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Early-treatment cerebral blood flow change as a predictive biomarker of antidepressant treatment response: evidence from the EMBARC clinical trial

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Original Article

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Abstract

Background. Major depressive disorder (MDD) is one of the most prevalent and disabling illnesses worldwide. Treatment of MDD typically relies on trial-and-error to find an effective approach. Identifying early response-related biomarkers that predict response to antidepressants would help clinicians to decide, as early as possible, whether a particular treatment might be suitable for a given patient.

Methods. Data were from the two-stage Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) trial. A whole-brain, voxel-wise, mixed-effects model was applied to identify early-treatment cerebral blood flow (CBF) changes as biomarkers of treatment response. We examined changes in CBF measured with arterial spin labeling 1-week after initiating double-masked sertraline/placebo. We tested whether these early 1-week scans could be used to predict response observed after 8-weeks of treatment.

Results. Response to 8-week placebo treatment was associated with increased cerebral perfusion in temporal cortex and reduced cerebral perfusion in postcentral region captured at 1-week of treatment. Additionally, CBF response in these brain regions was significantly correlated with improvement in Hamilton Depression Rating Scale score in the placebo group. No significant associations were found for selective serotonin reuptake inhibitor treatment.

Conclusions. We conclude that early CBF responses to placebo administration in multiple brain regions represent candidate neural biomarkers of longer-term antidepressant effects.

Introduction

Major depressive disorder (MDD), one of the most prevalent and disabling illnesses, is a serious public health problem worldwide (Global Health Data Exchange (GHDx), 2021; Mathers and Loncar, 2006). This prevalent mental health ailment not only exacts a profound toll on individuals but also places a substantial burden on healthcare systems and societal well-being. When considering antidepressants in terms of efficacy, acceptability and tolerability, sertraline is many prescribers' first-line choice for people with major depression (Cipriani et al., 2010). This preference aligns with the neuroimaging focus of the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study, which concentrates on neural circuits modulated by serotonin. Sertraline, known for its impact on serotonin levels, is particularly pertinent to the study's objectives (Trivedi et al., 2016).

Though antidepressant medications are used as a first-line treatment for MDD, fewer than 40% of patients achieve remission with the initial treatment (Gaynes et al., 2009; Holtzheimer & Mayberg, 2011). Thus, MDD treatment continues to rely on a trial-and-error approach for each patient to find an effective approach. As suggested by current treatment guidelines, at least 4 weeks at a therapeutic dose are required to assess if a particular antidepressant is working (Gautam, Jain, Gautam, Vahia, & Grover, 2017). Many patients have to try two or more different antidepressants before finding one that works (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). This lengthy process due to choosing the 'wrong' initial treatment can increase the risks of morbidity, suicidality, and treatment discontinuation, and requires significant health care resources and high patient motivation and compliance.

Identifying early response-related biomarkers that can predict antidepressant responses would help clinicians to decide as early as possible whether a particular treatment is likely suitable for a given patient (Breitenstein, Scheuer, & Holsboer, 2014; McGrath et al., 2013). This would improve the efficiency of MDD treatment trials, would free up much-needed healthcare resources, and could ultimately speed remission for many patients (Dunlop & Mayberg, 2014).

In recent decades, the use of non-invasive neuroimaging techniques to try to identify biomarkers that can predict treatment response in MDD has been growing rapidly. Neuroimaging methods include brain volumetric magnetic resonance imaging (MRI), functional MRI (fMRI), electroencephalography (EEG), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), near-infrared spectroscopy (NIRS), and molecular imaging, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) (Kang & Cho, 2020). One such technique is fMRI, which uses the blood-oxygenation-level-dependent (BOLD) signal to indirectly measure neural activity, and it is most frequently used to estimate functional connectivity relationships in the brain (Dunlop, Talishinsky, & Liston, 2019; Fan et al., 2020).

The clinical trial EMBARC (Trial registration number: NCT01407094, http://clinicaltrials.gov/show/NCT01407094) was designed to address critical gaps in the MDD literature with a large, multisite, randomized, placebo-controlled structure (Trivedi et al., 2016). Unique to EMBARC's study design is the acquisition of both pretreatment and early-treatment (1 week into treatment) BOLD and perfusion fMRI scans, with the goal of investigating associations with the treatment's eventual efficacy.

Several studies have used functional connectivity or brain activity data obtained from pre-treatment BOLD fMRI in EMBARC to predict the outcome of antidepressant treatment, including response or remission (Fatt et al., 2020, 2021a, 2021b; Greenberg et al., 2020; Nguyen et al., 2022). These studies have yielded interesting findings, such as that higher connectivity within the default mode network predicted better outcomes specifically for sertraline, as did greater between-network connectivity of the default mode and executive control networks (Fatt et al., 2020). Other findings include the association of increased connectivity (i) within the limbic network, (ii) between the hippocampus and visual network, and (iii) between the salience network and dorsal attention network in subgroups that experienced greater improvement with placebo (Fatt et al., 2021b). In addition, lower reward-related ventral striatum activity was associated with better response to medication treatment (Greenberg et al., 2020). BOLD fMRI has thus provided valuable insights into the brain's functioning and how it relates to antidepressant treatment outcomes.

