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Cerebral Blood Perfusion Predicts Response to Sertraline versus Placebo for Major Depressive Disorder in the EMBARC Trial

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ABSTRACT

Background: Major Depressive Disorder (MDD) has been associated with brain-related changes. However, biomarkers have yet to be defined that could "accurately" identify antidepressant-responsive patterns and reduce the trial-and-error process in treatment selection. Cerebral blood perfusion, as measured by Arterial Spin Labelling (ASL), has been used to understand resting-state brain function, detect abnormalities in MDD, and could serve as a marker for treatment selection. As part of a larger trial to identify predictors of treatment outcome, the current investigation aimed to identify perfusion predictors of treatment response in MDD.

Methods: For this secondary analysis, participants include 231 individuals with MDD from the EMBARC study, a randomised, placebo-controlled trial investigating clinical, behavioural, and biological predictors of antidepressant response. Participants received sertraline (n = 114) or placebo (n = 117) and response was monitored for 8 weeks. Pre-treatment neuroimaging was completed, including ASL. A whole-brain, voxel-wise linear mixed-effects model was conducted to identify brain regions in which perfusion levels differentially predict (moderate) treatment response. Clinical effectiveness of perfusion moderators was investigated by composite moderator analysis and remission rates. Composite moderator analysis combined the effect of individual perfusion moderators and identified which contribute to sertraline or placebo as the "preferred" treatment. Remission rates were calculated for participants "accurately" treated based on the composite moderator (*lucky*) versus "inaccurately" treated (*unlucky*).

Findings: Perfusion levels in multiple brain regions differentially predicted improvement with sertraline over placebo. Of these regions, perfusion in the putamen and anterior insula, inferior temporal gyrus, fusiform, parahippocampus, inferior parietal lobule, and orbital frontal gyrus contributed to sertraline response. Remission rates increased from 37% for all those who received sertraline to 53% for those who were *lucky* to have received it and sertraline was their perfusion-preferred treatment.

Interpretation: This large study showed that perfusion patterns in brain regions involved with reward, salience, affective, and default mode processing moderate treatment response favouring sertraline over placebo. Accurately matching patients with defined perfusion patterns could significantly increase remission rates.

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Trial Registration.

Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMARC) Registration Number: NCT01407094 (https://clinicaltrials.gov/ct2/show/NCT01407094).

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Research in context

Evidence before this study

Cerebral blood perfusion, as measured by Arterial Spin Labelling (ASL), is a robust, widely available, quantitative measure of brain function. ASL-derived perfusion is comparable to other perfusion techniques, such as positron emission tomography, providing information on oxygen and nutrient delivery to brain tissue noninvasively. While ASL-derived perfusion has been mainly used to investigate cerebrovascular disease, dementia and neuro-oncology, it is gaining traction in psychiatry. At the time of this investigation, ASL-derived perfusion was only used in 19 biosignature investigations of Major Depressive Disorder (MDD) to understand perfusion-markers of disease (15 studies) or to understand perfusion-markers of treatment response (4 studies). These results were derived from a search of Pubmed and Google Scholar for any article published up to August 2018. These studies either constituted small sample sizes, lacked placebo-control, or did not investigate differential prediction of response using pre-treatment perfusion. Studies investigating perfusion-markers of treatment response in MDD have used outcome (response or non-response) to treatment to divide the scans (pre-treatment, post-treatment when available) by response group for analyses. Perfusion differences between treatment response groups do not identify which perfusion-markers are differential predictors (moderators) of outcome prior to starting treatment, but rather only characterise perfusion differences between response groups.

Added value of this study

This is the first and largest randomised, placebo-controlled trial to investigate biosignatures of treatment response to antidepressant medication using ASL-derived cerebral blood perfusion. This data-driven study used pre-treatment perfusion levels to identify moderators of response over time to SSRI or placebo in major functional networks. Regions identified to be moderators of treatment response overlap with prior work that aimed to characterise perfusion-markers or treatment response of MDD, including key brain regions of major functional networks disrupted in MDD (e.g., reward, affective, and resting-state processing networks). Remission rates doubled for those participants who accurately received the treatment that their perfusion-markers indicated, post hoc, they should be preferentially assigned.

Implications of all the available evidence

In primary care and psychiatric settings, MDD treatment is provided by trial-and-error, solely based on clinical information over months. As part of a 2002 research agenda report by the American Psychiatric Association, the neuroscience research agenda aimed to guide development of a pathophysiologically-based classification system that may aid clinical decisions. Pre-treatment perfusion-derived predictors of treatment response found in this study provide evidence that such biosignatures, if validated, hold promise to aid treatment decision-making at the individual-patient level and improve remission rates in MDD.

1. Introduction

Major Depressive Disorder (MDD) is stated to be the leading cause of disability worldwide by the World Health Organization. With remission rates for MDD remaining low, roughly 30%, change is needed to improve outcomes [1]. While MDD is associated with brain-related changes, such biologically-based markers to aid diagnosis and treatment selection remain elusive [2]. The current trial-and-error treatment paradigm then results in mismatched treatment selection, thereby delaying the identification of the most appropriate, effective treatments for an individual [3,4]. Magnetic resonance neuroimaging has shown promising results in MDD and yet, brain imaging-based moderators of treatment outcome have not been established, especially through placebo-controlled trials [5]. Of the modalities to assess brain function, Arterial Spin Labelling (ASL) is a short, noninvasive neuroimaging technique that reliably measures cerebral blood flow (CBF; perfusion) using a magnetic pulse, opposed to a radioligand, to label blood as it perfuses through the brain to provide oxygen and other nutrients to tissue. This generates a quantifiable measure of perfusion without radiation exposure that can be compared within and across individuals to identify brain function associated with neuropsychiatric disorders and their treatment [6,7].

