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Anterior-Posterior Gradient Differences in Lobar and Cingulate Cortex Cerebral Blood Flow in Late-Life Depression

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Abstract

Vascular pathology is common in late-life depression, contributing to changes in cerebral function. We examined whether late-life depression was associated with differences in cerebral blood flow (CBF) and whether such differences were related to vascular risk and cerebrovascular pathology, specifically white matter hyperintensity (WMH) volumes. Twenty-three depressed elders and 20 age- and sex-matched elders with no psychiatric history completed cranial 3T MRI. MRI procedures included a pseudo-continuous Arterial Spin Labeling (pcASL) acquisition obtained while on room air and during a hypercapnia challenge allowing for calculation of cerebrovascular reactivity (CVR). Brain segmentation identified frontal, temporal, parietal and cingulate sub-regions in which CBF and CVR were calculated. The depressed group exhibited an anterior-posterior gradient in CBF, with lower CBF throughout the frontal lobe but higher CBF in the parietal lobe, temporal lobe, thalamus and hippocampus. A similar anterior to posterior gradient was observed in the cingulate cortex, with anterior regions exhibiting lower CBF and posterior regions exhibiting higher CBF. We did not observe any group differences in CVR measures. We did not observe significant relationships between CBF and CVR with vascular risk or WMH volumes, aside from an isolated finding associating higher WMH volumes with lower CBF in the

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Dr. Abi Zeid Daou contributed to the analytic plan, data interpretation, and wrote the initial draft of the manuscript. Mr. Boyd contributed to analysis of imaging data. Dr. Donahue contributed to study methods, image acquisition, and guided image analysis. Dr. Albert contributed to image analysis and data interpretation. Dr. Taylor designed the study, evaluated study participants, and contributed to data analysis and data interpretation. All authors have reviewed and approved the final manuscript.

Declaration of Interest Statement:

Conflicts of interest: None

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rostral anterior cingulate cortex. Decreased anterior CBF in depressed elders might reflect decreased metabolic activity in these regions, while increased posterior CBF may represent either compensatory processes or different activity of posterior intrinsic functional networks. Future work should examine how these findings are related to compensatory changes with aging.

Keywords

Aging; geriatric; perfusion; depression; depressive disorder; arterial spin labeling

1. Introduction

Late life depression (LLD), or Major Depressive Disorder (MDD) occurring in individuals age 60 years or older (Taylor, 2014), is a heterogeneous disorder affecting approximately 5% of community elders and is more prevalent in patients with greater medical morbidity and higher vascular burden (Taylor, 2014; Taylor et al., 2004). This observation contributed to the vascular depression hypothesis, positing that cerebrovascular disease predisposes, precipitates and perpetuates some late-life depressive syndromes (Alexopoulos et al., 1997). Despite a significant body of work linking LLD with vascular disease and vascular pathology (Aizenstein et al., 2016; Taylor et al., 2013), the exact mechanisms underlying the association between vascular risk factors and LLD remain elusive. One potential explanatory theory is the “Hypoperfusion Hypothesis,” proposing that decreased brain perfusion negatively affects the function of brain circuits involved in cognition and mood regulation, thus contributing to depressive symptoms and behavior (Taylor et al., 2013).

Past work using a range of imaging modalities have examined brain perfusion in depressed populations. Supporting the hypoperfusion hypothesis, a single-photon emission computed tomography (SPECT) study found that elders with chronic LLD exhibit reduced cerebral blood flow (CBF) in the prefrontal cortex, cingulate cortex, caudate, temporal and parietal lobes (Awata et al., 1998). Subsequent studies in adult MDD using positron emission tomography (PET) imaging or MRI-based arterial spin labeling (ASL), report localized reductions in CBF in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, and parahippocampal region (Lui et al., 2009; Monkul et al., 2012; Ota et al., 2014; Vasic et al., 2015). However, depression is not exclusively associated with hypoperfusion as studies in younger or midlife depression show increased CBF in the subgenual ACC, lateral orbitofrontal cortex (LOFC), hippocampus and pallidum (Duhamel et al., 2010; Lui et al., 2009; Vasic et al., 2015). ASL studies in LLD have been less clear, with some reporting no difference in gray matter CBF but observing increased white matter CBF in LLD, primarily in remitted LLD (Colloby et al., 2012). In our previous work, poor antidepressant response in LLD was associated with higher pre-treatment CBF in the caudal ACC and LOFC (Abi Zeid Daou et al., 2017).