Another less-used MRI-based measure is cerebral blood flow (CBF). CBF is considered a more direct marker of brain activity and metabolism, which has been shown to be sensitive even to regional differences in neural activity and metabolic demands (Riedl et al., 2014). CBF reflects neural activity through neurovascular coupling which enables a more straightforward physiological interpretation. It has typically been assessed using nuclear medicine techniques like SPECT and PET. In studies of individuals with MDD, PET scans have shown a significant reduction in regional CBF in the frontal, parietal, and temporal regions (Drevets, Bogers, & Raichle, 2002; Smith & Cavanagh, 2005). Arterial Spin Labeling (ASL) is a newer technique that enables researchers to quantify CBF using MRI data. ASL uses arterial blood water as an endogenous diffusible tracer by using radiofrequency pulses to invert magnetization of blood as it enters the cerebral circulation. The signal difference between control and labeled images provides a measure of labeled arterial blood delivered to tissues by perfusion, providing a reliable quantification of CBF without the use of radiation or contrast (Alsop et al., 2015). Unlike PET or SPECT, it has a relatively short scan-time, is suitable for automated processing, and enables direct interpretability of a quantifiable physiological measure. These characteristics make ASL an advantageous option for use in clinical studies and biomarker research, and ultimately would make it well-suited for use in clinical practice.

Both the reliability of CBF measures obtained by ASL and its potential as a disease-state marker in MDD have been previously investigated. ASL has been shown to identify reliable differences in perfusion for multiple brain regions implicated in MDD (Cooper et al., 2020; He et al., 2019; Orosz et al., 2012; Yin et al., 2018). Of particular relevance here, two previous studies have demonstrated that pre-treatment ASL perfusion levels are predictive of treatment outcome. Relative to placebo, pretreatment perfusion levels in multiple brain regions contributed to predicting sertraline response (Cooper et al., 2019). In addition, increased pre-treatment perfusion levels of the orbitofrontal cortex and the anterior cingulate cortex were associated with poor antidepressant response (Daou, Boyd, Donahue, Albert, & Taylor, 2017).

One challenge to this promising line of inquiry is that pretreatment perfusion levels may differ by age and sex (Liu et al., 2012) and/or by depression severity (Orosz et al., 2012). This variability currently limits the utility of pretreatment perfusion levels as a diagnostic marker of MDD. One way to partially mitigate these challenges is to leverage within-subject measures of signal change. Behaviorally, studies have reported that improvement of clinical symptoms within the first weeks of antidepressant treatment can predict subsequent treatment outcome with high sensitivity in patients with MDD (Nierenberg, 2003; Szegedi et al., 2009), so looking for an early, immediate marker of subsequent response fits with clinical impressions. Certain factors suggest that ASL may be especially well-suited for capturing meaningful longitudinal changes in CBF which could be used to predict treatment outcome. For example, ASL was shown to be sensitive to short-term medication effects, including after a single dose of citalopram (Chen et al., 2011). The observed effects of citalopram appeared to normalize or downregulate CBF in specific regions that were known to be elevated in MDD, and these results were only observed in regions known to be highly serotonergic. Additionally, a SPECT study revealed that increased CBF in the left and mid anterior cingulate, left superior temporal gyrus and orbital prefrontal cortex was associated with better treatment response to serotoninergic antidepressants (Vlassenko, Sheline, Fischer, & Mintun, 2004). Despite these promising results, the use of ASL to identify early perfusion-based markers of later antidepressant response has not yet been investigated, including in EMBARC data.

The aim of the current study was to determine whether early CBF response (measured with ASL from fMRI data) predicts subsequent antidepressant response. We leveraged longitudinal data from the two-stage EMBARC trial to test our hypotheses. We hypothesized that CBF changes after 1-week of treatment would be predictive of treatment response to 8-weeks of sertraline/placebo treatment.

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Materials and methods

Participants

EMBARC is a large, multicenter, double-blind, randomized, placebo-controlled trial evaluating treatment response to sertraline in patients with MDD. EMBARC aims to identify clinical, behavioral, and biological moderators of antidepressant response in MDD, with the goal of developing differential Treatment Response Indices of multiple biosignatures. MDD participants were scanned using MRI that included a resting ASL sequence before treatment initiation and one-week after starting treatment. The rationale and full study design for EMBARC has been previously described (Trivedi et al., 2016). Briefly, outpatients were recruited into EMBARC after approval by the institutional review board at each site. All enrolled participants provided written informed consent and were between 18 and 65 years of age. Patients met criteria for MDD based on the Structured Clinical Interview for DSM-IV Axis I Disorders, scored ⩾14 on the Quick Inventory of Depressive Symptomatology Self-Report at both screening and randomization visits, and were free of antidepressant medication for >3 weeks prior to completing any study measures. To reduce heterogeneity, only patients with early onset MDD (before age 30 years) and chronic (episode duration >2 years) or recurrent MDD (⩾2 recurrences) were enrolled. Study procedures were approved by the Institutional Review Boards of all sites. Participants provided written informed consent after receiving a complete study description.

Prior to treatment, patients were assessed with the 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1986). Patients were then randomized to placebo or sertraline (titrated to 200 mg daily), with at least a 21-day medication free period prior to randomization. The course of treatment was restricted to 8 weeks, at which time participants were re-administered the HDRS-17. At week 8, participants were assessed with the Clinical Global Improvement scale (CGI) and participants who received a score of less than 'much improved' were considered non-responders. This designation was also given to participants who completed 8 weeks with unacceptable/intolerable adverse effects despite dose reduction. Participants who did not complete the eighth week assessment were classified as 'not available'. Primary outcomes were reduction in depressive symptoms measured using HDRS-17 and medication tolerability measured with the Frequency, Intensity, and Burden of Side Effects Rating (Wisniewski, Rush, Balasubramani, Trivedi, & Nierenberg, 2006).