In recent work, both reliability of cerebral blood perfusion and its potential as a disease-state marker have been investigated. Perfusion has been observed to be reliable in healthy controls across time and in detecting abnormalities in MDD participants as compared to healthy controls [8,9]. Differences in perfusion have been identified between MDD participants and healthy controls in some but not all studies [10–13]. Perfusion abnormalities have been detected in the temporal, frontal, cingulate, and limbic regions [10–12]. Differences in perfusion in the anterior cingulate cortex have also accurately distinguished unipolar from bipolar depression [13].

Recent studies suggest that pre-treatment perfusion can predict antidepressant treatment outcomes. One study compared baseline perfusion in responders and nonresponders to repetitive transcranial magnetic stimulation (TMS) in 13 MDD participants [14]. Baseline perfusion in the left dorsolateral prefrontal cortex was greater in TMS responders, whereas baseline perfusion in the left medial frontal cortex was greater in nonresponders. Another study observed some initial perfusion differences in MDD at baseline compared to healthy controls to normalise after 6 weeks of antidepressant treatment [15]. However, the small samples in these studies and lack of placebo control are significant limitations, hindering the ability to identify moderators of treatment outcome that could be applied clinically.

The current study is a secondary analysis to investigate perfusion *moderators* of treatment response and their *clinical effectiveness* from the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study [3]. Unlike predictors (non-specific variables associated with outcome to any treatment), moderators are pre-treatment variables associated with *differential* treatment outcome to provide information for *patient-treatment matching*. Relative CBF, a normalised measure of perfusion (nCBF), was evaluated as a potential *moderator* of antidepressant response in MDD using a *whole-brain, voxel-wise, linear mixed-effects model*. We predicted that perfusion moderators would be observed in brain regions across networks, those involved in resting-state brain function (default mode) as well as those involved in emotion, reward, and salience processing (e.g., prefrontal, insula, and cingulate cortices; see review on multi-modal imaging and these pathophysiologic processes in MDD [5]). Clinical effectiveness of the perfusion moderators was then evaluated using a *composite moderator* analysis and *remission rates*. We predicted perfusion contributors to optimal treatment assignment would increase remission rates for those that received their perfusion-matched treatment. Our model and sample size allow for an unbiased, exploratory approach to identify moderators and their clinical effectiveness.

2. Methods

2.1. Design and Overview

The EMBARC trial aims to identify clinical, behavioural, and biological moderators of antidepressant response in MDD in order to develop a