Relevant to LLD, perfusion changes are also associated with vascular risk factors. A higher vascular burden is associated with lower CBF (Bangen et al., 2014) as conditions such as hypertension, diabetes and smoking damage the cerebral vasculature. Although white matter is less perfused than gray matter, hypoperfusion may adversely affect white matter structure

and contribute to white matter hyperintensities (WMH) development (Herrmann et al., 2008; Taylor et al., 2013) or microbleeds (Gregg et al., 2015).

Vascular function can be measured as cerebrovascular reactivity (CVR), or the capacity of cerebral arteries to dilate in response to increased arterial partial pressure of carbon dioxide (PCO₂). Experimentally, hypercapnia can be induced through breath holding, CO₂ inhalation, or the infusion of acetazolamide (Neu et al., 2004). Similar to CBF (Chen et al., 2011), CVR decreases with age (Leoni et al., 2017; Lu et al., 2011). Depressed adults exhibit lower CVR than nondepressed controls (Neu et al., 2004), even independently of vascular risk factors (de Castro et al., 2008). This reduction in CVR may improve with successful antidepressant treatment, although the mechanism by which this occurs is unclear (Lemke et al., 2010).

The purpose of this study was to examine group differences in CBF and CVR between older individuals with and without LLD. Although our hypoperfusion hypothesis was not supported in our previous report associating regionally lower CBF with a more robust treatment response (Abi Zeid Daou et al., 2017), we continued to explore the same theory in the current study. We sought to determine whether depressed elders exhibited reduced CBF and CVR in cortical and subcortical regions. Given our previous findings associating response with reduced CBF in specific frontocingulate regions (Abi Zeid Daou et al., 2017), we also examined subregions of the frontal lobe and cingulate cortex. In secondary analyses, we additionally examined the relationship between ASL measures and a) vascular burden, assessed radiologically as WMH volume and clinically with the Framingham stroke risk scale, and b) global cognitive performance measured with the Mini-Mental State Exam (MMSE).

2. Methods

2.1. Design and sample

The study included 23 depressed subjects and 20 non-depressed individuals, all aged 60 years or older. The non-depressed group was age- and sex-matched with the depressed group. Each non-depressed subject was recruited after the corresponding matched depressed subject, and required to be of the same sex and of an age within 2 years of the depressed participant. The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was administered to assess psychiatric diagnoses with the results being confirmed by clinical interview. Depressed individuals met DSM-IV-TR criteria for Major Depressive Disorder and had a Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score of 15 or higher. Nondepressed individuals had no current or past psychiatric diagnosis on both MINI and clinical exam and no history of psychotropic medication use. A MMSE score of 22 or more was required for all participants (Folstein et al., 1975).

Exclusion criteria included (1) current or past diagnoses of other Axis I psychiatric disorders, including substance dependence; (2) any use of illicit substances (such as marijuana or cocaine) or abuse of prescription medications (such as benzodiazepines or opiates) within the last three months; (3) presence of acute suicidality; (4) current or past

psychosis; (5) primary neurologic disorders, including dementia; (6) chronic untreated medical disorders where treatment was warranted; (7) need for continuous oxygen use or any medical disorder where the hypercapnia challenge would put the subject at increased risk; and (8) contraindications for magnetic resonance imaging (MRI). For the depressed group, who would subsequently receive open-label treatment with sertraline (Abi Zeid Daou et al., 2017), additional exclusion criteria included (1) ECT in last 6 months; (2) known allergy or hypersensitivity to sertraline; (3) a failed therapeutic trial of sertraline in the current depressive episode; and (4) current or planned psychotherapy.

