Trajectories in Cerebral Blood Flow Following Antidepressant Treatment in Late-Life Depression: Support for the Vascular Depression Hypothesis

Wenjing Wei, MD[a,b]; Helmet T. Karim, PhD[c]; Chemin Lin, MD[d,e]; Akiko Mizuno, PhD[c]; Carmen Andreescu, MD[c]; Jordan F. Karp, MD[c]; Charles F. Reynolds III, MD[c]; and Howard J. Aizenstein, MD, PhD[c,f,*]

ABSTRACT

Objective: Studies have identified longitudinally that there exists an association between depression, cerebral blood flow (CBF), and white matter hyperintensities that are thought to be due to vascular pathologies in the brain. However, the changes in CBF, a measure that reflects cerebrovascular integrity, following pharmacotherapy are not well understood. In this study, we investigated the dynamic CBF changes over the course of antidepressant treatment and the association of these changes with depressive symptoms.

Methods: We used pseudocontinuous arterial spin labeling to investigate CBF changes in a sample of older patients (≥ 50 years of age; N = 46; 29 female) with a *DSM-IV* diagnosis of major depressive disorder. Participants had 5 magnetic resonance imaging scans (at baseline, the day after receiving a placebo, the day after receiving a first dose of venlafaxine, a week after starting venlafaxine treatment, and at the end of trial [12 weeks]). Montgomery-Asberg Depression Rating Scale (MADRS) was used to evaluate depression severity and treatment outcome. We investigated the association between changes in depression severity with changes in voxel-wise CBF while adjusting for potential confounding factors.

Results: Increased CBF in the middle and posterior cingulate between baseline and end of treatment was significantly associated with percent decrease in MADRS score, independent of sex and Mini-Mental State Examination score (5,000 permutations, cluster forming threshold $P < .005$, family-wise error $P < .05$). No significant effects were detected between baseline and other scans (ie, placebo, acute [single dose], or subacute [after a week]).

Conclusions: Regional CBF increases were associated with decreases in depressive symptoms. This observation is consistent with the vascular depression hypothesis in late-life depression.

Trial Registration: ClinicalTrials.gov identifiers: NCT00892047 and NCT01124188

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[a]The Third Xiangya Hospital of Central South University, Changsha, Hunan, China
[b]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
[c]Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania
[d]Department of Psychiatry, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan
[e]College of Medicine, Chang Gung University, Taoyuan, Taiwan
[f]Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania
**Corresponding author:* Howard J. Aizenstein, MD, PhD, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213 (aizen@pitt.edu).

Depression is a leading cause of global burden of illness-related disability,[1,2] affecting up to 16% of older adults.[3–5] Treatment response of depression is approximately 50%,[6–8] and treatment resistance is common, such that patients frequently need multiple trials before finding an effective treatment.[9] This delay increases the risk for suicide, medical comorbidity, disability, and family caregiving burden, especially in older adults.[10]

Thus, identifying biomarkers of treatment response variability is important to improving treatment outcomes in late-life depression (LLD). While several putative structural and functional neuroimaging markers of treatment response have been reported,[11–16] most of these are static markers identified at the initiation of treatment. We currently have limited knowledge about dynamic markers of response or how physiological changes early in treatment predict final response. Recently, our group has shown that changes in resting blood-oxygen-level–dependent (BOLD) connectivity differ depending on treatment response and can occur as early as 1 day after exposure to antidepressant medication.[17] However, the BOLD signal may not be the only dynamic marker associated with treatment response.

The vascular depression hypothesis states that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes.[18] The major conceptual driver may be small vessel disease leading to white matter hyperintensities (WMH)[19] in midline structures, ventricles, and cingulum that disrupt white matter connectivity[20] but also decrease cerebral blood flow (CBF).[21] Together, this may both support a frontolimbic dysconnectivity hypothesis[22] as well as drive functional differences due to decreased CBF,[23] although it is possible that the reverse pattern is also true. In fact, this pattern (greater small vessel disease—worsened CBF—worsened neural functioning—greater depressive symptoms) may be highly circular and interdependent.