For this study, we included data from 230 participants with two usable ASL scans both at baseline and week 1 (EMBARC data available at https://nda.nih.gov/edit_collection.html?id=2199). This included 117 participants randomized under double-masked conditions to receive sertraline and 113 to receive placebo.

Data acquisition and imaging parameters

MRI scans were performed at pretreatment and 1 week into treatment. MRI scanning took place across 4 sites using 3 Tesla scanners: Columbia University (CU – General Electric scanner), Massachusetts General Hospital (MGH – Siemens scanner), University of Michigan (UM – Philips scanner), and the University of Texas Southwestern (UTSW – Philips scanner). T1-weighted images were acquired. MPRAGE sequences were acquired at UTSW, UM and MGH, while an IR-FSPGR sequence was acquired at CU. Sequence parameters were as follows: TR/TE = 5.9–8.2/2.4–4.6 ms, 8–12° flip angle, 1 mm slice thickness, 4.4–5.5 min acquisition, and 1 mm isotropic voxel dimensions.

All ASL sequences implemented a resting-state, pseudo-continuous technique (pCASL) with a 1516 ms labeling duration and 1500 ms post-labeling delay across sites. Other ASL parameters were: TR/TE = 4460 ms/17 ms, in-plane resolution $3.4 \times 3.4\ mm^2$, with 5 mm thickness covering the whole brain, field of view = 220 × 220 × 145 mm, matrix = 64 × 64; flip angle = 90°, multi-slice acquisition in ascending order, 29 slices, 70 dynamics, no background suppression, with scan duration of approximately 5 min.

Image processing

MRI data were preprocessed and analyzed with ASLPrep version 0.2.8 (Adebimpe et al., 2022). The anatomical preprocessing workflow in ASLPrep leverages sMRIPrep (version 0.6.1), a structural magnetic resonance imaging (sMRI) processing pipeline. sMRIPrep performs basic processing steps including subject-wise averaging, bias field correction, segmentation, and spatial normalization.

ASL preprocessing workflows include reference volume selection, motion estimation, co-registration and distortion correction. After ASL preprocessing, the stream for CBF computation and denoising used FSL's Bayesian Inference for Arterial Spin Labeling (BASIL) toolbox. CBF maps calculated using BASIL were then normalized to the Montreal Neurological Institute (MNI) 152 brain template using parameters derived from the segmentation, resampled to 2 × 2 × 2 mm and smoothed with full-width at half maximum 8 mm kernel using the toolbox for Data Processing & Analysis for Brain Imaging (DPABI; Yan and Zang, 2010; Yan, Wang, Zuo, and Zang, 2016).

A quality evaluation index (QEI), an excellent proxy of CBF image quality (Dolui, Wolf, Nabavizadeh, Wolk, & Detre, 2017), was also computed for CBF using ASLPrep. The QEI provides an objective quality evaluation of CBF maps. It quantifies the quality of the CBF image based on structural similarity, spatial variability, and percentage of voxels in gray matter with negative CBF values.

Structural similarity

Structural images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) tissue probability maps (TPMs) and structural pseudo CBF (SPCBF) maps were constructed for each subject by $50GM_{TPM} + 20WM_{TPM}$, assuming mean CBF in GM and WM to be 50 and 20, respectively. The Pearson's correlation coefficient between SPCBF and the actual CBF map for each subject constituted the first metric.

Spatial variability

Considered the pooled variance of GM, WM and CSF CBF and normalized by the mean GM CBF, yielding an Index of dispersion = variance/mean.

Negative GM CBF

Percentage of voxels in GM with negative CBF was the third metric.

The ratings follow a $1\text{-}\exp(-a\ x^b)$ relationship with structural similarity and a $\exp(-a\ x^b)$ relationship with the other two metrics, where x stands for the different metrics. Consequently, models

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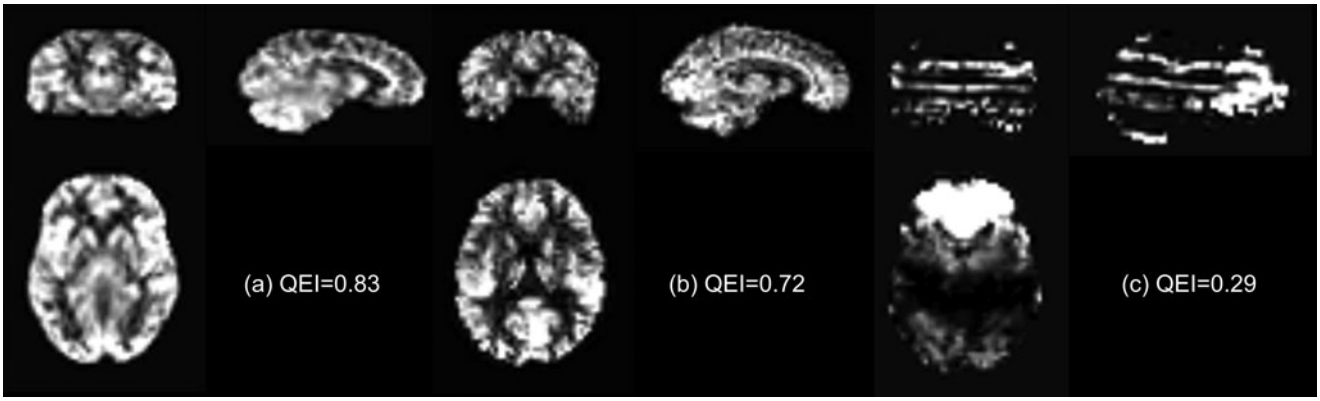

