



Excellent test-retest reliability of cerebral blood flow in healthy individuals measured with arterial spin labeling: EMBARC study preliminary results

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Sponsor: Linda Carpenter- Abstract has been updated since submission

Background: Cerebral blood flow (CBF) at rest is a widely used method of examining baseline states in both healthy individuals and those with neurological or psychiatric disorders. Most of the studies measuring CBF used invasive technologies, due radioligands, to measure CBF, such as, positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Arterial spin labeling (ASL) is a magnetic resonance imaging technologies to measure CBF using endogenous water as a tracer and, therefore, ASL is non-invasive technique. ASL has been used to measure blood flow in different areas of the body (e.g. lungs and kidney) for more than two decades. Only recently ASL was applied to study CBF in healthy and psychiatric populations. The simplicity of the MRI protocol, and the strength and reliability of emerging analysis makes it a promising avenue for the development of biomarkers to examine longitudinal changes during the treatment process. Previous investigations of the test-retest reliability of resting ASL have generally revealed an optimistic picture. In the present study, we seek to add to this literature and compare test-retest reliability across experimental sessions in a group of healthy control individuals. This will provide information about the relative magnitude of the reliability of the resting across different experimental sessions. We will examine test-retest reliability within relative mean cerebral blood flow in regions of interest (default mode network, salience network). We hypothesize that intraclass correlations (ICC) will be around 0.6-0.8. Furthermore, we will examine the effect of site on the cerebral blood flow measures within these regions.

Methods: We measured cerebral blood flow in forty healthy controls in two different scan sessions one week apart in four different experimental sites. Columbia University used GE scanner, University of Texas Southwestern and University of Michigan used a Philips scanner, while Massachusetts General Hospital used a Siemens scanner. All scanners were 3 Tesla. Pseudo-continuous arterial spin labeling protocols were maximized to achieve best balance between performance, and quality while maintaining similar parameters. Data was processed using SPM4s and cerebral blood flow was derived from arterial spin labeling images with an automated algorithm. Regions of interest for the default mode and salience network included: bilateral ventrolateral and dorsolateral, ventromedial, dorsomedial prefrontal cortex, bilateral amygdala, bilateral insula, anterior and posterior cingulate cortex and bilateral ventral striatum. ICCs were calculated using IBM SPSSv21. Cronbach's Alpha was considered poor if lower than 0.40, fair if between 0.40 and 0.58, good if between 0.59 and 0.75, and excellent if greater than 0.75.

Results: All Cronbach's Alpha measures were good or excellent. The highest alpha was associated with the anterior cingulate cortex (0.9) and the lowest was associated with the left ventral striatum (0.6).

Discussion: Cerebral blood flow measured with arterial spin labeling revealed excellent/good reliability across sessions in both networks. Site had a variable impact on cerebral blood flow measure depending on the region of interest. The salience network was more stable across sites compared to the default mode network. Our excellent/good reliability measure paralleled other arterial spin labeling studies and highlights the importance of this non-invasive technique to investigate biomarkers in psychiatric populations using magnetic resonance imaging.

Background:

Cerebral blood flow (CBF) at rest is a widely used method of examining baseline states in both healthy individuals and those with neurological or psychiatric disorders. Increased blood flow anterior cingulate cortex (ACC) is a well-replicated finding in MDD^{1,2}.

Invasive technologies: radioligands - positron emission tomography (PET) and single-photon emission computed tomography (SPECT).

Non-invasive technology: endogenous water as a tracer - arterial spin labeling (ASL) protocol - magnetic resonance imaging.

Promising biomarker: simplicity of the MRI protocol, strength and reliability of emerging ASL analysis: examine longitudinal changes during the treatment process.

Previous studies: test-retest reliability of resting ASL have generally revealed an optimistic picture, with high indices of reliability across sessions^{3,4}.

Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC): Randomized, placebo-controlled trial of a serotonin selective reuptake inhibitor and placebo for participants with major depressive disorder (MDD).

Aim: examine test-retest reliability within relative mean cerebral blood flow in regions of interest (default mode network, salience network).

Hypothesizes: intraclass correlations (ICC) will be around 0.6-0.8. Scan site will have a variable effect on ICC.

Methods and Materials

Subjects: 40 healthy control participants (HC): 10 in each site - Columbia University (CU), Massachusetts General Hospital (MGH), University of Texas Southwestern Medical Center (UTSW) and University of Michigan (UM).

Each subject was tested twice in the same site, one week apart.

Data from six participants were not included in the analysis: four participants had only one data point and two had severe artifact in at least one data point.

The study was approved by the IRB of each institution. Written informed consent was obtained from all participants.

Arterial Spin Labeling*

Tag Image Control Image

1. Tag inflowing arterial blood by magnetic inversion

2. Acquire the TAG IMAGE

3. Repeat experiment without tag the blood flow

4. Acquire the CONTROL IMAGE

5. The difference in magnetization between control and tag conditions is proportional to regional cerebral blood flow.

Non invasive and short duration

Academic and clinical MRI centers

At rest

MRI Acquisition and Image Processing

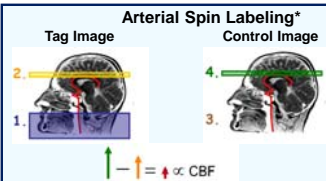
3.0 Tesla MRI scanner: MGH= Siemens; UTSW and UM=Philips and CU= GE

pCASL Parameters: Labeling duration of 1650ms and post-labeling delay of 1525ms. TR/TE = 4000ms/14ms, in-plane resolution 3x3mm², 29 slices, 5mm thickness, whole brain, scan duration of appr. 6 min.