Given the association of vascular integrity and depression in older adults, measuring neurovascular function may provide clinically relevant insight on late-life depression. Arterial spin labeling (ASL) has been shown to be useful as a biomarker of brain response to

Clinical Points

- Increased white matter hyperintensities (WMH) are associated with decreased cerebral blood flow (CBF) in late-life depression. This study found that CBF increases following treatment in regions that are typically more affected by WMH (as some past studies have found) but failed to identify early (within a week) changes.
- The vascular depression hypothesis posits that cerebrovascular disease may predispose, precipitate, or perpetuate depressive symptoms in late life. Although this was not tested directly, the authors believe that remission may partially break this cycle due to increased CBF in these afflicted areas. The direct mechanism by which this occurs is still unclear.

antidepressants.[24] Compared to the BOLD signal, ASL has the advantage that it is not confounded by blood volume or oxygen consumption.[25]

Regional CBF alterations have been linked to major depressive disorder (MDD). Several studies have reported that, compared with nondepressed controls, midlife and young adults with MDD have mixed CBF changes in multiple regions.[26–30] However, these abnormalities may not characterize CBF in the elderly, given the anatomic and pathophysiologic changes observed in the aging brain. Studies in LLD using positron emission tomography (PET) or single photon emission computed tomography (SPECT) have found that LLD individuals had lower regional CBF compared with nondepressed controls.[31–34] The changes in CBF are especially salient in LLD within the theoretical framework of the vascular depression hypothesis that cerebrovascular disease may predispose to, precipitate, or perpetuate some geriatric depressive syndromes.[18,35,36] Strictly speaking, the PET/SPECT mainly measures brain metabolism through tracer coupling, which reflects CBF to some degree, and good agreement exists between PET/SPECT measurement and ASL measurement,[37] but the invasiveness of PET/SPECT does not allow for repeated measurement in a relatively short time. The transcranial Doppler (TCD) mainly measures the velocity of the CBF in major vessels, which reflects the brain tissue pulsatility and vessel elasticity, but the actual CBF also depends on the diameter of the vessel, and the TCD fails to provide voxel-wise information of deeper brain tissue. With the use of inner tracer and the subtraction of tagged and untagged images, the ASL measures CBF more directly and voxel-wise without introducing exposure to radiation. Finally, WMH may be a consequence of low CBF; however, the reverse may also be true. There is very little research that focuses on this aspect of the causality of WMH and low CBF; however, it is possible, since WMH are in part due to ischemia. Therefore, we investigated the changes associated with regional CBF alterations as measured by ASL.

For this study, we used pseudocontinuous ASL (pCASL) to investigate dynamic gray matter CBF changes in older depressed patients receiving antidepressant pharmacotherapy. We measured whole brain CBF at baseline, after placebo, and then at 3 time points (a single dose, a week after, and at the end of trial) during a 12-week open-label venlafaxine treatment trial. As per the vascular depression model, we predicted that depression remission would be associated with increased CBF in gray matter. As LLD has been associated with multiple gray matter regions across the brain, we used a voxel-wise approach to characterize where in the gray matter the ASL changes occurred.

METHODS

Participants

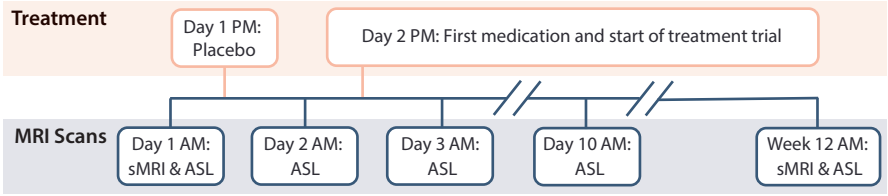
The present study recruited participants from the open-label phase of 2 longitudinal clinical trials (IRL-GRAY[38] and ADAPT[39]: NCT00892047 and NCT01124188, respectively), and all data were collected between July 2011 and December 2015. All participants (at least 50 years old) met *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition) criteria for MDD and had Montgomery-Asberg Depression Rating Scale (MADRS) scores of at least 15 at the time of scanning. Exclusion criteria were any history of mania or psychosis, alcohol or substance abuse (last 3 months), or disease with known effects on mood (eg, dementia, stroke, multiple sclerosis, vasculitis, significant head trauma, unstable hypertension, or diabetes), current psychotic symptoms, uncontrolled medical illnesses, contraindication to venlafaxine extended release, or ineligibility for magnetic resonance imaging (MRI) (eg, implanted metal, overweight, claustrophobia, or pregnancy). Participants were involved in a 12-week treatment trial for venlafaxine, and MRI was performed at 5 time points: baseline, a day after receiving a placebo, a day after receiving the first dose of venlafaxine, a week following continued medication, and at the end of the trial (Figure 1). Patients started initially on 37.5 mg/d and increased by 37.5 mg up to 150 mg/d; those who did not respond at week 6 had their target increased to 300 mg/d (for detailed dosage information, see Lenze et al[38]).

