Medial temporal lobe volumes in late-life depression: effects of age and vascular risk factors

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Abstract

Substantial work associates late-life depression with hippocampal pathology. However, there is less information about differences in hippocampal subfields and other connected temporal lobe regions and how these regions may be influenced by vascular factors. Individuals aged 60 years or older with and without a DSM-IV diagnosis of Major Depressive Disorder completed clinical assessments and 3T cranial MRI using a protocol allowing for automated measurement of medial temporal lobe subfield volumes. A subset also completed pseudo-continuous arterial spin labeling, allowing for the measurement of hippocampal cerebral blood flow. In 59 depressed and 21 never-depressed elders (mean age = 66.4 years, SD=5.8y, range 60–86y), the depressed group did not exhibit statistically significant volumetric differences for the total hippocampus or hippocampal subfields but did exhibit significantly smaller volumes of the perirhinal cortex, specifically in the BA36 region. Additionally, age had a greater effect in the depressed group on volumes of the cornu ammonis, entorhinal cortex, and BA36 region. Finally, both clinical and radiological markers of vascular risk were associated with smaller BA36 volumes, while reduced hippocampal blood flow was associated with smaller hippocampal and cornu ammonis volumes. In conclusion,

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: All authors (Taylor, Deng, Boyd, Donahue, Albert, McHugo, Gandelman, Landman) deny any conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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while we did not observe group differences in hippocampal regions, we observed group differences and an effect of vascular pathology on the BA36 region, part of the perirhinal cortex. This is a critical region exhibiting atrophy in prodromal Alzheimer's disease. Moreover, the observed greater effect of age in the depressed groups is concordant with past longitudinal studies reporting greater hippocampal atrophy in late-life depression.

Keywords

depressive disorder; geriatric; hippocampus; perirhinal cortex; MRI; structural

INTRODUCTION

The hippocampus exhibits structural and functional differences in late-life depression (LLD) (Sexton, et al. 2013). Such alterations may be the result of repeated depressive episodes across the lifespan (Sheline, et al. 1996), persistent depressive symptoms (Taylor, et al. 2014), or related to early neurodegenerative processes. Although depression in younger adults is also associated with differences in hippocampal volumes, the relationship in older adults is more complicated, as LLD is associated with significant medical and vascular comorbidity (Taylor 2014; Taylor, et al. 2004) that may have deleterious effects on medial temporal lobe structure. LLD is also characterized by a range of cognitive deficits and increased risk of dementia (Diniz, et al. 2013; Koenig, et al. 2014), even in elders with an early life depression onset (Riddle, et al. 2017). This risk may be related to neurodegenerative processes or vascular injury to the hippocampal circuit. Crucially, although the hippocampus is often studied as a single brain region, it is a collection of structurally and functionally connected subregions with different functions and unique connections, including connections to other medial temporal lobe regions such as the entorhinal and perirhinal cortices. It is currently unclear whether specific medial temporal lobe regions are affected in non-demented individuals with LLD and how such differences are related to vascular pathology.

Despite numerous studies examining the hippocampus in LLD, fewer studies examine subfields of the hippocampus and connected medial temporal lobe regions. Past work in this area has not produced consistent results, variously associating LLD with smaller volumes of hippocampal subregions including the cornu ammonis (CA), dentate gyrus, and subiculum (Choi, et al. 2017; Lim, et al. 2012; Su, et al. 2016). In an effort to reduce sample heterogeneity, recent work examined late-life onset of depression, a population with greater medical morbidity and cognitive impairment, reporting smaller CA and dentate gyrus regions (Choi, et al. 2017). Data on other medial temporal lobe regions linked with the hippocampus, such as the entorhinal cortex and perirhinal cortex, are similarly limited, although some report smaller entorhinal cortex volumes in late-onset depression (Gerritsen, et al. 2011). There is even less work examining differences along the anterior-posterior axis of the hippocampus, despite regions along this axis exhibiting different functional roles (Strange, et al. 2014). Subfield differences may have scientific and prognostic value in understanding LLD's increased risk for cognitive decline and dementia (Diniz, et al. 2013;

Koenig, et al. 2014) as has been demonstrated for predicting and tracking early Alzheimer's-type cognitive decline and dementia (Teipel, et al. 2006).