Participants were recruited from community advertisements and clinical referrals to the Vanderbilt University Medical Center Psychiatry Outpatient Clinics. Participants were also recruited via Research Match (ResearchMatch.org), an online research volunteer registry matching individuals interested in participating in research with active research studies. The Vanderbilt Institutional Review Board approved the study and all participants provided written informed consent.

2.2. Assessments, antidepressant treatment and monitoring

At baseline, participants provided demographic data and completed screening assessments including the MINI and the MMSE. As part of their clinical interview, the study psychiatrist evaluated depression severity using the MADRS, assessed medical comorbidity using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992), and quantified vascular risk using Framingham Study stroke risk prediction tool (Wolf et al., 1991). As study procedures for depressed participants included open-label treatment with sertraline, those who met entry criteria but were currently taking antidepressant medications had those medications tapered and discontinued. Participants were antidepressant-free for at least two weeks prior to MRI. Data on MRI predictors of antidepressant response in this sample have been previously published (Abi Zeid Daou et al., 2017).

2.3. MRI Acquisition

All participants were scanned on the same research-dedicated 3.0T Philips Achieva whole-body scanner (Philips Medical Systems, Best, The Netherlands). They completed ASL and structural imaging with data acquired using body coil radiofrequency transmission and a 32-channel head coil for reception. Structural imaging utilized a whole-brain T1-weighted MPRAGE image with TR/TE = 8.7/4.6 and spatial resolution = $0.9 \times 0.9 \times 1.2$ mm. During scan sessions participants wore a close-fitting gas mask that covered the mouth and nose, with the attached reservoir bag tape closed. Air mixtures from compressed cylinders were provided continuously at 12 L/min using this setup. Physiological monitoring during ASL sequences was achieved using an In Vivo Research Inc. device and Millenia Vital Systems Monitoring System (3155 MVS). This allowed for the measurement of arterial oxygen saturation fraction and exhaled CO₂ (EtCO₂) using a nasal cannula throughout the gas delivery paradigms.

A pseudocontinuous ASL (pCASL) sequence was used for CBF and CVR assessments. This utilized a 1.65s labeling pulse train consisting of Hanning-windowed 0.7ms pulses, followed by a post-labeling delay of 1.6s (TR=4s, TE=14ms; spatial resolution = $3 \times 3 \times 7$ mm³). A

separate equilibrium magnetization image was acquired with identical geometry but spin labeling preparation removed for M_0 calculation. The entire sequence included 75 total dynamics alternating between room air and hypercapnia. For baseline CBF measures, participants received medical grade room air (approximately 20.9% O_2 and 78.1% N_2 , with a balance of other trace atmospheric elements). These data were drawn only from the first four minutes (30 dynamics).

For CVR assessment, identical pCASL sequences were obtained during a hypercapnic normoxia challenge where participants inhaled a mixture of 5% CO_2 21% O_2 and 74% N_2 . To prevent prolonged continuous exposure to hypercapnic conditions and assure safety, this stimulus paradigm consisted of two blocks of hypercapnic normoxia (2 min; 15 dynamics each) interleaved with medical-grade room air (2 min; 15 dynamics) (Abi Zeid Daou et al., 2017; Donahue et al., 2014). The hypercapnic blocks were combined for analyses, while the interleaved room air block was discarded.

2.4. MRI Analyses

After motion correcting using mcflirt (in the FSL package), ASL images were pair-wise subtracted to get a difference in the magnetization image for each dynamic. These data were then averaged across time. CBF was quantified via application of the flow-modified Bloch equation (Alsop et al., 2015) using a per-slice modified post-labeling delay (slicedit) of 23ms. The M_0 image was registered to the average control image to allow M_0 to be applied in a voxel-wise manner. As recommend by Alsop et al. (Alsop et al., 2015), we used a labeling efficiency of 0.85.