Older participants (N = 58) provided written informed consent for both the current protocol and the clinical trials they were enrolled in, which were all approved by the University of Pittsburgh institutional review board. Twelve participants were excluded due to drug side effects (n = 5), in-scanner anxiety (n = 1), no MRI (n = 2), missing behavioral data (n = 1), loss of communication (n = 2), and no desire to complete the end of trial scan (n = 1). Thus, 46 participants were included in the final analysis and had all neuroimaging and behavioral data at each time point.

Clinical Assessments

After demographic and clinical information was collected, the Cumulative Illness Rating Scale for Geriatrics (CIRSG)[40] and Mini-Mental State Examination (MMSE)[41] were administered. Remission was defined as MADRS score less than 10 for at least 2 consecutive weeks that lasted through the trial.

Figure 1. Study Design Protocol[a]



[a]Five magnetic resonance imaging scans were performed throughout the course of treatment. All scanning was done in the morning.
Abbreviations: ASL = arterial spin labeling, sMRI = structural MRI.

Clinicians saw participants once a week for the first 2 weeks and then every 2 weeks. On scanning dates, blood samples were taken to measure serum venlafaxine levels.

Image Acquisition

All scanning was conducted in the morning at the MR research center with a 3 Tesla Siemens Trio scanner (Munich, Germany) and a 12-channel head coil.

The scanner removed initial dummy scans. Structural data were collected at baseline and end scans. An axial, whole brain T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence was collected with echo time (TE) = 3.43 ms, repetition time (TR) = 2,300 ms, flip angle (FA) = 9 degrees, inversion time (TI) = 900 ms, field of view (FOV) = 256 × 224, 176 slices, and 1 mm isotropic resolution. An axial, whole brain T2-weighted fluid attenuated inversion recovery (FLAIR) sequence was also collected with TE = 90 ms, TR = 9,160 ms, FA = 150 degrees, TI = 2,500 ms, FOV = 256 × 212, 48 slices, and 1 × 1 × 3 mm resolution.

An axial, whole brain (except cerebellum) resting state pCASL sequence was collected. Participants were instructed to keep eyes open and fixated on a crosshair and to stay awake. The sequence lasted for approximately 5 minutes, with TE = 13 ms, TR = 4,000 ms, FA = 90 degrees, FOV = 64 × 64, 32 slices, 80 total tagged and untagged volumes, and 4 mm isotropic resolution.

Preprocessing and CBF Calculation

All preprocessing was performed with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB 2015b (MathWorks; Natick, Massachusetts) except where specifically mentioned. The interpolation used was a fourth-degree B-spline interpolation, and the similarity metrics were mutual information for images of the same type (eg, between functional sequences) and normalized mutual information for images of differing types (eg, between functional-structural).

For structural preprocessing, we coregistered the FLAIR to the MPRAGE and then performed a multispectral segmentation into gray matter, white matter, cerebrospinal fluid (CSF), soft tissue, skull, and air (after light bias regularization). This segmentation outputs a deformation field that normalizes images into a standard anatomic space (Montreal Neurological Institute [MNI] space). We generated an intracranial volume (ICV) mask by combining all voxels with probability greater than 0.1 in gray matter, white matter, or CSF and then filling holes with the image filling algorithm (imfill), followed by an image closing algorithm to smooth out and close holes at the border (imclose). We skull stripped the MPRAGE and FLAIR using the mask. Structural volumes were normalized, and then the mean was calculated across participants to overlay neuroimaging results.

White matter hyperintensities were segmented using FLAIR images with a previously established automatic algorithm.[42] WMH probability map was generated by overlapping WMH segmentations of each subject and calculating the probability of having WMH in each voxel in this sample. Total and regional brain volumes were estimated using previously established automated labeling pathway.[42,43]

Functional pCASL images were motion corrected (tagged and untagged corrected separately and then together) to the first volume and then to the mean image (rigid transformation). The skull-stripped MPRAGE was coregistered (affine) to the mean ASL image, and this transformation was used to subsequently also coregister the ICV mask and white matter probability map (nearest-neighbor interpolation for ICV mask). ASL data were smoothed with a Gaussian kernel with full width at half maximum of 8 mm. Similar processing was also performed on the M0 image. Participants exhibited little in-scanner motion (below 2 mm translation). White matter masks were generated by thresholding the white matter probability map at 0.6. CBF was then calculated using ASL toolbox.[44] The following parameters were input: simple subtraction type (tagged-untagged), labeling time 1.16 s, delay time 1.1 s, slice time 43.5 ms, labeling efficiency 0.85, and TE of 13 ms. ICV mask was used to determine where to calculate CBF, while the white matter mask was used to determine the equilibrium magnetization of white matter.

