing CBF to global CBF for each subject. rCBF images were normalized to the Montreal Neurological Institute (MNI) brain template using the program SPM. Spatial smoothing was applied with a 3D isotropic Gaussian kernel (FWHM=8 mm). Group-level analyses were performed using the FMRIB Software Library [5]. Group difference maps were generated via t-tests carried out at each intracerebral voxel. Resulting maps were subject to a voxel-wise threshold ($p < 0.01$) and FSL's Gaussian random field theory cluster correction ($p<0.05$). Regions of interest for post-hoc analyses (i.e., amygdala) were defined on a per-participant basis by running the MPRAGE volumes through the Desikan-Killiany parcellation scheme available in Freesurfer [6].

Fig. 2



Results: The ASD group showed decreased CBF in large portions of the temporal lobes within or adjacent to multiple brain areas involved in social perception, including fusiform gyrus and amygdala (see Fig. 1) as compared to the TDC group. The only area where the ASD group showed increased rCBF was in precuneus. Post-hoc analyses indicated that CBF in amygdala was significantly correlated with the Emotional Control scale of the BRIEF (see Fig. 2).

Conclusion: This study is among the first to establish absolute CBF deficits within critical social intelligence regions in a sample of children with ASD. These data add to the growing literature associating the social deficits of ASD with abnormalities in temporal lobe structures. Correlations between amygdala CBF and emotional control are consistent with emerging findings regarding amygdala hyperactivation and abnormal emotion regulation processes in ASD. The unexpected finding of increased precuneus rCBF is consistent with prior reports of reduced deactivation in default mode network regions during fMRI tasks for individuals with ASD [7,8] as well as siblings [8]. This study supports the growing use of ASL as a measure of functional brain phenotype in the study of region-specific deficits associated with psychiatric conditions.

References: 1. Detre et al., JMRI 2012; 35: 1026-37. **2.** Lainhart et al., Am J Med Genet A 2006; 140A: 2257-74. **3.** Wang et al., MRI 2008; 26: 261-9. **4.** Wang et al., MRM 2003; 50: 599-607. **5.** Jenkinson et al., NeuroImage 2012; 62: 782-90. **6.** Desikan et al., Neuroimage 2007; 31: 968-980. **7.** Kennedy et al., PNAS 2006; 103: 8275-8280. **8.** Spencer et al., Brain 2012; 135: 3469-3480.

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