We utilized FreeSurfer tissue segmentation and cortical parcellation of the T1 data to obtain regions-of-interest limited to gray matter regions in the frontal lobe and cingulate cortex. FreeSurfer (version 5.1) analyses were conducted in a high-performance Linux cluster environment using standard previously published methods (Fischl et al., 2004a; Fischl et al., 2004b). All FreeSurfer parcellations were inspected and manual edits performed as needed. To allow for comparison across subjects and utilize region-of-interest analyses, all ASL images were co-registered to the T1 images using FSL's flirt with a mutual information cost function limited to six degrees of freedom. To avoid altering the ASL data, we then inverted that transform to register the T1 images into the ASL space and applied this transform to the FreeSurfer parcellation using nearest-neighbor interpolation. This allowed us to calculate the mean and median CBF value for each region of interest. To eliminate outliers of potential voxels with high endovascular signal from biasing the median and mean calculations, we only included voxels within a reasonable CBF range between 1 and 100 ml/100g/min.

White matter hyperintensity (WMH) volumes, findings on T2-weighted or FLAIR images that are related to cerebral ischemia, were measured using the Lesion Segmentation Toolbox (Schmidt et al., 2012). This was implemented through the VBM8 toolbox in SPM8, using the default threshold of 0.3. In native space, each voxel on the T1 image is assigned as gray matter, white matter, or CSF. After bias-correction the FLAIR is co-registered to the T1 image. The toolbox initially creates a conservative binary WMH map based on outlier values across the T1 and FLAIR images. Next, a lesion-growth algorithm using Markov Random Fields modeling extends this conservative map to define the extent of the WMH. This lesion

map is then used to calculate total cerebral WMH volume. Using an approach similar to that described for the ASL data, we then applied FreeSurfer parcellations to the WMH map, allowing us to calculate WMH volume within each region of interest.

2.5. Statistical Analyses

All data analyses were conducted using SAS 9.4 (Cary, NC). Regional CBF measures utilized medical air ASL data only. Regional CVR measures were calculated as the difference in CBF between hypercapnic normoxia and medical air conditions, divided by CBF on medical air. After examining the main cortical and subcortical regions, based on our hypotheses and prior findings (Abi Zeid Daou et al., 2017), we then focused on frontal lobe and cingulate cortex subregions as delineated by FreeSurfer segmentation.

Using these ASL measures, we conducted three sets of analyses. First, we examined whether ASL measures of CBF and CVR differed between depressed and nondepressed participants. Analyses of CBF controlled for age, sex and mean cortical CBF, while analyses of CVR controlled only for age and sex. These analyses initially focused on key cortical and subcortical regions followed by subregions of the frontal lobe and cingulate cortex as identified by FreeSurfer segmentation. Second, we examined whether markers of vascular risk were associated with regional ASL measures. Using the same covariates described above in addition to the group diagnosis variable, we included the Framingham stroke risk score as a clinical marker of risk and total WMH volume as a marker of cerebral vascular disease. In additional analyses of frontal lobe and cingulate cortex subregions, we replaced total WMH volume with regional WMH volumes of the frontal lobe and cingulate cortex. Finally, we examined models where MMSE score was the dependent variable and ASL measures were an independent variable, along with covariates of age, sex, depression, and mean cerebral CBF. Within each set of analyses, we controlled for multiple comparisons with the False Discovery Rate (FDR) approach to correct the significance level (Benjamini and Hochberg, 1995).

3. Results

3.1. Group characteristics

In univariate analyses, there were no statistically significant diagnostic group differences in demographic variables or measures of medical comorbidity (Table 1). However, the depressed group did exhibit a significantly lower MMSE score and higher baseline MADRS score. Despite only requiring a MMSE score of 22 or higher for study entry, the sample was cognitively intact per MMSE, exhibiting a range of 26 to 30. The depressed group also exhibited higher exhaled CO₂ levels on medical air.