Mean CBF images were coregistered to the skull stripped MPRAGE via the mean ASL image (affine) and then subsequently normalized to MNI space using the deformation field (4 mm isotropic). Considering the inaccuracy of CBF measurements in white matter[45,46] and extreme values, we limited CBF within gray matter and included values between 0–200. The threshold gray matter CBF maps were divided by the mean CBF in gray matter to

Table 1. Group Differences in Demographic and Clinical Variables Between Remitters and Nonremitters[a]

Variable	Nonremitters (n = 22)	Remitters (n = 24)	Group Comparison, P[b]
Age, y	64.5 (8.0)	66.0 (11.5)	.574
Race, Caucasian/African-American, n	18/4	20/4	1.000
Gender, female, n	11	18	.126
Education, y	16.0 (2.0)	13.0 (6.0)	.269
MMSE score	29.0 (1.8)[e]	29.0 (2.0)	.857
CIRSG total score	8.0 (4.8)[g]	9.0 (4.3)[e]	.918
CIRSG vascular item	2.0 (2.0)	2.0 (2.0)	.818
Depression onset age, y	30.0 (32.0)[c]	43.0 (39.3)[e]	.563
Years lived with depression	31.0 (32.3)[c]	25.0 (42.3)[e]	.772
Depression type, single/recurrent, n	11/9	7/16[c]	.130
MADRS baseline score	27.0 (7.0)	23.5 (11.0)	.069
MADRS score at 1 week	24.5 (7.0)	19.5 (10.5)	.034*
MADRS score at end	20.0 (8.5)[c]	3.0 (6.0)	< .001*
MADRS change ratio, %	32.3 (33.0)[c]	87.5 (26.2)	< .001*
Venlafaxine level first dose, ng/mL	26.0 (14.4)[g]	21.0 (13.5)[f]	.185
Venlafaxine level 1 week, ng/mL	102.5 (103.0)[d]	75.0 (23.9)[c]	.381
Venlafaxine level end, ng/mL	270.0 (355.8)[d]	107.5 (138)[d]	.003*
CBF baseline score	43.3 (19.1)	46.5 (13.7)	.429
CBF change score	2.8 (12.9)	0.3 (15.8)	.403

[a]Values expressed as median (IQR) unless otherwise noted.
[b]Group comparisons of race, gender, and depression type were conducted with Fisher exact test, while others were conducted with Mann-Whitney *U* test.
[c]1, [d]2, [e]3, [f]4, or [g]5 participants had missing data.
*$P < .05$ (significant difference).
Abbreviations: CIRSG = Cumulative Illness Rating Scale for Geriatrics, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination.

control for the individual differences in mean gray matter CBF. We wanted to also investigate whether the mean CBF map was a reliable indicator of CBF, so for each individual, we computed a voxel-wise map that indicated the percent of volumes that had a value greater than 3 standard deviations from the mean and found that within the significant region, a *maximum* 7.5% of volumes had values 3 standard deviations above the mean, which translates to approximately 3 volumes. On average, most individuals had only a single volume whose value was 3 standard deviations above the mean CBF. This indicated that the mean CBF was stable.

Statistical Analysis

Group differences in demographic/clinical variables between remitters and nonremitters were tested using Mann-Whitney *U* test or Fisher exact test in SPSS 24.0 (Statistical Package for the Social Sciences, IBM Corp, Armonk, New York).

Voxel-wise analyses were conducted using SnPM13 (http://warwick.ac.uk/snpm) and utilized permutation testing (5,000 permutations). All voxel-wise analyses used a cluster forming threshold of $P < .005$ and then were corrected to control for family-wise error (FWE, $P < .05$). While these results passed cluster-wise significance testing, in response to Eklund et al,[47] we also report that these results did not pass voxel-wise FWE.

Our primary analysis involved testing the association between the change in MADRS (or remission group) and change in CBF (baseline vs end). We also investigated whether the placebo, acute (single dose), or subacute (after a week) changes in CBF were associated with total change in MADRS and that this was not dependent on serum venlafaxine levels or years lived with depression (the number of years between current age and age of first lifetime episode of depression). Other exploratory analyses were done to (1) investigate associations with mean gray matter CBF (as this may be driving local differences); (2) investigate associations with baseline CBF; and (3) explore potential confounding variables and adjust for them in the primary analysis.

Another exploratory analysis was conducted to understand baseline CBF and its correlates; thus, we conducted a series of analyses using only the baseline CBF. We conducted regressions to investigate the association between baseline CBF and baseline/change in MADRS as well as years lived with depression. We conducted an independent *t* test to investigate baseline CBF differences between remission groups.