Figure 1. Representative images from Quality Evaluation Index (QEI) assessments.
Examples of CBF maps (a) Excellent (QEI = 0.83) (b) Average (QEI = 0.72) (c) Poor (QEI = 0.29).

were fit to the data to compute these three terms and the final QEI was computed as the geometric mean of the three terms.

QEI ranges from 0 from 1, with higher values indicating higher quality CBF maps. Figure 1 shows representative cases from this sample. CBF maps with QEI $\geqslant$ 0.7 were included for further analysis. This excluded 17 subjects from the SER group and 14 subjects from the PLA group.

Statistical analysis

Demographic and clinical characteristics were analyzed using the Statistical Package for Social Sciences software (SPSS, version 22; IBM). Chi-square was calculated to determine whether the sex distributions between responders and non-responders, within and between datasets, differed significantly, and an independent Mann–Whitney U test was used to determine differences in age and baseline HDRS-17 scores. For all analyses, the level of significance was set at $p < 0.05$, two-tailed.

Linear mixed effect analysis

A voxel-wise analysis of CBF change was performed to determine the effects of treatment (sertraline v. placebo), response (responders *v.* non-responders after 8 weeks), and treatment response interaction on cerebral blood flow changes from baseline (pretreatment) to week 1 (early treatment) with age, sex, and site as covariates using the statistical analysis module from DPABI toolbox. The resulting statistical map was set to $p < 0.01$ at the single voxel level, and to $p < 0.05$ at the cluster level, two-tailed, with Gaussian random field (GRF) correction. CBF changes were calculated from baseline to one week after treatment initiation: CBF changes = (post-treatment$_{1st-week}$ - pre-treatment) / pre-treatment.

Exploratory post hoc ROI-based analyses

Any significant regional post hoc CBF effects found were further examined in exploratory analyses to determine if the neuroimaging effect predicted the HDRS-17 scores change during the 8-week trial. CBF changes here were calculated as percent-change from baseline to one week after treatment initiation: CBF changes = 100% × (post-treatment$_{1st-week}$ - pre-treatment)/pre-treatment. HDRS score changes were calculated as percent-change from baseline to after eight weeks of treatment: HDRS-17 changes = 100% × (pre-treatment - post-treatment $_{8th-week}$)/pre-treatment. Linear regression models were fit with HDRS-17 score change as the outcome for the significant predictors from primary testing.

Results

Participant characteristics

A total of 199 participants had high-quality ASL data both at baseline and 1-week after treatment. Participants included in the analyses were 18 to 65 years of age (119 women, mean age 38.0 ± 13.3 years).

Of the total patient sample with two usable ASL scans (QEI $\geqslant$ 0.7; $N = 199$), 40% were considered responders, including 44% (44/100) of those who received sertraline and 35% (35/99) who received placebo. Twenty percent (20/100) of the MDD participants who received sertraline and 13% (13/99) of the MDD participants who received placebo failed to complete the eighth week assessment. In summary, the following analyses include 44 sertraline responders *v.* 36 sertraline non-responders, and 35 placebo responders *v.* 51 placebo non-responders. Demographic and clinical data are shown in Table 1. No significant differences were identified between the groups in terms of age, race, or male/female ratio across the assigned treatment arms.

Whole-brain mixed effects model shows treatment × response interactions

A whole-brain voxel-wise linear mixed-effects model was applied to determine the effects of treatment (sertraline *v.* placebo), response (responders *v.* non-responders after 8 weeks), and treatment response interaction on cerebral blood flow changes from baseline (pretreatment) to week 1 (early treatment). This analysis revealed two statistically significant moderators of treatment outcome (treatment × response interaction). We observed significant group differences in CBF changes in temporal cortex and postcentral region as shown in Fig. 2a and 3a (voxel $p < 0.01$, cluster $p < 0.05$, two-tailed, GRF corrected). For only non-chronic subjects, we observed significant group differences in CBF changes in the similar postcentral region as shown in Fig. 3a (voxel $p < 0.01$, cluster $p < 0.05$, two-tailed, GRF corrected).