3.2. Group differences in cortical and subcortical CBF

We first examined CBF in cortical lobes and key subcortical regions. Initial models controlled for age, sex, mean cortical CBF, and exhaled CO₂ level. Mean exhaled CO₂ levels on medical air were not significantly associated with CBF in any region, so that variable was removed from subsequent models.

After controlling for age, sex and mean cortical CBF, we found statistically significant differences in mean CBF between depressed and nondepressed groups in the frontal, temporal and parietal lobes (Table 2)(Figure 1). Compared with nondepressed participants, the depressed group exhibited lower mean CBF in the frontal lobe and higher CBF in temporal and parietal lobes and the insular cortex. In the cingulate cortex, no statistically significant group differences were observed. In subcortical areas, depressed subjects exhibited higher mean CBF in the thalamus and the hippocampus but not in the caudate. These group differences remained statistically significant after FDR adjustment for multiple comparisons.

3.3 Group differences in CBF of cingulate cortex and frontal lobe subregions

After evaluating group differences in lobar CBF measures, we further examined CBF in subregions of the cingulate cortex and frontal lobe. After FDR correction for multiple comparisons, all cingulate cortex subregions exhibited statistically significant group differences in mean CBF (Table 3). The depressed group exhibited lower mean CBF in anterior cingulate cortex (ACC) subregions (the caudal ACC and the rostral ACC) and higher mean CBF in posterior regions (the posterior cingulate cortex and isthmus).

In frontal subregions, after FDR correction for multiple comparisons, statistically significant group differences were observed in almost all areas (Table 3). Exceptions that did not differ between groups included the paracingulate gyrus, the pars opercularis, and pars triangularis. Across all frontal subregions, mean CBF was consistently lower in the depressed group than the nondepressed group.

3.4. Vascular measure effects on regional CBF

In secondary analyses, we examined the relationship between mean CBF and vascular risk factors, including the WMH and the Framingham score. Both sets of analyses controlled for age, sex, cortical CBF, and depressed status. After FDR correction, models examining the relationship between Framingham score and mean CBF did not find statistically significant associations in any region examined (data not shown). In analyses of WMH volume effects, after adjusting for multiple comparisons we did not find any statistically significant associations with CBF in cortical and subcortical regions or frontal subregions. However, we did observe a significant negative association between total WMH volume and rostral ACC CBF ($F_{1,38} = 7.64$, $p = 0.0089$, Benjamini-Hochberg corrected significance level = 0.0125), where greater WMH volumes were associated with lower rostral ACC CBF.

In additional analyses of frontal lobe and cingulate cortex subregions, we replaced total WMH volume respectively with frontal lobe WMH volume and cingulate cortex WMH volume. After FDR correction, we did not observe any statistically significant association between frontal WMH volume and frontal CBF measures. Additionally, after FDR correction, we did not observe any statistically significant association between cingulate cortex WMH volume and cingulate cortex CBF measures.

3.5. Assessment of CVR: Group differences and effects of vascular measures

Nineteen depressed and 16 nondepressed subjects completed the hypercapnia challenge and had usable CVR data. All participants exhibited the expected increase in exhaled CO₂ levels during the hypercapnia challenge and there was no statistically significant group difference in change in exhaled CO₂ levels (depressed: 6.5 mmHg (2.4); nondepressed: 8.1 mmHg (6.0); Satterthwaite $t = 1.05$, 18.99 df, $p = 0.3067$). The mean increase in CO₂ levels for all subjects was 7.2 mmHg (SD=4.4, $t = 9.64$, 34 df, $p < 0.0001$).

In models controlling for age and sex, after correction for multiple comparisons we did not observe any statistically significant group differences in any region. Similarly, we did not find any statistically significant association in any region between CVR and either Framingham score or WMH volume (data not shown). This did not change when we replaced total WMH volume with frontal lobe WMH volume or cingulate cortex WMH volume.

3.6. Relationship between ASL measures and total MMSE score

In exploratory analyses, we examined the relationship between ASL measures and MMSE score. After controlling for covariates and FDR correction, MMSE score was not significantly associated with CBF or CVR in any region.