Consideration is also needed for the influence of vascular disease on medial temporal structure. Vascular disease influences the course of LLD (Aizenstein, et al. 2016; Taylor, et al. 2013) and is similarly associated with cognitive decline as vascular disease may aggravate the effects of Alzheimer's disease pathology (Iadecola 2010; Jefferson, et al. 2015; Provenzano, et al. 2013). Greater severity of cerebral white matter hyperintensities, an MRI marker of vascular disease, is associated with atrophy of the entorhinal cortex but not necessarily the hippocampus itself (Gattringer, et al. 2012; Guzman, et al. 2013; Tosto, et al. 2015). However, smaller hippocampal volumes are associated with vascular risk factors including adiposity and proinflammatory markers (Hsu, et al. 2016; Schmidt, et al. 2016) and with genetic variants influencing inflammatory and vascular processes (Raz, et al. 2015; Zannas, et al. 2014). Mechanistically, vascular pathology may contribute to reduced regional cerebral blood flow (CBF) as observed in mild cognitive impairment and early Alzheimer's disease (Alsop, et al. 2010; Binnewijzend, et al. 2013). It is unclear whether CBF alterations observed in LLD (Abi Zeid Daou, et al. 2018) may be related to differences in hippocampal morphology. If so, this could inform new therapeutic approaches designed to optimize vascular function in order to improve mood or cognitive outcomes.

The purpose of this study was to test for differences in medial temporal lobe volumes in nondemented older adults with and without depression. Based on past work (Choi, et al. 2017), we hypothesized that we would associate LLD with smaller volumes of the CA and dentate gyrus. We also anticipated observing smaller volumes of connected regions, specifically the entorhinal and perirhinal cortices. As we have previously demonstrated that LLD is associated with greater longitudinal hippocampal atrophy (Taylor, et al. 2014), we hypothesized that age would exhibit a greater effect on medial temporal lobe volumes in the depressed cohort. Finally, as vascular disease both influences depression and contributes to cognitive impairment (Jefferson, et al. 2015; Taylor, et al. 2013), we hypothesized that clinical measures of vascular risk or MRI measures of vascular pathology would be associated with smaller medial temporal volumes.

METHODS

Sample

Participants were enrolled in one of three studies with comparable entry criteria and study procedures. Eligible subjects were age 60 years or older who met DSM-IV-TR criteria for Major Depressive Disorder, single episode or recurrent. The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) assessment was administered at the start of the study to determine psychiatric diagnoses and results confirmed by a clinical interview conducted by a geriatric psychiatrist. At study entry, eligible participants had a Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) score of 15 or more and a Mini-Mental State Exam (MMSE) (Folstein, et al. 1975) of 24 or more, or for one study a Montreal Cognitive Assessment (MoCA) score of 24 or more.

Exclusion criteria included (1) current or past diagnoses of other psychiatric disorders, including panic disorder and 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 years; (3) presence of acute suicidality assessed on clinical exam; (4) acute grief; (5) current or past psychosis; (6) primary neurologic disorders, including dementia or history of stroke or transient ischemic attacks; (7) chronic untreated medical disorders where treatment was warranted; (8) contraindications for magnetic resonance imaging (MRI); (9) receiving ECT in last 6 months; (10) use of antidepressant medications in the last two weeks; and (11) current psychotherapy.

Nondepressed participants met similar entry criteria, except they could not have any current or past psychiatric diagnoses. They also could not have a history of receiving any psychopharmacological treatment, psychotherapy, or brain stimulation treatment, except for brief couples or marital counseling.

Participants were recruited from community advertisements and clinical referrals to the Vanderbilt University Medical Center Psychiatry Outpatient Clinics. Recruitment also included ResearchMatch, a national health volunteer registry supported by the Clinical Translational Science Award program. The Vanderbilt Institutional Review Board approved the study and all participants provided written informed consent.