As the voxel-wise CBF is measured relative to the mean gray matter CBF, we conducted an exploratory analysis to investigate whether there were any associations (as these may be driving local differences) with mean gray matter CBF (baseline or change) and MADRS, years lived with depression, remission group, and blood venlafaxine levels. We also tested for any associations with MADRS (baseline or change) using Mann-Whitney *U* tests, Pearson, or Spearman rank correlation. We performed false discovery rate (FDR) correction ($\alpha < .05$) to control for multiple comparisons.[48]

To explore potential confounds, we investigated whether there were any regional associations between baseline or change in CBF and the following: age, sex, race, education, MMSE, CIRSG, baseline WMH, and WMH changes (slope of change in WMH). After these analyses, we found covariates that were significantly associated with either baseline CBF or CBF change. We conducted a final model to test the association between CBF and MADRS that adjusted for all the significant covariates simultaneously.

RESULTS

Demographic

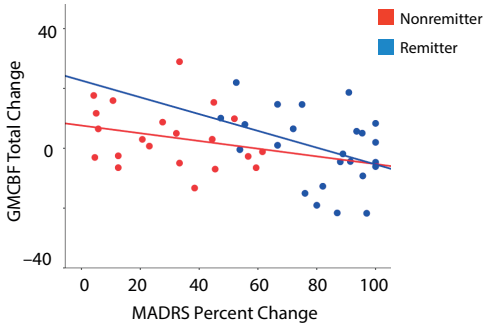
All participants showed improvement in MADRS following a 12-week treatment, and 24 met remission criteria. As expected, there were significant differences between remitters and nonremitters in end of trial MADRS score, end of trial serum venlafaxine levels, and percent change in MADRS score (Table 1).

Significant Voxel-Wise CBF Associations

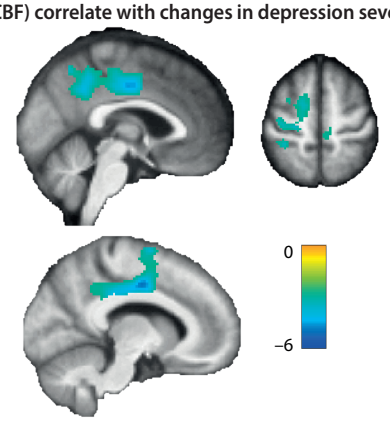
We found a significant negative association between total changes in CBF (baseline vs end) and percent change in MADRS in multiple structures (angular/supramarginal gyrus, middle and posterior cingulate, and precuneus; not shown). In this region, we found that sex and MMSE were

Figure 2. CBF Imaging Results, Association with Changes in Depression Severity, and Colocalization with WMH

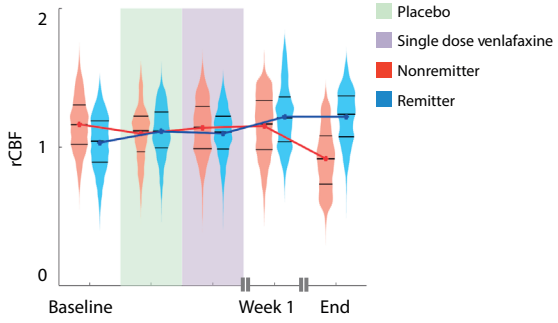
A. Association between changes in global CBF and changes in depression severity[a]



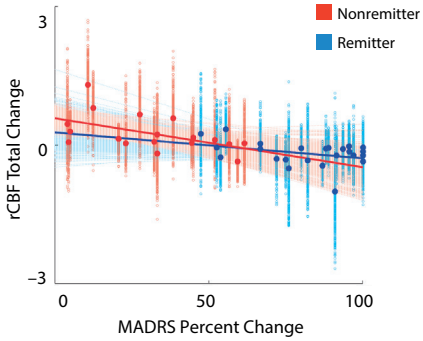
B. Significant cluster where changes in regional CBF (rCBF) correlate with changes in depression severity[b]



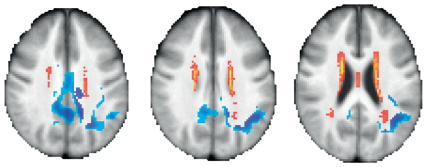
C. Trajectory plotting rCBF in significant cluster[c]