Early-treatment CBF alterations were differentially associated with clinical response across the treatment arms. This effect was driven by early treatment changes in temporal cortex and

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Table 1. Demographic and clinical characteristics for responder and non-responder status stratification

	Sertraline responder (N = 44)	*Sertraline non-responder (N = 36)*	*P value*	*Placebo responder (N = 35)*	*Placebo non-responder (N = 51)*	*P value*
Sex	16 M 28 F	11 M 25 F	0.585[a]	14 M 21 F	20 M 31 F	0.942[a]
Age	38.4 ± 14.0	39.1 ± 14.7	0.881[b]	36.0 ± 12.1	38.5 ± 12.3	0.318[b]
Race	32 White, 7 African American, 1 Asian, 4 Other	24 White, 8 African American, 2 Asian, 2 Other	0.700[a]	24 White, 5 African American, 4 Asian, 1 Other, 1 Alas	38 White, 7 African American, 1 Asian, 5 Other	0.191[a]
Pretreatment HDRS-17	18.7 ± 4.65	19.4 ± 4.04	0.435[b]	18.0 ± 4.16	19.7 ± 4.09	0.035[b]
Posttreatment HDRS-17	6.36 ± 3.59	16.9 ± 4.56		5.23 ± 4.67	16.55 ± 5.61	

Values are presented as the mean ± standard deviation. F, female; HDRS, Hamilton Depression Rating Scale; M, male.
[a]Determined by x^2 test.
[b]Determined by independent Mann–Whitney U test.

postcentral regions in the placebo group. Post hoc analysis revealed that individuals responding to the placebo exhibited notable increases in CBF within the temporal cortex from baseline to the first week of treatment ($p = 0.002$; Figure 2b). Early-treatment CBF decreases were identified in individuals responding to the placebo, particularly in postcentral regions ($p < 0.001$; Figure 3b). The difference in the association between the early treatment changes observed in temporal cortex and postcentral region and response to placebo had effect sizes of $d = 0.657$ and 0.884, respectively. No significant associations were observed for the sertraline group.

Association between CBF response and 8-week treatment response

To investigate whether early treatment CBF change predicts treatment outcome at week 8, linear regression models were fit with HDRS-17 score change as the outcome for the significant predictors from primary testing (i.e. temporal cortex and postcentral CBF change with placebo) within all participants of each treatment group separately. Results showed a significant positive relationship between HDRS-17 score and perfusion changes in the temporal cortex after placebo ($r = 0.306$; $p = 0.004$; Figure 4a) and a negative relationship between HDRS-17 score and perfusion changes in the postcentral region ($r = -0.292$; $p = 0.006$; Figure 4b). There was no significant relationship between regional CBF changes in either ROI and HDRS score changes in sertraline group (Fig. 4c and d).

Discussion

The EMBARC dataset provides a unique opportunity to examine baseline and short-term alterations in brain activity occurring after one week of sertraline or placebo administration. Cerebral blood flow alterations in the 1-week interval used in this study have been shown to be detectable via 3 T ASL MRI. Our primary whole-brain analysis revealed a significant effect of placebo on ASL-derived measures of cerebral blood flow following one week of treatment in the EMBARC trial. These CBF alterations differentially associate with clinical treatment response across placebo and sertraline treatment groups and were associated with change in symptom severity for participants in the placebo treatment arm. When used as ROIs for secondary correlational analyses, early CBF response in temporal cortex and postcentral region was related to longer-term depression improvement in the placebo group (HDRS-17 score changes after 8 weeks). Taken together, this study shows that ASL can be used to identify early, within-subject changes in CBF that relate to subsequent

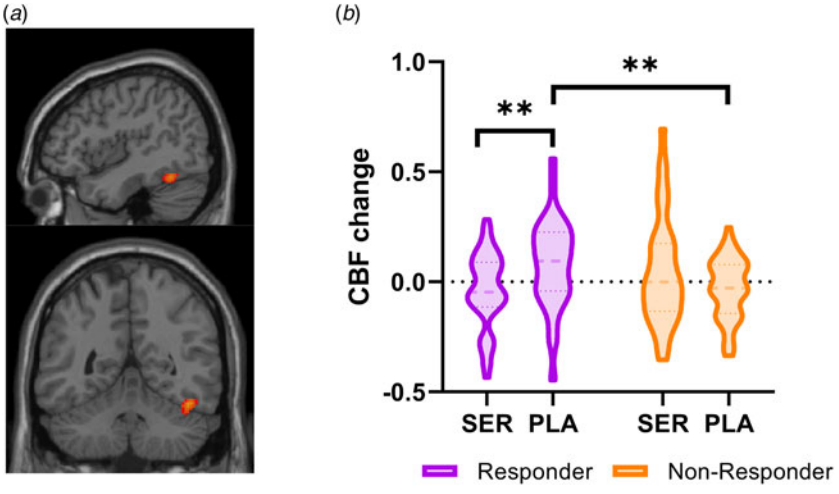

Figure 2. Treatment (sertraline v. placebo) × response (responders v. non-responders) interaction.
(a) Cluster of temporal cortex that showed significant treatment × time interaction among the sertraline responder and non-responder groups and placebo responder and non-responder groups, overlaid on mean structural image (cluster forming threshold $p < 0.01$, GRF corrected $p < 0.05$). (b) The bar plots show the results of the post-hoc t tests of the early-treatment CBF differences in temporal cortex between sertraline responder and non-responder groups and placebo responder and non-responder groups. The asterisks ** represent $p < 0.01$.