Clinical Assessment

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 with the MADRS, assessed medical comorbidity using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller, et al. 1992), and quantified vascular risk using the Framingham Study stroke risk prediction tool (Wolf, et al. 1991). Age of initial depressive episode was initially assessed through a structured interview then confirmed with the study psychiatrist. As these studies included a treatment component, individuals who met entry criteria but were currently taking antidepressant medications had those medications tapered and discontinued. Depressed participants were antidepressant-free for at least two weeks prior to MRI.

MRI Acquisition and Analyses

All participants were scanned on a research-dedicated 3.0T Philips Achieva whole-body scanner (Philips Medical Systems, Best, The Netherlands). MRI was obtained using body coil radiofrequency transmission and a 32-channel head coil for reception. Structural imaging for the entire brain utilized a whole-brain T1-weighted MPRAGE image with TR/TE = 8.8 ms / 4.6 ms, flip angle = 9, and spatial resolution = $0.9 \times 0.9 \times 1.2$ mm, along with a FLAIR image for hyperintensity assessment, using TR = 10,000 ms, TI = 2700 ms, TE = 125 ms. It also included a dedicated T2-weighted scan with partial coverage across an oblique coronal slice orientation positioned orthogonally to the main axis of the hippocampus, with TR/TE = 4785 ms / 90 ms and resolution of $0.5 \times 0.5 \times 2.0$ mm.

We utilized FreeSurfer (version 5.1) tissue segmentation and cortical parcellation of the T1 data to obtain total intracranial volume. FreeSurfer analyses were conducted in a high-

performance Linux cluster environment using standard previously published methods (Fischl, et al. 2004). All FreeSurfer parcellations were inspected and manual edits performed as needed.

Following published methods, the Automated Segmentation of Hippocampal Subfields (ASHS) software was used to measure medial temporal lobe subfield volumes (Yushkevich, et al. 2015) (Figure 1). ASHS registers each subject's dedicated T2-weighted image to the ASHS UPENN PMC atlas, a manually labeled atlas of 29 older adults with and without MCI. Candidate segmentations combine into a consensus segmentation using a voting scheme weighted by image intensity. Each voxel is then corrected by a classifier that recognizes systematic errors. This process was followed by a hippocampal multi-atlas segmentation based on the T1 image allowing further division of hippocampal subfields (but not other medial temporal areas) into anterior and posterior regions (Plassard, et al. 2017) as these regions exhibit different functional roles (Strange, et al. 2014). When compared to other techniques separating the hippocampus into head, body, and tail (Malykhin, et al. 2017), our anterior region is analogous to the head while our posterior region combines the body and tail.

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 coregistered 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. We also used the map to identify lobar WMH volumes with FreeSurfer, as it will parcellate the brain into lobar regions including white matter, based on the nearest corresponding cortical gray matter region.

A representative subset of 32 participants enrolled in one of the three studies (Abi Zeid Daou, et al. 2018) additionally completed a pseudocontinuous ASL (pCASL) sequence for CBF assessment. 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 = $3 \times 3 \times 7 \text{ mm}^3$). A separate equilibrium magnetization image was acquired with long TR=15,000ms and identical geometry but spin labeling preparation removed, who provided a measurement of M_0 . ASL images were co-registered to the T1 images using the fMRIB Image Registration Tool (Jenkinson, et al. 2002) using 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 final, corrected FreeSurfer parcellation using nearest-neighbor interpolation. This allowed us to measure CBF in the hippocampus as identified by FreeSurfer.

Statistical Analyses

SAS 9.4 (Cary, NC) was used for all data analyses. We tested for group differences in categorical variables using chi square tests and continuous variables using pooled, two-tailed

t- tests, or Satterthwaite t-tests when variances were unequal. ASHS provides the volume of numerous middle temporal lobe regions. To reduce the number of comparisons, initial analyses examined the mean volume across hemispheres of larger identified regions, including the total hippocampus, CA (CA regions 1–3), dentate gyrus (including CA4), subiculum, entorhinal cortex, and perirhinal cortex (including BA35 and BA36). Models identifying group differences in larger regions were further explored by testing for differences in subregions and across hemispheres. For hippocampal subfields, we then examined differences in anterior and posterior divisions (Plassard, et al. 2017). Although we applied this approach to reduce the number of comparisons made, we did not statistically control for multiple comparisons.