Image Processing: pre-processed and analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) and matlab toolbox⁵ that was specifically adapted to EMBARC at the University of Pittsburgh.

ICC analysis: calculated using IBM SPSS v21. Cronbach's Alpha was considered poor if lower than 0.40, fair if between 0.40 and 0.58, good if between 0.59 and 0.75, and excellent if greater than 0.75.

Regions of interest: default mode and salience network - bilateral ventrolateral and dorsolateral, dorsomedial prefrontal cortex, bilateral amygdala, bilateral insula, anterior and posterior cingulate cortex and bilateral ventral striatum.



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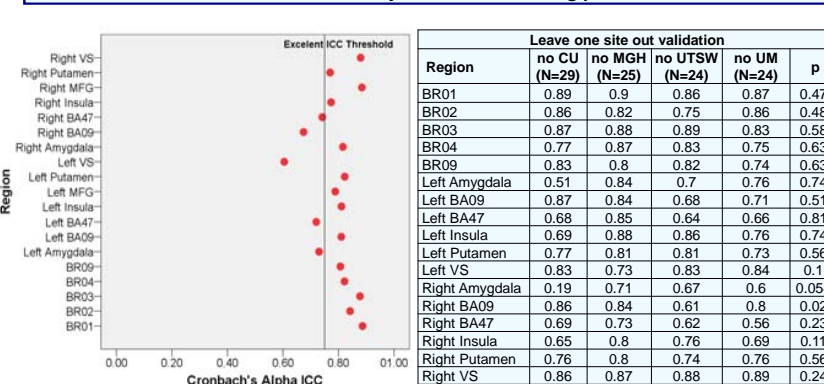
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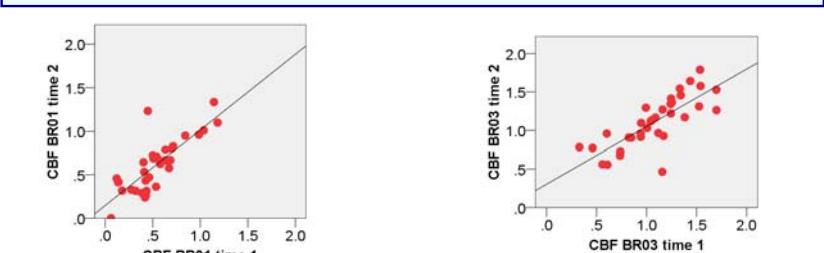
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References:1) Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology*. 2010. 2) Almeida JR, et al. Pattern recognition analysis of anterior cingulate cortex blood flow to classify depression polarity. *Br J Psychiatry*. 2013. 3) Wu B, et al. Intra- and interscanner reliability and reproducibility of 3D whole-brain pseudo-continuous arterial spin-labeling MR perfusion at 3T. *J Magn Reson Imaging*. 2013. 4) Pfefferbaum A, et al. Volumetric cerebral perfusion imaging in healthy adults: regional distribution, laterality, and repeatability of pulsed continuous arterial spin labeling (pCASL). *Psychiatry Res*. 2010. 5) Wang Z, et al. Assessment of functional development in normal infant brain using arterial spin labeled perfusion MRI. *Neuroimage*. 2008. 6) Klomp A, et al. Feasibility of ASL-based pMRI with a single dose of oral citalopram for repeated assessment of serotonin function. *Neuroimage*. 2012.

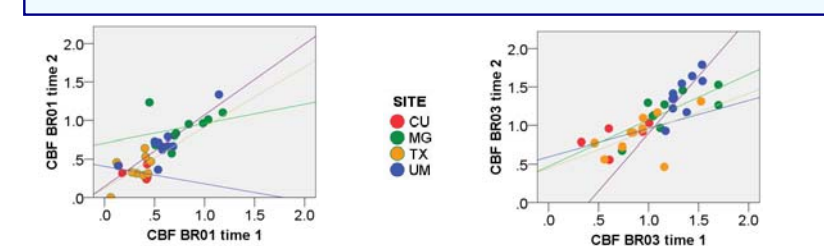
Test-retest reliability of CBF in HC using pCASL



Excellent ICC in Anterior Cingulate Cortex Cerebral Blood Flow



Site Effect on Test-retest Reliability



Discussion and conclusions

- Cerebral blood flow measured with pseudo-continuous arterial spin labeling revealed excellent/good reliability across sessions in both networks.
- Site had a variable impact on cerebral blood flow measure depending on the region of interest. Both networks were reasonable stable over time.
- Significant SSRI challenge on CBF values measured with pASL, but not replicated over time⁶.
- Our excellent/good reliability measure paralleled other arterial spin labeling studies and highlights the importance of this non-invasive technique to investigate biomarkers and treatment effect in psychiatric populations using MRI.

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