D. Association between changes in rCBF and changes in depression severity[d]



E. Colocalization of WMH and significant rCBF associations with depression severity[e]



[a]The association between the total change in mean GMCBF and the total percent change in MADRS ($P = .03$, uncorrected) is shown.
[b]Cluster that showed significant association between overall CBF difference and overall MADRS percent change, independent of gender and MMSE overlaid on mean structural image (5,000 permutations, cluster forming threshold $P < .005$, FWE corrected $P < .05$).
[c]Trajectories of region of interest mean regional CBF (rCBF) change in remitters and nonremitters. To better indicate the variability across this cluster, we also used violin plots that show a mirrored histogram alongside the median and 25th and 75th percentiles (black lines).
[d]The CBF change from baseline to end of trial was negatively associated with MADRS percent change from baseline to end of trial. To better indicate the variability across this cluster, each voxel-wise point is presented alongside each voxel-wise best-fit line, while the larger highlighted points are the mean CBF and bold best-fit lines are fit to that as well.
[e]The significant cluster (shown in blue) and WMH probability map (shown in red) overlaid on the mean structural image to demonstrate their spatial relationship.
Abbreviations: CBF = cerebral blood flow, FWE = family-wise error, GMCBF = gray matter cerebral blood flow, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination, WMH = white matter hyperintensities.

also associated. After adjusting for sex and MMSE, we found that increased CBF in middle/posterior cingulate, precuneus, angular/supramarginal gyrii, middle/superior frontal gyrii, supplemental motor area, and inferior/superior parietal lobes was significantly associated with improvement in MADRS (depression severity) even after adjusting for sex and MMSE (Figure 2B and Table 2).

Mean CBF from this cluster was plotted by remission group across the study (Figure 2C). Further, we plotted the negative association between the CBF total change and percent change in MADRS for both groups (Figure 2D). Finally, we overlaid the significant cluster alongside the WMH probability map to demonstrate the spatial relationship (Figure 2E).

Summary of Null Findings

Importantly, we did not find any association between total changes in CBF (baseline vs end) and years lived with depression, remission group, venlafaxine serum levels, or baseline MADRS score. We found no associations between

Table 2. Report of Regions (Part of a Single Cluster) That Showed Significant Association Between Overall CBF Difference and Overall MADRS Percent Change, Independent of Gender and MMSE Score

Region of Interest	Brodmann Area	No. of Voxels	T_{max} ($df = 38$)	Coordinate of Peak (x, y, z)
Right hemisphere				
Angular/supramarginal		229	4.25	−40, −50, 26
Middle cingulate	24, 31	1,008	4.92	−10, −8, 42
Posterior cingulate		74	3.75	0, −46, 34
Middle frontal		55	3.13	−24, −4, 52
Superior frontal		160	3.88	−18, 0, 54
Middle occipital		123	3.73	−26, −56, 34
Inferior parietal		182	3.90	−36, −32, 40
Superior parietal		78	3.31	−20, −54, 46
Post-central		201	3.87	−36, −34, 42
Pre-central		178	3.57	−22, −22, 62
Precuneus	7	403	4.33	−2, −48, 38
Supplemental motor/ medial frontal	6	289	3.76	−12, −2, 48
Supramarginal		85	3.62	−48, −48, 30
Middle temporal		79	3.59	−40, −52, 22
Left hemisphere				
Middle cingulate	31, 24	913	4.42	2, −12, 40
Posterior cingulate		104	3.46	10, −44, 32
Precuneus/posterior cingulate		355	3.85	2, −44, 44

Abbreviations: CBF = cerebral blood flow, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination.

percent changes in MADRS (baseline vs end) and changes in CBF following placebo, first dose of venlafaxine, or a week after treatment (ie, changes occurred in a later period). In our exploratory analysis, we found no significant associations between baseline CBF and baseline MADRS, percent change in MADRS, years lived with depression, or group.

Associations With Mean Gray Matter CBF

As voxel-wise CBF is relative to mean gray matter CBF, it is possible that these local associations are driven more by the global factor. Thus, we investigated the associations between mean gray matter CBF and depression severity, years lived with depression, and venlafaxine metabolite levels—as well as the associations between the changes in these measures (Supplementary Table 1). After correcting for multiple comparisons (FDR), we found no significant associations. However, we did observe that total change in depression severity was associated ($P = .03$, uncorrected) with total change in mean gray matter CBF (Figure 2A).

DISCUSSION

In this 12-week open-label trial of venlafaxine for LLD, we observed an association between increased CBF and depressive symptom improvement. The changes in CBF were detected in midline structures: the middle cingulate, precuneus, and posterior cingulate cortex. Although we did not detect early (less than 1 week) regional CBF changes, we demonstrated a robust association between CBF changes and MADRS changes over the entire 12-week venlafaxine treatment trial.