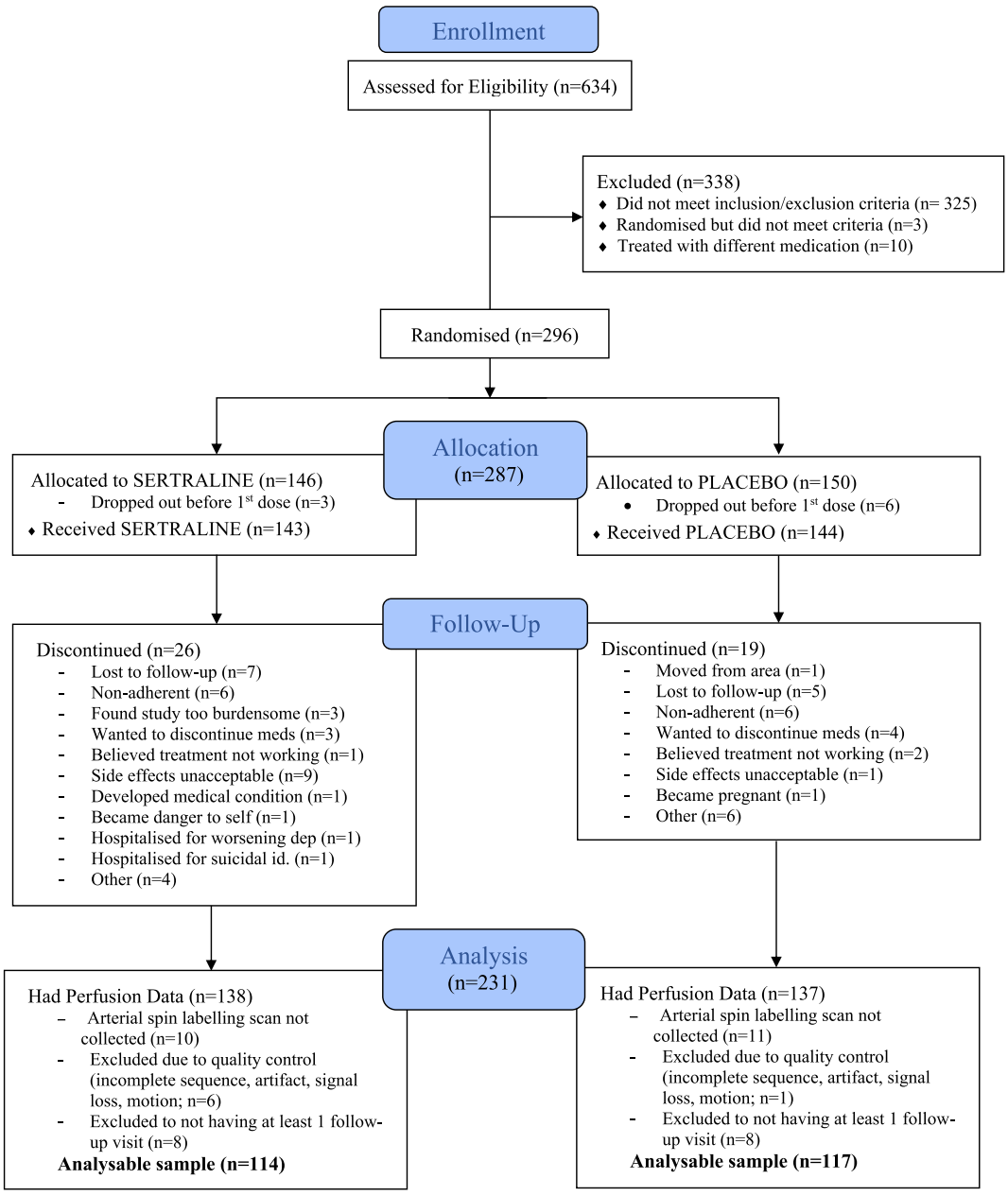

Fig. 1. EMBARC CONSORT Flow Diagram. For this analysis patients were included (1) regardless of their $HAMD_{17}$ score, (2) had relative cerebral blood flow scans pass quality control, and (3) had at least one follow up visit.

differential Treatment Response Index of multiple biosignatures. MDD participants were scanned using MRI, including a resting ASL sequence, before treatment initiation and one-week after starting treatment, to detect any early signals of response in the brain. Treatment response was measured for 8 weeks for Phase-1 and an additional 8 weeks for Phase-2, which involved maintenance treatment for responders and a cross-over for nonresponders to alternate treatment. The 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) was used to track response at baseline and weeks-1, 2, 3, 4, 6, 8 after starting treatment for Phase-1. For the full design and rationale with measures and descriptions, see the Trivedi et al. [3]. The study was approved by the Institutional Review Board at each participating site: Columbia University (CU), Massachusetts General Hospital (MG), University of Michigan (UM), and the University of Texas Southwestern Medical Center (TX).

2.2. Participants

Of the 296 participants included in the EMBARC trial, 231 individuals completed the baseline ASL scan, had usable data that passed quality control, had at least one follow-up visit, and constitute the intent-to-treat analytic sample in this secondary report (Fig. 1). MDD participants were diagnosed using the Structural Clinical Interview for DSM-IV. Participants were 18–65 years old, fluent in English, and had chronic, early-onset MDD (first major depressive episode prior to age 30). MDD participants were excluded if they scored <14 on the Quick Inventory of Depressive Symptomatology–Self Report, if any other mental disorder was primary to MDD (e.g., Generalized Anxiety Disorder), if they had a lifetime history of a psychotic or bipolar disorder, had a substance abuse disorder within six months (except for nicotine dependence), or had the presence of a medical condition that would compromise

MDD-specific findings.[1] General MRI exclusion criteria were implemented. See Table 1 for demographics. All participants signed informed consent.

2.3. Data Acquisition and Imaging Parameters

EMBARC MRI data were collected at four sites (CU, MG, TX, UM). All ASL sequences were acquired using 3T scanners. Each implemented a 2D-EPI, resting-state, pseudo-continuous ASL (pCASL) technique that was optimized for each scanner while maintaining similar parameters. Generally, pCASL parameters consisted of a 1516 ms labelling duration, 1500 ms post-labelling delay, 4460 ms/17 ms TR/TE, 3.44 × 3.44 × 5 mm [3] in-plane resolution, multi-slice acquisition in ascending order, 29 slices covering the whole brain, 35 pairs, 220 × 220 mm FOV, 64 × 64 matrix, 90° excitation flip angle, with scan duration of approximately 5 min. For further details on the pCASL sequence, refer to Almeida et al. [9]. These imaging parameters are comparable and consistent with recommendations from a recent consensus paper [7]. T1-weighted, high-resolution, structural-3D sagittal images were acquired in the same session.

2.4. Data Processing and Statistical Analysis

2.4.1. Relative Cerebral Blood Flow

Of the 231 participants with usable ASL scans and follow-up data, 114 MDD participants were randomised under double-masked conditions to receive sertraline and 117 to receive placebo. We implemented nCBF to identify perfusion moderators of antidepressant treatment response. Each participant's nCBF is their relative measure of perfusion, i.e., normalisation of their absolute CBF (aCBF), which divides the aCBF of each voxel by the whole-brain averaged aCBF. nCBF's normalisation process is useful to decrease intra- and inter-subject variations as well as some cross-site scanner differences, which assists in controlling for basic individual differences that may not be disease-specific. nCBF has high test–retest reliability, as does aCBF (e.g., EMBARC healthy control CBF across time [10]), but has greater sensitivity and reliability in detecting differences in perfusion between groups when compared to aCBF [16].