The initial approach used general linear models to test for group differences while adjusting for age, sex, medical morbidity measured by CIRS score, and intracranial volume. We subsequently dichotomized the depressed group into early-onset and late-onset subjects based on age of the first depressive episode, utilizing our published approach of a threshold age of 50 years (Taylor, et al. 2005). This three-tier group variable (early-onset, late-onset, and never depressed) was incorporated into models with covariates of age, sex, medical morbidity, and intracranial volume. Effect sizes for group differences were calculated using Cohen's *d*.

Next, we examined whether the effect of age on medial temporal lobe volumes differed by diagnostic group. We utilized Spearman's rank correlations to examine the association between age and regional volume for each diagnostic group. In subsequent models, we included covariates of diagnostic group, age, sex, medical morbidity, and intracranial volume. To test for a different effect of age, we added an interaction term between age and group.

Finally, we sought to determine whether vascular risk factors or cerebrovascular pathology was associated with regional volume differences. First, we replaced CIRS score in the models with a more specific measure of cerebrovascular risk, total Framingham risk score. Second, we added total white matter hyperintensity volume measures to models that included covariates of diagnostic group, age, sex, CIRS score, and intracranial volume. In the subset of participants with ASL data, we examined similar models that included a measure of mean hippocampal CBF, normalized to total cortical cerebral CBF.

RESULTS

The study included 80 older adults, 59 in a current episode of depression and 21 with no depression history (Table 1). There were no statistically significant group differences in demographic variables, medical morbidity scales, or MMSE scores. The depressed group had a mean age of initial depression onset of 36.3 years (*SD* = 19.2 years, range: 12–84 years).

Diagnostic group differences in medial temporal subfields

Initial models tested for diagnostic group differences while controlling for relevant covariates. There were no statistically significant group differences in volumes of the total

hippocampus, hippocampal subfields, or entorhinal cortex volume, but the depressed group exhibited a significantly smaller perirhinal cortex, specifically in its BA36 subregion (Table 2). In subsequent analyses, this difference was observed in the left (D: 1.802 (0.284); ND: 1.946 (0.340); Wald $\chi^2 = 6.60$, 74df, $p=0.0102$) but not right perirhinal cortex (D: 1.759 (0.246); ND: 1.793 (0.280); Wald $\chi^2 = 0.77$, 74df, $p=0.3812$). This difference was observed in the left BA36 subregion (D: 1.409 (0.242); ND: 1.551 (0.320); Wald $\chi^2 = 6.76$, 74df, $p=0.0093$) but not right BA36 (D: 1.361 (0.196); ND: 1.402 (0.247); Wald $\chi^2 = 0.69$, 74df, $p=0.4063$). Group differences were not observed in either hemisphere for the BA35 subregion.

We next dichotomized the depressed group based on age of onset. On examining a three-tier diagnostic group variable (early-onset depressed, $N=45$; late-onset depressed, $N=14$; and never-depressed, $N=21$), we did not observe statistically significant group differences in the mean volumes of the total hippocampus, hippocampal subfields, or entorhinal cortex (data not shown). In models controlling for covariates, we observed significant group differences in the left hemisphere perirhinal cortex and left BA36 volumes, but not left BA35 (Table 3). Compared with the nondepressed group, the early-onset group exhibited significantly smaller volumes of the left perirhinal cortex and BA36 regions, but not left BA35. In contrast, volumes in the early-onset group did not significantly differ from the late-onset group, despite a robust effect size for left BA35 volumes. Similarly, volumes of the late-onset group did not significantly differ from the nondepressed group despite medium effect sizes.