4. Discussion

In this cross-sectional study, CBF patterns in LLD follow a gradient of hypoperfusion in frontal regions with hyperperfusion in parietotemporal regions. Patterns of CBF in cingulate cortex subregions follow a similar anterior to posterior gradient. Although these findings are concordant with some past studies of perfusion in adulthood depression (Lui et al., 2009; Monkul et al., 2012; Ota et al., 2014), they are distinct from a prior study in LLD that did not observe group differences in gray matter CBF (Colloby et al., 2012). Contrary to initial hypotheses, we did not observe any group differences in regional CVR. Moreover, aside from an isolated relationship between WMH volume and rostral ACC CBF, we did not observe statistically significant relationships between regional CBF, WMH volume, or Framingham stroke risk score.

Despite the LLD group exhibiting lower CBF in the frontal lobe and ACC, these findings do not clearly support the Hypoperfusion Hypothesis as a potential mechanism by which vascular processes may influence LLD. The Hypoperfusion Hypothesis (Taylor et al., 2013) posits that perfusion deficits would be related to underlying vascular pathology such as increased arterial stiffness, increased intima media thickness, and endothelial dysfunction, findings reported in LLD (Paranthaman et al., 2010; Tiemeier et al., 2003). In the current study, if such vascular pathology was contributing to lower anterior CBF, we would expect to also observe group differences in CVR, a more direct measure of vascular function. We would also expect to observe associations between CBF, WMH volume, and the Framingham stroke risk score. Interestingly, the only relationship we observed between CBF and cerebral WMH volume was CBF in the rostral ACC. The rostral ACC has long been implicated in depression (Pizzagalli, 2011) and our finding support past work in LLD that

greater WMH severity is associated with altered function of this region (Aizenstein et al., 2011). However, it is important to recognize that due to a relatively small sample size we may have been limited in our ability to detect group differences in some measures, so the lack of a finding should not be construed to be strong support for the null hypothesis. This critique also applies to our lack of an association between ASL measures and MMSE, although these analyses are complicated as over half of our sample was actively depressed.

Moving beyond the contributions of vascular pathology, our findings lead to two alternative hypotheses. These hypotheses are dependent on the concept that regional CBF is tightly correlated with underlying cerebral metabolic activity (de la Torre, 2012; Iadecola, 2004), so differences in CBF may reflect underlying differences in metabolic activity. CBF may thus be related to activity of key regions in intrinsic functional networks. First, depression is characterized by increased activity in regions implicated in emotion and arousal. This activity could explain the observed increases in CBF observed in the hippocampus, thalamus, insula, and PCC. More broadly, depression is associated with increased activity in regions of the default mode network (DMN) (Sheline et al., 2009), a network whose posterior hub includes connections across parietal and temporal lobes. Depression is further associated with decreased activity in frontal and cingulate regions of the executive control network (ECN) (Mayberg et al., 1999; Pizzagalli et al., 2006). Thus, differences in CBF may be related to depression-related differences in activity of these underlying networks. However, this rationale does not capture the complexity of the networks as there is overlap in network location, with the DMN having an anterior component and the ECN including parietal regions.

Alternatively, building on the concept that depression is characterized by reduced activity in dorsal frontocingulate regions involved in mood regulation and cognitive processes (Mayberg et al., 1999; Pizzagalli et al., 2006), it may be possible we are observing a compensatory phenomenon. The increased CBF in temporal, parietal, and posterior cingulate cortex regions may represent increased activity of these regions in an effort to bolster cognitive performance given relatively reduced frontal metabolic activity. However, such a compensatory process in LLD may be problematic as in normal aging we observe compensatory processes occurring in the opposite direction. Normal aging is characterized by a posterior-anterior shift in brain activity during cognitive tasks, where in order to maintain stable cognitive performance there is an age-related reduction in occipitotemporal activity with an increase in frontal activity (Davis et al., 2008). It is thus possible that our CBF observations represent a compensatory process in LLD that overwhelms the process in normal aging, or may represent a failure of this normal posterior-to-anterior shift to occur in older adults with LLD. If correct, the cause underlying the failure of the expected posterior to anterior shift is unclear. However, it is unlikely that our findings are secondary to Alzheimer's disease neuropathology, as both Mild Cognitive Impairment and Alzheimer's disease are associated with reductions in parietal-temporal CBF that parallel changes in cognition (Zhang et al., 2017).