2.4.2. Image Processing

The ASL data were preprocessed and analysed with SPM8 (Wellcome Department of Cognitive Neurology, UK) in Matlab (MathWorks, Natick, MA). The processing pipeline included: 1) realignment of the ASL time-series to the first image to correct for head motion; 2) generation of perfusion-weighted image series by pairwise subtraction of the label and control images; 3) conversion to aCBF image series based on a single-compartment ASL perfusion model; 4) generation of a mean CBF image for each participant; 5) co-registration of the mean image with the anatomical image; 6) normalisation to the MNI template; 7) resampling of CBF image to 2 × 2 × 2 mm [3] and smoothed with full-width at half-maximum 8 mm kernel; and 8) extracting the nCBF image by dividing out the aCBF global individual mean from each aCBF voxel.[2]

2.4.3. Moderator Analysis

An exploratory whole-brain, voxel-wise, linear mixed-effects model was conducted to identify moderators of treatment response. The full model conformed to a moderator definition based on interaction effects by Kraemer et al. [17] and was implemented in R. Moderators were identified by a significant Treatment (sertraline, placebo) by Time (Weeks 0–8) by nCBF value (voxel-wise correction false discovery rate $p < .05$) interaction controlling for Site (CU, MG, TX, UM) with $HAMD_{17}$ as the dependent measure (see list of model terms in Supplemental Table 1). Baseline $HAMD_{17}$ was included as a dependent variable and the group main effect was excluded to ensure equality between groups in $HAMD_{17}$ at baseline. A significant three-way interaction suggests perfusion in that brain region (nCBF moderator) predicted differential rate of change in $HAMD_{17}$ with sertraline vs placebo. All nCBF moderators (112 clusters) are presented in Fig. 2. For interpretation, only clusters of >100 voxels for the moderator effect (Treatment × Time × nCBF interaction; 30 clusters) are discussed based on prior ASL work and clinical applicability [16]. For additional details on software, related packages, atlas and coordinate system used, see Supplemental Methods.

Table 1
Demographic and clinical characteristics for the sertraline and placebo groups.

	Sertraline		Placebo	
	n	%	n	%
Gender				
Male	35	30.70%	41	35.04%
Female	79	69.30%	76	64.96%
Race				
White	74	64.91%	81	69.23%
African American	26	22.81%	18	15.38%
Asian	5	4.39%	10	8.55%
Other	9	7.89%	8	6.84%
Employment status				
Employed	63	57.27%	68	59.65%
Unemployed	47	42.73%	46	40.35%
	Mean	SD	Mean	SD
Age	37.65	13.71	36.58	12.33
Age of onset	16.32	6.04	16.24	5.67
Years of education	14.98	2.63	15.15	2.65
Number of MDE	15.82	30.02	14.61	25.82
Duration of current episode (months)	46.07	74.76	40.66	76.16
$HAMD_{17}$	18.72	4.57	18.98	4.31
STAI (Pre-scan)	48.27	11.99	47.32	11.28
SHAPS	5.79	3.49	5.48	3.62

Note: Major Depressive Disorder (MDD); Standard Error (SE); Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR); Hamilton Scale for Depression ($HAMD_{17}$). Major Depressive Episode (MDE). State–Trait Anxiety Inventory (STAI). Snaith-Hamilton Pleasure Scale (SHAPS). For number of MDE: Number with too many to count = 17 (8 placebo, 9 sertraline); Number with missing data = 7 (4 placebo, 3 sertraline).

2.4.4. Clinical Effectiveness

Combining individual moderators to form a composite moderator provides a comprehensive evaluation and can result in a clinically usable prediction of individual response to a specific treatment in order to determine which treatment will have greatest benefit [18]. The 30 clusters containing >100 voxels comprised the individual perfusion moderators. They were combined into a composite moderator (a weighted sum of the individual moderators as described by Kraemer) [18] to determine which participants would benefit more from sertraline vs placebo. Benefit was defined by the change in depression severity over time expressed as a slope (rate of change in $HAMD_{17}$ per week). Slopes were derived from a mixed-effects model corrected for site and computed separately for each treatment arm as described in Petkova et al. [19]. A negative slope indicates improvement. Participants were assigned to a preferred treatment based on the relationship between the composite moderator and the slope for sertraline and placebo groups presented in Fig. 3. Those below the crossover point of the two lines benefit more from sertraline (i.e., assigned sertraline as their perfusion-based, statistically-preferred treatment). Those above that point benefit more from placebo (i.e., assigned placebo as their

[1] Presence of a neurological condition requiring an anticonvulsant; a medical condition not stable with medication, required hospitalisation or deemed clinically relevant by the investigators; or any abnormal laboratory results the site principal investigator considered clinically significant

[2] aCBF means were confirmed to be equivalent between the SERT (M = 42.50; SE = 0.96) and placebo (M = 41.08; SE = 0.94) groups, t = 1.06; p = 0.29.