Differential effects of age on medial temporal subfield volumes between diagnostic groups

Given the findings described above, we subsequently examined hemispheric regions separately. To determine whether age had different effects on medial temporal morphology in the diagnostic groups, we developed models testing for an interaction between age and diagnosis. This interaction term was statistically significant for right hemisphere measures of the hippocampus, CA, entorhinal cortex, and perirhinal cortex/BA36 (Table 4). In these cases, increasing age had a greater negative correlation with medial temporal volumes in the depressed group than in the nondepressed group (Table 4, Figure 2). We subsequently developed separate models examining the anterior and posterior CA regions. In these models, we found a statistically significant interaction between age and diagnosis for the right posterior (Wald $\chi^2=7.09$, $p=0.0077$) but not right anterior CA (Wald $\chi^2=0.07$, $p=0.7972$).

Effects of clinical vascular risk factors on medial temporal subfield volumes

Next, we examined the relationship between temporal subfield volumes and vascular risk factors. Greater vascular risk burden measured by the Framingham Stroke Risk Scale was not related to hippocampal subfield volumes or entorhinal cortex volume but was associated with smaller perirhinal cortex volumes. This was observed in the right hemisphere (right perirhinal cortex: Wald $\chi^2 = 10.02$, 74df, $p=0.0015$; right BA36: Wald $\chi^2 = 12.72$, 74df, $p=0.0004$) but not the left (left perirhinal cortex: Wald $\chi^2 = 1.11$, 74df, $p=0.2921$; left BA36: Wald $\chi^2 = 2.00$, 74df, $p=0.1578$). Framingham score was not significantly associated with BA35 volume.

Effects of MRI measures of vascular pathology on medial temporal subfield volumes

We finally examined the relationship between temporal subfield volumes and cerebral WMH volume, a marker of vascular pathology. Greater temporal lobe WMH volume was associated with smaller volumes of the right perirhinal cortex (Wald $\chi^2 = 5.58$, 73df, $p=0.0182$), right BA36 (Wald $\chi^2 = 4.32$, 73df, $p=0.0377$) and right BA35 (Wald $\chi^2 = 4.38$, 73df, $p=0.0363$). However, temporal lobe WMH volume was not significantly associated with hippocampal subfield volumes, entorhinal cortex volume, or any left hemisphere perirhinal cortex measure. Total cerebral WMH volume was not significantly associated with any medial temporal region (data not shown).

We then examined the relationship between hippocampal CBF and medial temporal volumes in the subsample of 32 individuals (13 depressed, 19 never-depressed) with ASL data. Decreased hippocampal CBF was associated with reduced volumes of the total hippocampus (Wald $\chi^2 = 5.90$, 25df, $p=0.0152$) and more prominent in the left (Wald $\chi^2 = 8.13$, 25df, $p=0.0043$) than the right hippocampus (Wald $\chi^2 = 2.87$, 25df, $p=0.0901$). In subfield analyses, hippocampal CBF was positively associated with CA volume (Wald $\chi^2 = 6.96$, 25df, $p = 0.0083$) but not other subfield regions. Hippocampal CBF was not significantly associated with entorhinal cortex or perirhinal cortex volumes.

DISCUSSION

This study has several key findings. First, compared with nondepressed older adults, depressed elders exhibited smaller left hemispheric perirhinal cortex volumes, specifically in the BA36 region. Individuals with early life depression onset exhibited smaller left perirhinal cortex and left BA36 volumes than those without depression. There were no group differences in hippocampal subfield or entorhinal volumes. Second, depressed elders exhibit a more negative association between age and medial temporal volumes, specifically for the CA, entorhinal cortex, and perirhinal cortex in the right hemisphere. Within the CA, this effect was strongest in the posterior right CA. Third, vascular pathology is also related to right hemisphere measures of the perirhinal cortex. In contrast, CBF measured in a subsample was positively associated with left hippocampus and left CA volume but not entorhinal cortex volume or perirhinal cortex volume.

Although smaller hippocampal volumes are reported in LLD in 7 of 15 prior studies (Sexton, et al. 2013) our study did not find that LLD is characterized by smaller cross-sectional hippocampal volumes. Similarly, while others associate LLD with smaller volumes of the CA, dentate gyrus, subiculum, and entorhinal cortex (Choi, et al. 2017; Gerritsen, et al. 2011; Su, et al. 2016), contrary to our hypotheses we did not observe similar findings. The lack of observable subfields differences is comparable to recent work in midlife adult depression (Cao, et al. 2017). Differences across studies are likely also related to variation in spatial resolution, image quality or study methodology, as many past reports used manual or other automated measurement techniques to segment the medial temporal lobe. The study by Choi and colleagues (Choi, et al. 2017) was most comparable to the current study as they used the same hippocampal subfields segmentation technique. This discrepancy between our results and the Choi, et al. study may be explained as their sample focused on late onset

depression while our sample included a large proportion of individuals with early-onset depression.