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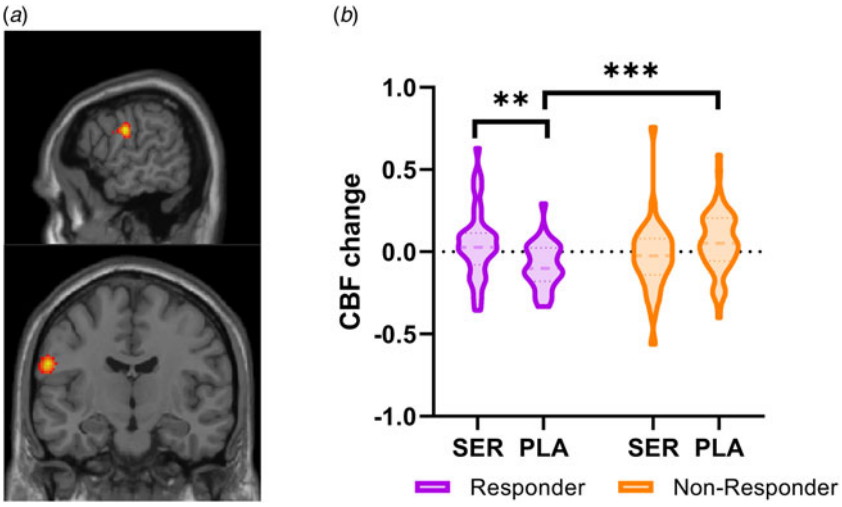

Figure 3. Treatment (sertraline v. placebo) × response (responders v. non-responders) interaction.
(a) Cluster of the postcentral region that showed significant treatment × time interaction among the sertraline responder and non-responder groups and placebo responder and non-responder groups, overlaid on the mean structural image (cluster forming threshold $p < 0.01$, GRF corrected $p < 0.05$). (b) The bar plots show the results of the post-hoc t tests of the early-treatment CBF differences in temporal cortex between sertraline responder and non-responder groups and placebo responder and non-responder groups. The asterisks ** represent $p < 0.01$, *** represents $p < 0.001$.

clinical outcomes in MDD that are treatment-specific. In this case, the identified changes associated only to placebo, but the specificity and clinical relevance of the findings suggests that this paradigm – the use of longitudinal, within-subject ASL measures at baseline and early treatment perfusion scans – could potentially be used clinically to inform treatment selection, fulfilling a primary aim of the current study.

Despite the presence of significant antidepressant-induced alterations in CBF, these early changes did not differ significantly between sertraline responders and non-responders (i.e. there was no interaction-related difference observed). This is contrary to previous work in which baseline CBF was related to sertraline treatment response (Cooper et al., 2019). Consistent with previous findings (Leuchter, Cook, Witte, Morgan, & Abrams, 2002),