Previous studies demonstrate that cerebral hypoperfusion is common in aging,[49,50] that vascular diseases or vascular risk factors are associated with LLD,[51–53] and that individuals with LLD show lower global or regional CBF compared with healthy controls.[31–34] In general, several studies point to a hypoperfusion in the frontal and limbic cortex as well as the parietal cortex, including the anterior cingulate,[31,54,55] posterior cingulate,[55,56] frontal cortex (superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, dorsolateral prefrontal cortex, orbital frontal gyrus),[31,34,54,55,57–59] motor/ sensory cortex,[31,55] hippocampus,[31] temporal cortex,[31,34,55–59] superior middle gyrus,[31] parietal cortex (inferior parietal gyrus, superior parietal gyrus),[55,57–59] caudate,[31,55,60] and thalamus.[60] From this perspective, it may mean that these are normalizing changes (as these may be hypoperfused); however, we did not test this explicitly (as we lack a never-depressed group). We also identified 3 other studies exploring ASL-defined CBF in LLD investigating treatment response.[61–63] All used baseline ASL to explain variability in treatment response and showed mixed results, where higher or lower baseline CBF in some regions was associated with worse treatment outcome. Since CBF is not a static measure within an individual, but rather can vary with depressive state, the change in CBF over the course of treatment may be more predictive of remission than baseline CBF. Thus, in the current study, we focused on the change in CBF over the course of treatment. Our study investigated the CBF trajectory following LLD antidepressant treatment. Our results supported the vascular depression model by showing that changes in CBF were associated with symptom improvement.[64,65] Past studies have shown increased perfusion in the precuneus/parietal cortex after successful remission,[32,66] which aligns well with our own results; however, there are multiple other regions (that we did not find) that have shown an increased perfusion following successful remission, including left dorsolateral prefrontal cortex and precentral regions,[32] basal ganglia,[67] anterior cingulate cortex,[67] dorsal anterior cingulate,[68–70] left superior frontal,[66] and temporal cortex.[66]

Previous studies have shown associations between WMH burden and treatment response in LLD,[71,72] and others have shown an association of WMH burden and ASL measures (higher WMH is associated with lower CBF).[73–75] However, our current study did not find an association between baseline or change in CBF and WMH burden. This may also be due to a lower effect size of these associations and the limited temporal scope of the observations (previous studies investigated changes across years). The subtle effect of WMH could still lead to hypoperfusion in and around the middle and posterior cingulate, regions that are reported to be the most vulnerable to changes in blood flow due to specific anatomic vascularization.[76] This hypothesis was partially supported by the colocalization of the significant CBF alteration region and the WMH probability map (Figure 2E).

Recently, our group reported the existence of early changes in resting-state connectivity following a single dose of medication.[17] In the current study, the difference

in CBF was not apparent before the first week (although it is possible that these changes occur before 12 weeks). This finding may be due to the longer latency in changes in CBF compared with potentially brisker changes in neuronal activity and connectivity, changes known to be sensitive to acute pharmacotherapy.[77–79] The ASL signal is less sensitive to acute change compared with BOLD signal, which might be due to less time-varying changes and lower overall temporal resolution (eg, mean perfusion across 5 minutes of scanning was calculated in ASL) compared with BOLD. However, it may also mean that the changes in connectivity are related to a required mechanism to remission, while the CBF (as they are lagged) may reflect a change that occurs as a result. In our study, in which we found changes in connectivity, we used a region of interest (ROI) connectivity analysis, which included a posterior cingulate ROI. While these results may be associated, it is less likely, as the cingulate ROI (ventral aspect of the posterior cingulate) from our previous work and the identified regions in this analysis (more dorsal aspect of the posterior cingulate) do not overlap. It is possible that the change in CBF may be linked more directly to depressive state than to the action of the drug itself. Further studies with a larger sample and more frequent assessments may allow detection of early CBF changes that could potentially serve as treatment predictors.

One possible interpretation is that the increase in CBF in these areas might reflect a correction for hypoperfusion in deep watershed areas. These areas, near the centrum semiovale, are affected to a greater degree by small vessel disease (evidenced by WMH burden), which is associated with decreased CBF. This study supports a relationship between cerebral blood flow and depression but cannot distinguish the direction of the relationship. A longitudinal study with longer-term follow-up could help distinguish the principal direction of the relationship of CBF and depressive symptoms. The posterior cingulate is a core node in the default node network, a network of primarily midline structures that shows high connectivity during task-free states. Functional MRI studies using the BOLD contrast have shown impaired functioning of the DMN. The CBF changes could help explain the cause of the DMN functional alterations in vascular depression. Decreased perfusion of these regions may lead to functional alterations in the circuit.