Differences in conclusions across cross-sectional studies may be related to our observation that the correlations between age and medial temporal volumes are more negative in depressed elders, specifically in the right hemisphere (Table 4, Figure 2). Our findings related to age are concordant with past longitudinal reports demonstrating that the hippocampus exhibits greater atrophy in older depressed populations (Geerlings, et al. 2013; O'Brien, et al. 2004; Taylor, et al. 2014). Thus the likelihood of observing cross-sectional differences may depend on the relative age of the sample. Our sample included primarily younger depressed elders with a mean age of 65 years, so cross-sectional results may have been different had the mean age been higher. Of note, despite there being no difference in hippocampal atrophy across hemispheres in normal aging (Fraser, et al. 2015), we observed group differences in the effect of age only in the right hemisphere. Despite not observing a significant difference between groups in the correlations between age and left hemispheric temporal volumes (Table 4), it is possible that the hemispheric difference in the age-diagnosis interaction may have disappeared with a larger sample. However, our localization of this difference to the posterior CA region is concordant with reports that age has the greatest effect on the CA within the body of the hippocampus (Malykhin, et al. 2017).

Our findings implicating the perirhinal cortex are particularly important as LDD is associated with cognitive deficits, greater cognitive decline, and increased risk for dementia. The perirhinal cortex is the first region affected by neurofibrillary tangle pathology in early AD (Braak and Braak 1991) and BA36 volumes exhibit atrophy in early prodromal AD (Wolk, et al. 2017). We may be observing a similar process in our sample. Additionally, the early onset depression group exhibited smaller left perirhinal cortex and left BA36 volumes than the non-depressed group. This is concordant with observations that individuals with early depression onset exhibit a more rapid cognitive decline than nondepressed elders (Riddle, et al. 2017). This may be related to neurotoxic effects of multiple depressive episodes on medial temporal structure, resulting in deteriorating cognitive performance (Sheline, et al. 1996). Alternatively, the group difference observed in the left BA36 region may represent a pre-existing difference that contributes to depression vulnerability and is not related to neurodegenerative processes or neurotoxic effects. This alternative hypothesis is viable as we did not observe a statistically significant group difference in the effects of age on BA36 volumes.

We did not observe statistically significant differences between the late-onset depressed group and other diagnostic groups, but this should not be taken as strong evidence that medial temporal pathology does not exist in that late-onset population. Given the small portion of the sample that exhibited late-onset depression, we were likely underpowered to detect group differences. This theory is supported by the moderate effect sizes we observed in perirhinal cortex volumes between the late-onset depressed group and the nondepressed group (Table 3).

We observed a range of associations between measures of vascular risk and middle temporal lobe morphology. Vascular risk measured by the Framingham stroke risk tool was associated

with perirhinal cortex and BA36 volume. Similarly, concordant with reports in MCI and Alzheimer's disease (Guzman, et al. 2013; Tosto, et al. 2015), we observed a relationship between temporal lobe WMH volume and regional middle temporal lobe volumes. However, we observed an effect of vascular measures on the perirhinal cortex, while studies of MCI and Alzheimer's disease found a relationship between WMH volumes and entorhinal cortex volumes. Testing a direct relationship with vascular pathology, we observed associations between lower regional CBF and smaller volumes of the hippocampus and CA volume, but these data should be viewed as preliminary given the relatively smaller sample. Further work is needed to determine the specificity of vascular effects across diagnoses and determine whether these different relationships between WMHs and medial temporal lobe subfields are related to different clinical presentations in these groups.