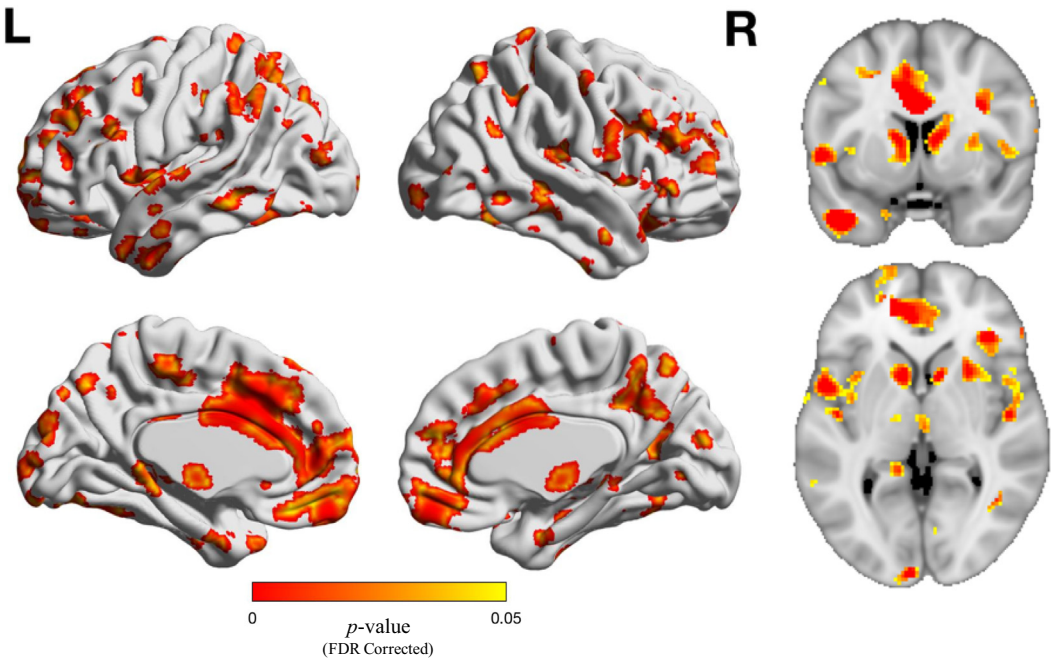

Fig. 2. Brain regions in which relative, normalised, cerebral blood flow (nCBF; perfusion) was a moderator of treatment response (scaled by FDR corrected *p*-values).

perfusion-based, statistically-preferred treatment). Remission rates and slopes were calculated for *lucky* (those who were randomised to their perfusion-based, statistically-preferred treatment) and *unlucky* (those who were randomised to their perfusion-based, statistically-not-preferred treatment) participants as identified by the composite moderator [20]. A participant was defined to be in remission if a $HAMD_{17}$ score of 7 or less was achieved by the last available acute phase visit. An effect size [18] was computed for the composite moderator, which is scaled like a correlation (−1–1) with larger values indicating stronger moderation (i.e., prediction of greater differential treatment response). Weights of each individual moderator are discussed based on their contribution to a greater benefit for sertraline or placebo. Negatively weighted moderators contribute to a greater benefit for sertraline. Conversely, positive weights indicate greater benefit for placebo. See Supplemental Methods for further details.

To aid in further describing the nCBF moderators (and contributors to sertraline or placebo assignment), regression coefficient analyses were conducted to characterise the relationship between higher vs lower nCBF levels and improvement in depression severity over time for both treatment groups. See Supplemental Methods and Results for regression coefficient analysis and findings.

2.5. Role of Funding Source

The study sponsor approved the overall trial design, study execution, and data collection, which was coordinated by the corresponding author. The study sponsor had no role in data analysis, data interpretation, or writing of the data in the current manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Perfusion Moderators

The whole-brain voxel-wise linear mixed-effects model revealed 112 statistically significant moderators of treatment outcome (Treatment × Time × nCBF interaction) with 30 clusters containing >100 voxels. These moderators are discussed below by their treatment contribution identified by the combined moderator. Brain regions where perfusion moderated treatment outcome are provided in Table 2. See Fig. 2 and Supplemental Table 2 for detailed cluster information for all significant moderators.

3.2. Clinical Effectiveness

For all participants included in the moderator analyses, 35% (81/231) achieved remission and 65% (150/231) did not achieve remission as the overall treatment outcome. Of the MDD participants that received sertraline, 37% (42/114) achieved remission, and 33% (39/117) of the MDD participants that received placebo achieved remission. To assess the clinical significance of the perfusion moderators, overall treatment efficacy was evaluated by comparing remission rates and slopes of those who either received, *lucky*, or did not receive, *unlucky*, their "preferred" treatment according to the composite perfusion moderator.[3] *Lucky* and *unlucky* participants were identified by each treatment arm. For both sertraline and placebo treatment, the *lucky* group demonstrated higher average remission rates as compared to the *unlucky* group (for sertraline, 53% vs 24%; for placebo, 49% vs 18%; respectively; Fig. 2) and more negative slopes indicating a faster rate of improvement (for sertraline, −1.289 (0.38) vs −0.931 (0.45); for placebo, −1.335 (0.40) vs −1.000 (0.42), respectively). The combined moderator produced an effect size of 0.557.

3.2.1. Sertraline Moderators

Sertraline moderators are regions where perfusion levels contribute to assignment to the sertraline group, i.e., sertraline should be observed as having greater improvement (decrease) in depression severity over the placebo group. This is revealed by negative weights in the composite moderator (−0.007 to −0.240; Table 2). Regions observed include those involved in affective and default mode networks. From highest to lowest contribution, these included: the right putamen (and anterior insula); left inferior temporal gyrus; right fusiform; right inferior (orbital) frontal gyrus; left parahippocampal gyrus; left inferior parietal lobule (the supramarginal gyrus); left fusiform gyrus; bilateral pons;

[3] Using the composite moderator, 48% of participants were identified to benefit more from sertraline and 52% to benefit more from placebo resulting in equivalent assignment.