Although informative, some study design elements limit our conclusions. A primary concern is that we examined a relatively small sample size. Thus, although we did detect statistically significant differences in some measures even when controlling for multiple comparisons,

we may have been underpowered to detect differences in more heterogeneous measures, such as CVR or the relationship between CBF and vascular pathology. Thus our findings should not be viewed as support for the null hypothesis.

Additional limitations include that, in an effort to explain our findings, we link our observed differences in CBF with underlying regional metabolism, although we do not have any measures of brain metabolism. Similarly, we discuss our findings in context of brain aging, however we cannot confirm these theories as we do not examine younger adults and do not have a longitudinal component where we can look at change with aging. Additionally, although our initial theories related to the effect of vascular pathology on brain CBF, beyond examining hypercapnia-induced CVR, we have no measures of vascular function or structure, such as endothelial function or intima media thickness. Instead, we have a stroke risk score, while our WMH measures may represent the end result of vascular disease rather than be related to current vascular function. Finally, although our ROI-based analysis of ASL imaging data was hypothesis-based and adhered to the original research strategy, it limits our ability to identify other regions exhibiting CBF or CVR differences as could be identified using a voxel-based analyses.

In conclusion, LLD is characterized by lower CBF in anterior brain regions and higher CBF in posterior parietotemporal regions. We did not find support for the theory that these changes are related to underlying vascular disease, although this conclusion is limited due to a small sample size. More work is needed to understand how our observed differences in CBF are related to underlying intrinsic network function. Future efforts should consider whether LLD is associated with altered compensatory processes with aging and whether the failure of compensatory processes may contribute to the risk of cognitive decline in this population (Riddle et al., 2017).

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Figure 1. Lobar, subcortical, and cingulate cortex differences in cerebral blood flow

Figures display group differences in regional cerebral blood flow displayed as ml/100g/min.

Horizontal bars with * indicate group differences achieving statistical significance at Benjamini and Hochberg corrected significance levels.

Figure 1. A. Lobar and subcortical regions. Caud = caudate nucleus; Cing = cingulate cortex; FLobe = frontal lobe; Hpc = hippocampus; PLobe = parietal lobe; TLobe = temporal lobe; Thal = Thalamus

Figure 1. B. CACC = caudal anterior cingulate cortex; ISCC = isthmus of the cingulate cortex; PCC = posterior cingulate cortex; RACC = rostral anterior cingulate cortex

Table 1

Differences between depressed and nondepressed groups.

	Depressed (N=23)	Nondepressed (N=20)	Test Value (df)	p value
Age (years)	68.10 (7.29)	68.00 (5.82)	t = 0.04 (41)	0.9661
Sex (women)	60.87 (14)	55.00 (11)	-	0.7631
Education (years)	15.45 (1.79)	16.35 (1.69)	t = 1.66 (41)	0.1048
MADRS	26.48 (7.46)	0.40 (0.68)	t = 16.69 (22.42)	< 0.0001
MMSE	28.30 (1.29)	29.10 (1.25)	t = 2.04 (41)	0.0477
CIRS total	4.74 (2.63)	4.30 (2.41)	t = 0.57 (41)	0.5735
Framingham total score	9.86 (3.72)	9.21 (3.65)	t = 0.57 (39)	0.5748
WMH volume (ml)	11.74 (20.65)	3.91 (5.23)	t = 1.76 (25.21)	0.0913
Resting cortical CBF	33.98 (5.68)	34.68 (3.20)	t = 0.51 (35.47)	0.6147
End-Tidal exhaled CO ₂ (mmHg)	42.9 (5.2)	38.0 (8.0)	2.22 (41)	0.0335

