

# Cerebral Blood Flow Differences in Major Depressive Disorder using Arterial Spin Labeling: Preliminary Results from the EMBARC Study



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## ABSTRACT

**Background:** Arterial spin labeling (ASL) is a noninvasive neuroimaging technique used to measure cerebral blood flow (CBF; i.e., perfusion) and could be used as an effective tool to understand resting state abnormalities in patient populations such as major depressive disorder (MDD). So far, previous research using ASL in depression revealed CBF abnormalities in the default mode network in some cases (Orosz et al., 2012). ASL has also been observed to accurately classify unipolar from bipolar depression based on differences in CBF of the anterior cingulate cortex (ACC; Almeida et al., 2013). Given these findings, ASL could become a prospective biomarker of disease state as well as treatment choice and monitoring in the clinical setting with more research. The EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) study is a nation-wide randomized control trial investigating such biomarkers in MDD. ASL is being investigated in order to identify differences in CBF between patients with MDD and healthy controls. **Methods:** Participants consist of 40 healthy controls and 100 patients with MDD before starting medication. All participants were scanned in one of four sites, and underwent 3T MRI scanning, which included an ASL scan that used pseudo-continuous labeling, i.e. PCASL, and lasted approximately 6 minutes. CBF was compared between the healthy control and MDD groups using a whole-brain voxel-by-voxel analysis. **Results:** Preliminary results show several regions of interest to be significantly different between the two groups. These include regions such as the ACC, insula cortex, and caudate. Clusters in these regions were significant at  $t = 3.21$ ;  $p < .001$ ; with at least 50 continuous voxels set at the extent threshold. Patients with MDD were observed to have reduced perfusion in the ACC, insula, and caudate relative to healthy controls. **Discussion:** While ASL has been more widely used as a research tool, it has the prospects of being used as a tool for clinical diagnostics and informing treatment decisions. Our present work provides further evidence to the role of ASL in detecting abnormalities in resting CBF for multiple brain regions including those that are implicated in the default mode network as well as other regions thought to be important in the phenotype of MDD. These preliminary results may have implications for future studies aimed at further developing CBF as a biomarker in clinical populations. In this regard, the final sample of the EMBARC study, which will include roughly 400 patients with MDD and their outcomes data, will provide evidence for the application of CBF to predict treatment outcomes in MDD.

## BACKGROUND

Arterial spin labeling (ASL) is a noninvasive neuroimaging technique used to measure cerebral blood flow (CBF).

Has promise to be used as an effective tool to understand resting abnormalities in patient populations such as major depressive disorder (MDD).

Past research has shown the following differences in CBF using ASL:

### Recent ASL Studies

Default Mode Network Abnormalities  
(Orosz et al., 2012)

Classify Unipolar from Bipolar Depression  
(Almeida et al., 2013)

Analytic Methodology  
(Aslan & Lu, 2010; also Almeida et al., 2013; Orosz et al., 2012)

**Goal:** Identify differences in CBF between patients with MDD and healthy controls using ASL.

## THE EMBARC STUDY

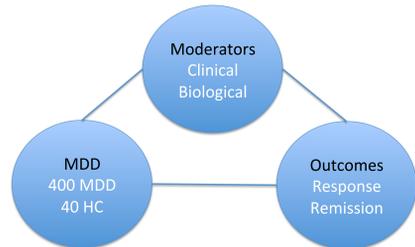
**Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC)**

Randomized, placebo-controlled trial of a serotonin selective reuptake inhibitor and placebo for participants with major depressive disorder (MDD).

Assess clinical (e.g., anxious depression, early life trauma, gender) and biological (i.e., neuroimaging, electrophysiology and behavioral neuropsychiatric) moderators and mediators of outcome.

Aim: Identify clinical, neuroimaging, neurophysiological, and behavioral moderators and mediators of differential treatment outcome (mean symptom change and tolerability) for MDD, which will then be used to develop a differential depression treatment response index (DTRI).