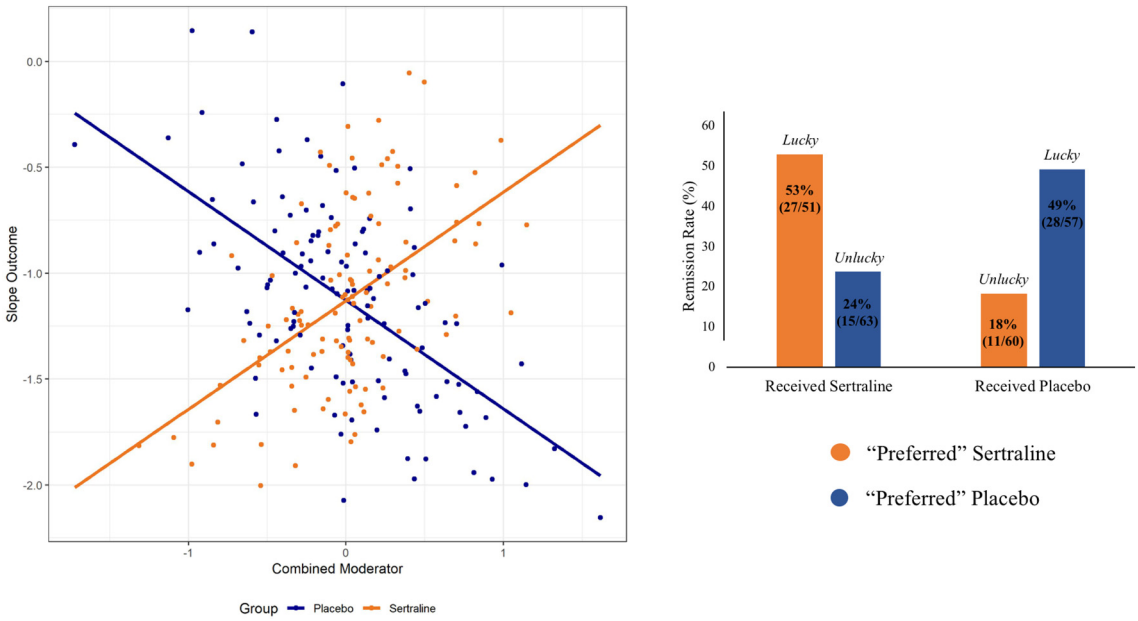

Fig. 3. The relationship between the combined moderator and the slope outcome is shown. Smaller values of the slope indicate a more favourable result, i.e., lower depression severity scores. The "preferred" treatment group is the line with the lowest position. Below the point where the two lines intersect (0.003), sertraline should be preferred as it has the smaller outcome values and above this point placebo should be preferred (left panel). Remission rates are presented for the *lucky* (those who were randomised to their statistically-preferred treatment) and *unlucky* (those who were randomised to their statistically-not-preferred treatment) as identified by the composite moderator (right panel).

right precuneus; left inferior parietal lobule (supramarginal and angular gyri); left superior temporal gyrus; left superior temporal gyrus (extending to insula); and the right calcarine cortex.

3.2.2. Placebo Moderators

Placebo moderators are regions where perfusion levels contribute to assignment to the placebo group, i.e., placebo should be observed as having greater improvement (decrease) in depression severity for placebo relative to sertraline. This is revealed by positive weights in composite moderator (0.002–0.136; Table 2). Regions observed include those involved in cognitive control and default mode networks (Table 2). From highest to lowest contribution, these included: the right posterior insula; left midbrain; right hippocampus; right inferior (orbital) frontal; right middle and inferior frontal gyri (including the dorsolateral prefrontal cortex); left precentral gyrus; left inferior (orbital) frontal; left middle temporal gyrus; right caudate; left cerebellum; right middle, superior, and inferior frontal gyri (and dorsolateral and frontopolar prefrontal cortices); left middle frontal gyrus (and dorsolateral prefrontal cortex); right middle temporal gyrus; left cuneus; left cingulate (ventral and dorsal anterior portions); left fusiform gyrus (and lingual gyrus); and the left inferior frontal gyrus (triangularis).

4. Discussion

In this large placebo-controlled study, we identified perfusion moderators of treatment outcome involved in functional networks, i.e., default mode, cognitive control, reward, salience, and affective processing, known to be disrupted in MDD [3]. Particularly, it was perfusion in regions involved in reward, salience, affective and default mode processing that were identified to be sertraline moderators. Conversely, perfusion in regions involved in cognitive control and default mode processing were identified as placebo moderators.

Perfusion in the putamen and anterior insula, inferior temporal gyrus, fusiform, parahippocampus, inferior parietal lobule, and orbital frontal gyrus contributed the most to assignment of sertraline as the preferred treatment, showing a faster rate of improvement and increasing remission status from 37% for all those who received sertraline to 53% for those that were assigned sertraline and were *lucky* to have received it.

Perfusion in the posterior insula, midbrain, hippocampus, orbital frontal gyrus, dorsolateral prefrontal cortex, precentral gyrus, caudate, and middle temporal gyrus contributed to assignment to placebo as the preferred treatment, showing a faster rate of improvement and increasing remission status from 33% for all those who received placebo to 49% for the *lucky* group. These results are in line with prior perfusion work (albeit not placebo-controlled) but are the first to identify moderators of treatment response (differential outcome for sertraline vs placebo) [14,15,21].