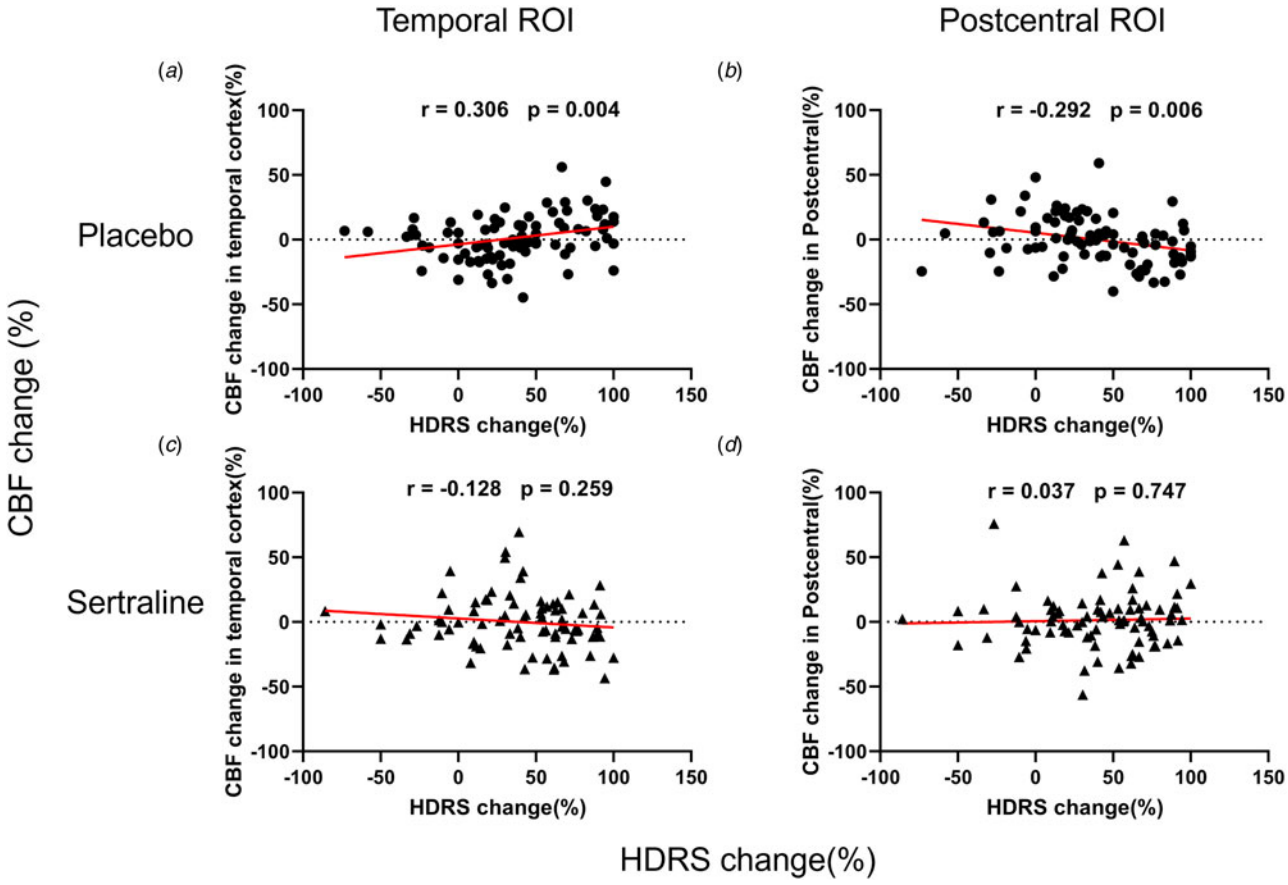

Figure 4. Linear regression model to represent associations between the 8-week symptom improvement as HDRS-17 score change and early-treatment CBF change in (a) temporal cortex and (b) postcentral region in the Placebo group.
Relationship of 8-week symptom improvement with early-treatment CBF change in (c) temporal cortex and (d) postcentral region in the Sertraline group.

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placebo and medication treatments have distinct effects on brain function and time courses, though the symptomatic improvement resulting from placebo and medication treatment may be similar. It is widely accepted that there is a 2–4 week delay in the onset of the therapeutic effects of SSRIs (Quitkin et al., 1987). The lack of change in CBF in the sertraline group may reflect this slower onset of action for sertraline compared to placebo. Additionally, 8-weeks is on the shorter side for SSRI treatments to take full effect, and our results may have been different if a longer treatment duration had been used. The small sample size of the sertraline group likely also limited our ability to identify a significant treatment-by-response interaction, particularly if sertraline response has more neural heterogeneity than placebo response.

In this study, the observed alterations in regional CBF associated with placebo response for MDD patients occurred mainly in temporal cortex and a postcentral region, demonstrating significant CBF differences following the 1-week placebo treatment.

The finding that the placebo responders showed an increased CBF in temporal cortex here may relate to previous work implicating CBF itself in putative pathophysiological mechanisms of MDD. Physiological control of CBF is critical to dynamically meet shifting neuronal metabolic energy needs throughout the brain. Decreased CBF can reflect cardiovascular dysfunction or disruption of neuronal micro-environmental homeostasis (Tarumi & Zhang, 2018). Lower CBF in MDD participants relative to healthy controls has been previously reported in temporal cortex regions (Chen et al., 2015; Cooper et al., 2020), which could be a common characteristic of brain hemodynamics in MDD. Reduced glucose metabolism in temporal cortex has also been found in depression patients (Su, Shi, Guan, Zuo, & Zhang, 2006). Anatomical studies also show differences in gray matter volumes involving temporal regions in MDD, such as lower volumes in the hippocampus and amygdala (Grieve, Korgaonkar, Koslow, Gordon, & Williams, 2013; Peng, Chen, Yin, Jia, & Gong, 2016; van Eijndhoven et al., 2013). These findings suggest a close relationship within temporal regions involving both CBF abnormalities and depressive symptoms, and the findings reported here reinforce the idea that the temporal cortex may be a critical neural substrate for depression.

To date, the most reliable markers of response to various modes of treatment for depression have been identified in temporal regions. For example, some studies have found that SSRIs increase activity in the amygdala, a key structure within the temporal cortex that is involved in the processing of emotional information (Godlewska, Browning, Norbury, Cowen, & Harmer, 2016; Victor, Furey, Fromm, Öhman, & Drevets, 2010). Another study found that electroconvulsive therapy responders showed CBF increases in right middle and left posterior hippocampus (Leaver et al., 2021). Increased neural activity in a region would lead to increased CBF, which is consistent with our findings that early increased CBF in temporal cortex was associated with later positive response to placebo. CBF remained decreased among non-responders, which may indicate continuing impairment of, and lower levels of activity in, those brain regions. The observed changes in CBF for responders could similarly be interpreted as a normalization of perfusion in affected regions.

However, decreased metabolism after 1 week of treatment was simultaneously observed in a postcentral region among the placebo responders. The postcentral gyrus includes the primary somatosensory cortex, which is structurally and functionally connected to the thalamus (Zhang et al., 2008; Zhang, Snyder, Shimony, Fox, & Raichle, 2010). Abnormal function of this area and its connectivity with the thalamus have been suggested as a potential biomarker for MDD, given their association with core clinical MDD symptoms including cognitive dysfunction (Kang et al., 2018). Although CBF is globally reduced in depressed patients compared to healthy controls (Chithiramohan et al., 2022), greater gray matter volume was found in the postcentral gyrus (Wise et al., 2017). Research studies have shown a positive correlation between gray matter volume and cerebral blood flow (Várkuti et al., 2011). Therefore, we speculate that hyperperfusion may exist in the postcentral region of MDD patients at baseline relative to healthy controls, and that this hyperperfusion significantly decreases towards normalization over time following placebo treatment.

Our study suggests that the placebo effect may be partly mediated by changes in cerebral blood flow in both the temporal cortex and postcentral brain regions. Specifically, we observed that the placebo effect was associated with increased CBF in cortices related to emotion processing and decreased CBF in sensory and association regions, which were in turn associated with therapeutic responses. Further studies are needed to confirm whether these changes reflect a compensatory mechanism for blood flow between different brain regions. One possible explanation is that as depressive symptoms subside, the patient's ability to regulate emotions improves, leading to increased activity in the relevant brain areas and decreased cerebral blood flow to the areas associated with somatosensory aspects. In addition, if compensatory mechanisms do exist between the two brain regions, alterations in cerebral blood flow in the temporal cortex and postcentral brain region portions of the brain may be able to be combined as potential moderators of treatment response.