Four Participating Sites  
(Data Collection):  
UT Southwestern Medical Center  
Columbia University  
University of Michigan  
Massachusetts General Hospital

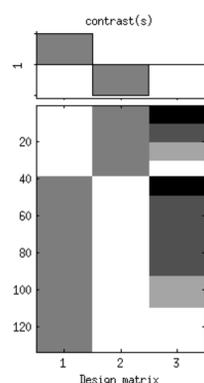


## ASL METHOD

**Preliminary Sample:**  
100 MDD Patients at Baseline  
40 Healthy Controls at Baseline

**ASL Parameters:**  
A pseudo-continuous labeling technique with a labeling duration of 1650ms and post-labeling delay of 1525ms was used. Other imaging parameters where: TR/TE = 4000ms/14ms, in-plane resolution 3x3mm<sup>2</sup>, 29 slices with 5mm thickness which cover the whole brain, 70 dynamics, with scan duration of approximately 6 minutes.

**ASL Processing and Analyses:**  
Both absolute and relative CBF for the healthy control (HC) group and the MDD clinical trial (MDD) group was processed. Two-way ANOVAs controlling for the effect of site were conducted using SPMS.

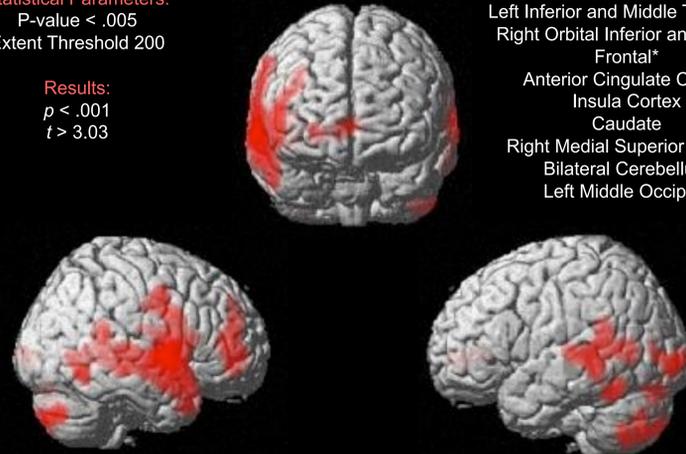


## ASL RESULTS

**Absolute CBF:**  
(HC > MDD)

**Statistical Parameters:**  
P-value < .005  
Extent Threshold 200

**Results:**  
 $p < .001$   
 $t > 3.03$

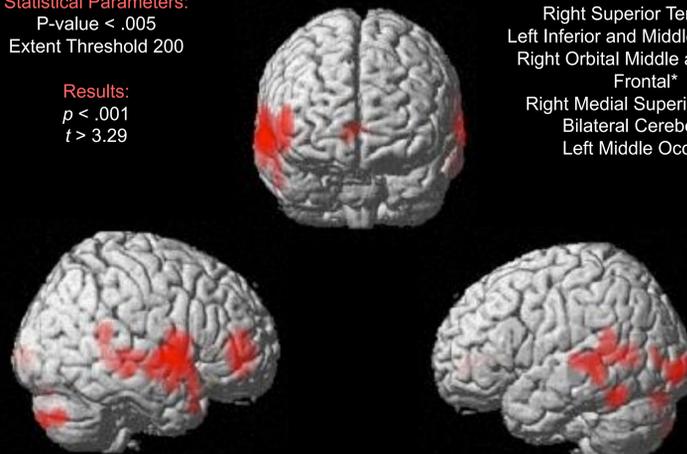


**Clusters:**  
Right Superior Temporal\*  
Left Inferior and Middle Temporal\*  
Right Orbital Inferior and Middle Frontal\*  
Anterior Cingulate Cortex  
Insula Cortex  
Caudate  
Right Medial Superior Frontal  
Bilateral Cerebellum  
Left Middle Occipital