The majority of regions where perfusion contributed to sertraline assignment were in lateral and posterior regions, aspects of default mode and association areas, namely temporal, parietal, and occipital regions. Perfusion in the temporal and occipital lobes have been observed, using positron emission tomography, to decrease from baseline to post-treatment in antidepressant responders [21]. A recent perfusion study identified regions in the inferior temporal and frontal gyri and anterior cingulate to normalise to that of healthy controls while on a SSRI for six weeks [15]. Our results indicate these regions can predict response to a SSRI. The opposite pattern observed for placebo, where the majority of the regions contributing to placebo assignment were in frontal regions, aspects of default mode and executive control networks, could be indicators of treatment sensitivity and a placebo effect to which other treatments may provide better response than sertraline, e.g., psychotherapy.

However, it must be noted that the highest contributors to sertraline or placebo assignment are part of the limbic system, i.e., putamen and insula (anterior for sertraline and posterior for placebo). Perfusion in the putamen has been observed 1) to be involved in reward processing [22], 2) to be higher in a group of depressed individuals relative to healthy controls [23], and 3) to reduce after a single dose of a SSRI in healthy controls (along with other serotonergic regions) [24]. As for the insula, this region 1) contains high concentrations of serotonin transporters [25], 2) is known to be involved in mood, salience, and affective processing [26,27], and 3) shows perfusion reduction upon SSRI

Table 2
Brain regions observed to be moderators of treatment response, as defined by the *treatment* (sertraline vs placebo) by *time* by *voxel-wise relative cerebral blood flow* (perfusion) interaction.

Brain Region at Peak Voxel in Cluster (Additional Brain Regions in Cluster)	MNI Coordinates (x, y, z)	Brodmann Area (BA)	# of Voxels	Weight in Composite Moderator
Sertraline Contributors				
Right Putamen (Claustrum, Anterior Insula)	28, 12, 6	31, 47	331	-0·23998
Left Inferior Temporal Gyrus (Middle Temporal, Fusiform Gyri)	-48, 2, -34	20, 36	674	-0·10646
Right Fusiform (Right Interior Temporal, Occipital Gyri)	42, -56, -12	37, 19	422	-0·10309
Right Inferior/Orbital Frontal Gyrus (Anterior Insula)	38, 32, 2	47	149	-0·06916
Left Parahippocampal Gyrus (Temporal Pole)	-18, -4, -31	35, 36, 38, 28	201	-0·06545
Left Inferior Parietal Lobule (Supramarginal Gyrus)	-60, -46, 42	40	282	-0·05842
Left Fusiform Gyrus (Cerebellum)	-38, -58, -16	37	667	-0·0502
Bilateral Pons	-0,-20,-32		156	-0·0453
Right Precuneus (Left Precuneus, Right Posterior Cingulate)	4, -56, 36	7, 23, 31	547	-0·03692
Left Inferior Parietal Lobule (Supramarginal and Angular Gyri, Superior Parietal Lobule, Precuneus)	-36, -56, 56	40, 39, 7	339	-0·02229
Left Superior Temporal Gyrus	-46, -12, 2	48, 22	108	-0·01324
Left Superior Temporal Gyrus (Insula)	-54, 4, 0	38	237	-0·0092
Right Calcarine Cortex	24, -64, 16	18, 17	126	-0·00724
Placebo Contributors				
Right Posterior Insula (Rolandic Operculum)	34, -24, 20	13, 40, 41	275	0·136269
Left Midbrain (Red Nucleus, Substantia Nigra, Lingual and Parahippocampal Gyri)	-8, -28, -10		311	0·111396
Right Hippocampus	32, -18, -8	20	109	0·10846
Right Inferior/Orbital Frontal Gyrus (Insula, Superior Temporal Gyrus)	34, 22, -22	47, 38	206	0·07918
Right Middle and Inferior Frontal Gyri (Dorsolateral Prefrontal Cortex, Precentral Gyrus)	28, 20, 36	9, 8, 46, 44	592	0·074757
Left Precentral Gyrus (Paracentral Lobule, Middle Cingulate)	-12, -28, 56	4	179	0·068112
Left Inferior/Orbital Frontal Gyrus	-26, 32, -14	11, 47	202	0·067751
Left Middle Temporal Gyrus	-60, -46, -2	21, 20	217	0·064534
Right Caudate Body and Head (Thalamus)	12, 12, 8		640	0·060906
Left Cerebellum	-44, -78, -32		398	0·052917
Right Middle, Superior, and Inferior Frontal Gyri (Dorsolateral and Frontopolar Prefrontal Cortices)	22, 44, 22	10, 45, 46	578	0·05214
Left Middle Frontal Gyrus (Dorsolateral Prefrontal Cortex)	-28, 18, 44	6, 8, 9	148	0·020262
Right Middle Temporal Gyrus (Inferior Temporal Gyrus)	66, -28, -14	20, 21	152	0·012107
Left Cuneus	-4, -90, 24	18	114	0·009888
Left Ventral and Dorsal Anterior Cingulate Cortices	-8 ,12, 32	24, 32, 33,10, 11	6,463	0·00676
Left Fusiform Gyrus (Lingual Gyrus, Cerebellum)	-26, -78, -18	18, 19	212	0·00225
Left Inferior Frontal Gyrus (Triangularis)	-50, 18, 26	45	104	0·001889

Note. False Discovery Rate correction of $p < .05$ was implemented voxel-wise. Clusters presented are those greater than 100 voxels organized by contribution to treatment assignment (sertraline or placebo in composite moderator).

response [28]. Our data provide evidence that the limbic system - particularly the basal ganglia due to its role in reward processing, reinforcement and implicit learning [29], and insula due to its role in salience and affective processing and serotonin function - is a target to further investigate assigning SSRI treatment. The overall pattern of findings suggest that limbic–cortical network regions should be considered together [30–32].