Continuous variables presented in mean (standard deviation), categorical as percent (number). Comparison of continuous variables with equal variances made using pooled, two-tailed t-tests with 41 degrees of freedom (df), except for group comparisons of Framingham score which had 39 degrees of freedom due to a smaller sample of 22 depressed and 20 nondepressed subjects. Comparison of continuous variables with unequal variances (MADRS, WMH volume, and resting cortical CBF) made using Satterthwaite t-tests. Comparison of categorical variables (sex) made using a Fisher's exact test.

CBF = cerebral blood flow, presented as ml/100g/min, CIRS = Cumulative Illness Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Exam, WMH = white matter hyperintensity

Table 2

Differences in mean CBF in cortical and subcortical regions

	Depressed (SD)	Non-depressed (SD)	F value	P value
Cortical Regions				
Frontal Lobe	34.06 (6.06)	39.73 (5.21)	43.85	<0.0001
Temporal Lobe	31.74 (5.13)	28.93 (3.55)	22.81	<0.0001
Parietal Lobe	35.02 (6.36)	33.72 (3.8)	17.36	0.0002
Cingulate Cortex	37.18 (6.85)	37.60 (4.13)	0.29	0.5949
Insula	31.71 (6.94)	29.59 (3.85)	8.14	0.0070
Subcortical Regions				
Caudate	24.24 (4.68)	22.25 (4.77)	3.38	0.0737
Thalamus	33.24 (7.67)	25.98 (7.22)	14.53	0.0005
Hippocampus	30.88 (6.69)	24.64 (5.90)	19.36	<0.0001

Models examined group differences while controlling for age, sex, and cortical CBF. Regional CBF presented as ml/100g/min. FDR correction for multiple comparisons resulted in a Benjamini and Hochberg corrected significance level of 0.0375.

Table 3

Differences in mean CBF in cingulate cortex and frontal lobe subregions

	Depressed	Non-depressed	F value	P value
Cingulate Cortex				
Caudal Anterior	34.63 (7.65)	38.09 (4.30)	7.04	0.0116
Rostral Anterior	32.61 (5.54)	38.76 (7.68)	13.09	0.0009
Posterior	41.35 (8.59)	38.96 (5.46)	6.82	0.0128
Isthmus	38.86 (9.24)	31.99 (8.22)	13.48	0.0007
Frontal Cortex				
Pars Orbitalis	35.77 (6.83)	46.07 (11.01)	20.34	<0.0001
Paracingulate Gyrus	32.81 (6.85)	32.44 (5.05)	0.68	0.4144
Precentral Gyrus	35.23 (7.11)	38.43 (4.68)	5.09	0.0299
Caudal Medial Frontal Gyrus	35.64 (8.53)	41.24 (7.90)	7.90	0.0078
Lateral OFC	32.98 (6.17)	39.58 (7.01)	15.08	0.0004
Superior Frontal Gyrus	32.11 (6.55)	39.08 (5.94)	30.31	<0.0001
Medial OFC	35.67 (5.64)	41.70 (8.06)	10.36	0.0026
Rostral Medial Frontal Gyrus	34.68 (7.02)	43.52 (7.98)	31.83	<0.0001
Frontal pole	33.80 (8.26)	49.54 (16.58)	16.74	0.0002
Pars Opercularis	35.27 (7.05)	34.93 (3.63)	2.98	0.0924
Pars Triangularis	34.54 (6.54)	37.40 (5.45)	4.35	0.0437

Models examined group differences in models controlling for age, sex, and cortical CBF. Regional CBF presented as ml/100g/min. FDR correction for multiple comparisons resulted in Benjamini and Hochberg corrected significance level of 0.05 for cingulate cortex subregions and 0.0364 for frontal lobe subregions.

OFC = orbitofrontal cortex