**Relative CBF:**  
(HC > MDD)

**Statistical Parameters:**  
P-value < .005  
Extent Threshold 200

**Results:**  
 $p < .001$   
 $t > 3.29$

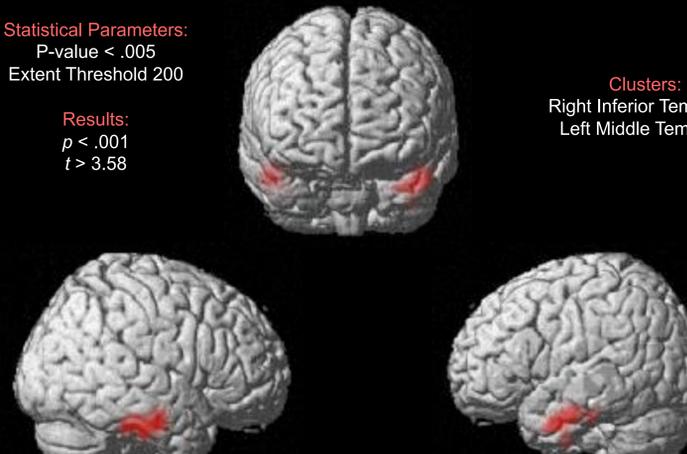


**Clusters:**  
Right Superior Temporal\*  
Left Inferior and Middle Temporal\*  
Right Orbital Middle and Middle Frontal\*  
Right Medial Superior Frontal  
Bilateral Cerebellum  
Left Middle Occipital

**Relative CBF:**  
(MDD > HC)

**Statistical Parameters:**  
P-value < .005  
Extent Threshold 200

**Results:**  
 $p < .001$   
 $t > 3.58$

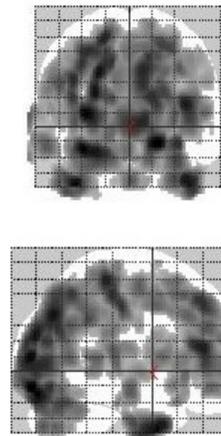
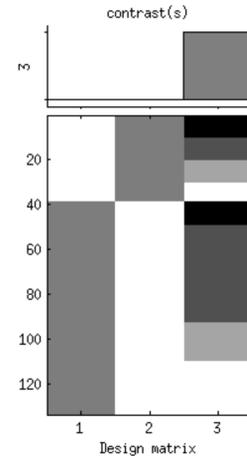


**Clusters:**  
Right Inferior Temporal\*  
Left Middle Temporal

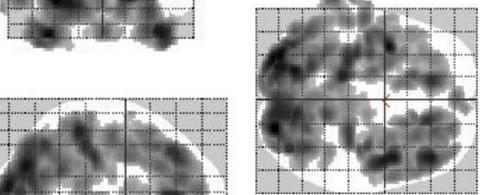
\*Significant Clusters that remained after increasing the extent threshold and controlling for site

## ASL RESULTS (CONT'D)

**Site Effect:**  
(Example from Absolute CBF)



**Statistical Parameters:**  
P-value < .005  
Extent Threshold 200



## CONCLUSIONS

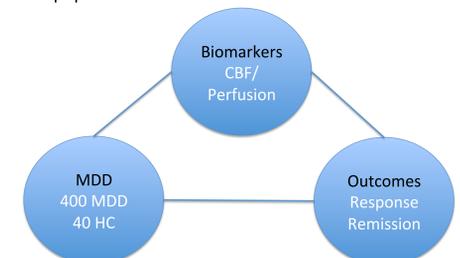
While ASL has been more widely used as a research tool, it has the prospects of being used as a tool for clinical diagnostics and informing treatment decisions.

Our present work provides further evidence of the role of ASL in detecting abnormalities in resting CBF for multiple brain regions thought to be important in the phenotype of MDD.

It should be noted, that throughout preliminary analyses, some brain regions appear to be more or less sensitive to site effects. This is important to understand, and should be investigated and considered further in future research and analyses using multiple sites.

These preliminary results may have implications for future studies aimed at further developing CBF as a biomarker in clinical populations.

The final sample of the EMBARC study, which will include roughly 400 MDD patients and their outcomes data, will provide evidence for the application of CBF to predict treatment outcomes.



## REFERENCES

- Almeida, JRC et al. Use of pattern recognition analysis of anterior cingulate cortex blood flow to classify bipolar v. unipolar depression. *British Journal of Psychiatry*. 2013
- Aslan S, Lu H. On the sensitivity of ASL MRI in detecting regional differences in cerebral blood flow. *Magn Reson Imaging*. 2010 Sep;28(7):928-35.
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## DISCLOSURES

Authors have no conflicts to disclose in relation to this study. Lifetime or other disclosures can be made available upon request.