The regions contributing highest to sertraline – generally related to reward, salience, affective, and default mode processing – and placebo – generally related executive control and default mode processing- response differ enough to consider that disruption in different large-scale networks play a role in how patients may respond to treatment. Disruption in large-scale networks that regulate information processing has been investigated and posited to underlie neuropsychiatric conditions [31,32]. Our parallel work in EMBARC investigating resting-state functional connectivity moderators of treatment response revealed connectivity patterns *within* and *between* major functional networks to moderate outcome (Chin Fatt, et al., unpublished [33]). Connectivity *within* dorsal attention, default mode, executive control and limbic networks, but *between* dorsal attention to limbic and salience networks predicted better outcomes on sertraline. Multiple perfusion moderators are involved in these functional networks. Interestingly, connectivity from the hippocampus to regions of the executive control network were moderators of placebo, mirroring our placebo contributors. Disruptions *within* or *between* networks as identified using perfusion could be potential treatment targets. An additional EMBARC finding to note, albeit in a different imaging modality, electroencephalography, involved the cingulate. Increased pre-treatment anterior cingulate theta activity was observed to be a non-specific predictor of treatment response [34]. Perfusion in the anterior cingulate moderated outcome in our model, but contributed less to treatment assignment compared to other regions suggesting it may not be a strong moderator of outcome.

4.1. Limitations and Future Directions

Important next steps would be to 1) replicate perfusion moderators of treatment response by using perfusion moderators to assign sertraline prior to starting treatment; and 2) investigate the ability of perfusion to differentiate between two or more active MDD treatments of differing modalities. These highlight the main limitations of the EMBARC trial. EMBARC data provided a relatively homogenous MDD sample, early-onset, chronic primary MDD, which likely provided a stronger signal to detect predictors of response to sertraline, but may also limit the transfer of these moderators to more heterogeneous populations of MDD. Replication is needed to determine if moderators observed in the current study will translate to other MDD populations, whether relatively homogenous or more heterogenous in nature. Despite symptom levels being equivalent between the groups (e.g., depression severity, anxiety, and anhedonia; see Table 1), the effect symptoms and even comorbid conditions might have on perfusion markers and their role as biosignatures is worth further investigation. EMBARC was also restricted to one active treatment (a SSRI), so inclusion of other depression treatment modalities such as SNRIs, psychotherapy and rTMS are warranted to understand the broader promise of using perfusion to predict response to treatment. Additional limitations include 1) residual site effects, and 2) overall response in the trial for sertraline did not outperform placebo. The current study did not investigate site effects beyond controlling for such effects through normalisation and analytic modelling. Other EMBARC work is focusing on such effects

across the investigated modalities. EMBARC was not a drug efficacy trial, so while the failure to observe sertraline response to be greater than placebo is initially disconcerting, the current work shows that brain function can be used to improve treatment response when treatments perform equivalent otherwise.

Our findings show baseline cerebral blood perfusion, a quantitative measure of brain function, can predict treatment outcome and increase remission rates on sertraline in MDD. Emerging data such as these aid the field of psychiatry in classifying and treating MDD beyond just clinically-derived symptom profiles, but rather augmented or partially replaced by pathophysiology-derived diagnostic and prognostic markers of illness and clinical response [6,35].

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Author Contributions

CC contributed to ASL collection, data processing, data analytic design, interpretation and wrote the manuscript; CCF contributed to data processing, conducting data analyses, and manuscript editing; MJ contributed to data analytic design, interpretation and manuscript editing; GF contributed to analytic design, analytic code, and manuscript editing; BG contributed to data analytic design and interpretation; TC contributed to data analytic design, conducting data analyses, and interpretation; AA contributed to ASL collection and manuscript editing; SA contributed to data processing and manuscript editing; JA contributed to ASL conceptualization on EMBARC and manuscript editing; TD coordinated data quality control centre, contributed to ASL quality control, and manuscript editing; MF is an EMBARC PI and contributed to EMBARC study design and manuscript editing; BK is an EMBARC PI and site investigator, and contributed to EMBARC study design and manuscript editing; PM is an EMBARC PI and site investigator, and contributed to EMBARC study design, ASL data analytic design, and manuscript editing; MM is a site investigator and contributed to manuscript editing; RP is an EMBARC PI, site investigator, coordinator of imaging data centre, and contributed to EMBARC study design and manuscript editing; MW is an EMBARC PI and contributed to EMBARC study design and manuscript editing; MP contributed to imaging study design, coordinating imaging processing centre, and manuscript editing; HL oversaw EMBARC ASL protocol, data processing pipeline and code, and manuscript editing; AE contributed to imaging study design, analytic design, interpretation, and manuscript editing; and MT is EMBARC's Coordinating PI and contributed to EMBARC study design and rationale, and contributed to data analytic design, data interpretation, and manuscript editing.

Data Sharing Statement

EMBARC data is publicly available at https://ndar.nih.gov, study #2199. All data is deidentified. Data available include the study protocol, data dictionary, scalar versions of clinical, behavioural, and imaging modalities, as well as raw behavioural and imaging files.

Declarations of Interest

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Appendix A. Supplementary Data

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