The present study has several limitations. The first is its relatively small sample size, and thus it requires further verification and replication. Related to a small sample size, we have used a cluster-wise family-wise error correction to control for multiple comparisons and a nonparametric permutation approach that is in line with the current literature regarding multiple comparisons correction.[47] We used a delay time of 1.1 seconds, which may be too short in elderly participants according to recent consensus work[80] (that suggested 2 seconds instead); this may mean that the signal is primarily generated inside the blood vessels. As our data were collected prior to this work, we are unable to adjust for this, and thus our result should be interpreted within this context. Therefore, we cannot rule out that an early change exists, as well as an association between CBF and WMH. Second, associations were computed using regression and thus do not imply causal links. Moreover, past studies have shown that hypertension was associated with a decline in CBF, while patients who were successfully treated for their hypertension did not show such a decline.[81] The mechanism may be that the chronic stress of hypertension causes thickening and hardening of the walls of arterioles with narrowing of lumen and leads to cerebral hypoperfusion.[82] In the context of the vascular depression hypothesis, blood pressure should be well controlled in an effort to protect the cerebral arteries and prevent and treat LLD. But the hypertension and CBF relationship cannot be verified in the present study due to an absence of blood pressure data.

In conclusion, this study is the first to investigate the trajectory of CBF alteration following LLD pharmacotherapy. The measurement of CBF using ASL is a promising tool for understanding the biological mechanisms of LLD. The association between increased CBF in precuneus, posterior cingulate, and middle cingulate and symptom improvement further supports the vascular depression hypothesis. Besides external validation in an independent sample with measurements of blood pressure and other relevant cardiovascular features, several critical aspects have yet to be addressed and should be addressed in future studies. While we showed changes in CBF, it is unclear how these changes relate to long-term changes in WMH, relapse, and even future CBF—it is possible that treatment partially improves the continuing cycle of high depressive symptoms—low CBF—high WMH. Additionally, while we showed that there does exist an association between depressive symptoms and CBF, we did not address the directional aspect of this change and whether the change in symptoms improves CBF or the change in CBF improves symptoms. Determining this would require a neuroimaging study with multiple time points during the 3–8 week period, which we did not have. Other important questions to answer would be, how changes in CBF affect changes in connectivity, and vice-versa, and whether these changes are necessary for improvement of depressive symptoms or just a consequence. Finally, future studies should also directly investigate the association between age at onset and CBF—this is an underrepresented area of research, with studies mainly reporting differences in WMH.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Trajectories in Cerebral Blood Flow Following Antidepressant Treatment in Late-Life Depression: Support for the Vascular Depression Hypothesis

Author(s): Wenjing Wei, MD; Helmet T. Karim, PhD; Chemin Lin, MD; Akiko Mizuno, PhD; Carmen Andreescu, MD; Jordan F. Karp, MD; Charles F. Reynolds III, MD; and Howard J. Aizenstein, MD, PhD

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List of Supplementary Material for the article

1. **Table 1** Average Gray Matter CBF and Associations With Change in MADRS, Years Lived With Depression, and Venlafaxine Levels

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Average Gray Matter CBF Variable	Other Variable of Interest	Analysis	Statistics	p value (uncorrected)
Baseline CBF	**Baseline MADRS**	Spearman	r (45) = -0.11	0.46
Baseline – End CBF	**Baseline MADRS**	Spearman	r (45) = -0.02	0.88
Baseline CBF	**Baseline – End MADRS**	Pearson	r (44) = 0.06	0.70
Baseline – Placebo CBF	**Baseline – End MADRS**	Pearson	r (44) = -0.16	0.31
Baseline – Single Dose CBF	**Baseline – End MADRS**	Pearson	r (44) = 0.10	0.52
Single Dose – Week Post-treatment CBF	**Baseline – End MADRS**	Pearson	r (44) = -0.11	0.46
Baseline – End CBF	**Baseline – End MADRS**	Pearson	r (44) = -0.33	0.03
Baseline CBF	**Years lived with depression**	Pearson	r (41) = -0.03	0.87
Baseline – End CBF	**Years lived with depression**	Pearson	r (41) = -0.08	0.57
Baseline – End CBF	**Venlafaxine end**	Pearson	r (44) = 0.04	0.78

Supplementary Table 1. Average gray matter CBF and associations with change in MADRS, years lived with depression, and venlafaxine levels.