In the EMBARC trial, the efficacy of placebo did not significantly differ from sertraline in the primary analysis. The patients who receive a placebo also reported experiencing significant improvements in their condition due to psychological factors like expectancy and belief. This may arise for the following reasons. First, in relatively small samples, random variation can lead to outcomes where there is no statistically significant difference between the placebo group and the group receiving the active drug. This is especially true if the sample size is not large enough to detect smaller differences. Second, individuals with MDD can have varying responses to treatment. Some patients may respond well to both the active drug (sertraline) and placebo, while others may not respond at all. This variability in patient response can make it more difficult to demonstrate a significant difference between the two groups. In addition, eight weeks may not be a sufficient duration to fully capture the therapeutic effects of sertraline. Some patients with MDD may require a longer treatment period to experience the full benefits of the medication.

Regardless, placebo effects can be quite powerful. In recent years, the placebo effect has garnered significant attention as a potential factor in treating depressive disorders. Randomized controlled trials have shown that the placebo effect may account for up to 67% of the treatment effect in patients receiving antidepressants (Rief et al., 2009).

Neuroimaging markers, such as resting-state between-network or within-network connectivity (Fatt et al., 2020, 2021b), brain activity in ventral striatum (Greenberg et al., 2020; Nguyen et al., 2022) or dorsolateral prefrontal cortex (Fatt et al., 2021a) and baseline perfusion level of multiple brain regions (Cooper et al., 2019) have been shown to be significantly associated with better clinical response to placebo. However, despite this progress, the underlying mechanism of the placebo effect remains poorly

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understood, and research indicates that it involves a complex interplay between psychological and physiological factors. Our study's findings on the placebo effect could aid future research into the mechanisms underlying placebo effects, pain mitigation, and/or resilience (Koban, Kross, Woo, Ruzic, & Wager, 2017; Wager & Atlas, 2015; Watanabe & Takeda, 2022). Furthermore, identifying the characteristics of participants more likely to respond to placebo could be valuable for future research studies, as individuals highly likely to respond to placebo could be screened out, reducing the necessary sample size and increasing the power of treatment trials to detect differences between active treatment and placebo.

Several study limitations must be considered. First, our stringent quality control criteria limited our subgroup sample sizes. In addition, sample size restricted our analysis to response rate rather than remission. Second, CBF differences have been observed to differ by race (Moonen et al., 2020), and most of the EMBARC sample is White. Thus, our findings may not generalize to other races (i.e. Asians, Blacks). Third, EMBARC participants had only chronic, early-onset MDD. Newly depressed or late-stage MDD populations should also be included in future studies. Fourth, as legacy data, EMBARC did not use currently recommended protocols for pseudo-continuous ASL, that is, post-labeling delay of 2000 ms and labeling duration of 1800 ms (Alsop et al., 2015). Differences in ASL protocol parameters may impact results. Additionally, ASL MRI scans incorporating background suppression can improve temporal SNR (Bokkers et al., 2012; Ghariq, Chappell, Schmid, Teeuwisse, & van Osch, 2014; Wang et al., 2012). As no background suppression was used in the EMBARC ASL protocol, future extensions of this approach may reveal additional or more extensive clusters predicting treatment response. Another limitation is that the current study lacked CBF measures at week 8, which might have revealed whether cortical CBF changes after a full course of treatment are associated with treatment response.

In conclusion, we found that cerebral perfusion in temporal cortex increased after 1-week of placebo treatment, while cerebral perfusion in the postcentral region decreased after 1-week of placebo treatment. These alterations predicted treatment efficacy after 8-weeks of placebo treatment. These data suggest that early CBF response measured within a patient across two scans may be a neural biomarker of longer-term response to placebo treatment. The incorporation of placebo response biomarkers into the treatment of MDD could help improve the efficiency of treatment trials, and the utility of this approach (a within-subject comparison of ASL measures early in treatment) should be explored further with larger samples and longer treatment durations for SSRIs.

Our study underscores the significance of early CBF changes in predicting clinical outcomes in major depressive disorder, particularly in the context of placebo treatment. In future, the full potential of these findings may be realized when integrated with other predictors, including inflammatory markers (Kofod, Elfving, Nielsen, Mors, & Köhler-Forsberg, 2022) and BDNF (Cavaleri et al., 2023) to create a holistic framework for personalized antidepressant treatment selection and monitoring. Future research in this direction holds promise for improving the effectiveness of depression management strategies.

Data availability statement. The data that support the findings of this study are openly available in 'Establishing Moderators/Biosignatures of Antidepressant Response - Clinical Care (EMBARC) MDD Treatment and Controls' at https://nda.nih.gov/edit_collection.html?id=2199.

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Competing interests. None.

Ethical standards. The EMBARC clinical trial was conducted according to the FDA guidelines and the Declaration of Helsinki and approved by Institutional Review Board at each clinical site.

Clinical Trial Registration Identifier: NCT01407094.

URL: http://clinicaltrials.gov/show/NCT01407094.

All EMBARC study components received approval from an ethical standards committee prior to study initiation.

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