The observed hemispheric differences are difficult to interpret, particularly in a cross-sectional study where longitudinal effects of aging cannot be assessed. Such differences may be related to study limitations and are complicated by the number of statistical comparisons. Importantly, the imaging methodology used produces a large amount of data. Although we did limit the number of statistical comparisons made, we did not adjust for multiple comparisons. Thus, both positive and negative findings should be viewed cautiously and require replication. Further limitations to consider include that the mean subject age is in our study is relatively early in late life, so our findings may not generalize to an older late-life population. Additionally, our sample size limited power to detect differences related to age of initial depression onset and this may have influenced results for the late-onset depressed group. Finally, the larger voxel size needed for measuring CBF may have resulted in our hippocampal CBF measure extending slightly past the boundaries of the hippocampus.

In conclusion, this report demonstrates that the perirhinal cortex exhibits differences in LLD. Moreover, vascular risk is associated with smaller perirhinal cortex volumes, while a wider range of medial temporal subfields may exhibit a greater sensitivity to aging. Future work should replicate these findings and prospectively examine change in medial temporal volumes in context of antidepressant treatment, while also examining whether these perirhinal cortex and BA36 volumes have prognostic value in predicting future cognitive decline and risk for dementia.

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Figure 1. Segmentation of medial temporal subfields

Segmentation of hippocampal and medial temporal subfields conducted using ASHS (Automated Segmentation of Hippocampal Subfields; Yushkevich, et al. 2015). BA35 – orange; BA36 – turquoise; CA1 – red; CA2 – green; CA3 – yellow; dentate gyrus – dark blue; entorhinal cortex – purple; subiculum – pink. Collateral sulcus indicated in light blue, but not included in analyses.

Figure 2. Effects of age by group on medial temporal volumes

Figures display the relationship between age (x-axis) and regional volume in milliliters (y-axis) for each diagnostic group. Depressed subjects are displayed using solid circles / solid line, while nondepressed subjects are displayed by open circles / dashed line. Left (L) and right (R) refer to each hemisphere.

Table 1.

Group demographic differences

	Depressed (N=59)	Nondepressed (N=21)	Test value	p value
Age	65.7 (5.9)	68.2 (5.7)	t = 1.65	0.1035
Sex (% female)	66.7% (38)	57.1% (12)	$\chi^2 = 0.60$	0.4367
Education	16.7 (2.4)	16.3 (1.6)	t = 0.76	0.4512
MMSE	(N=43) 28.8 (1.4)	(N=21) 29.1 (1.2)	t = 0.84	0.4054
MoCA	(N=14) 27.9 (1.5)	-	-	-
MADRS	27.3 (4.5)	0.4 (0.7)	t = 43.67	< 0.0001
CIRS	5.1 (2.9)	4.4 (2.3)	t = 0.94	0.3511
Framingham Risk Score	9.0 (4.0)	9.4 (3.7)	t = 0.47	0.6392
WMH volume (mL)	5.0 (8.2)	3.8 (5.1)	t = 0.72	0.4747
Intracranial Volume (mL)	1488.2 (144.1)	1508.1 (108.2)	t = 0.58	0.5658

Continuous measures presented as mean (standard deviation) and analyzed using pooled, two- tailed t-tests with 78 df. The exceptions to this utilized the Satterthwaite's t-test due to unequal variance, specifically for MADRS score comparisons with 62.4 df and WMH volume comparisons with 57.1 df. Categorical comparisons presented as % (N) and analyzed using the chi-square test with 1 df. Age and education presented in years, sex by percent representation of women, and WMH volume and intracranial volume presented in milliliters. MMSE = mini- mental state exam; MADRS = Montgomery-Asberg depression rating scale; MoCA = Montreal Cognitive Assessment; CIRS = cumulative illness rating scale; WMH = white matter hyperintensity.

Table 2.

Diagnostic group differences in medial temporal lobe volumes

	Depressed (N=59)	Nondepressed (N=21)	Effect Size	Wald χ^2	p value
Total Hippocampus	2.519 (0.312)	2.545 (0.238)	0.04	2.12	0.1457
• Left	2.488 (0.314)	2.494 (0.261)	0.02	0.93	0.3354
• Right	2.549 (0.318)	2.597 (0.238)	0.16	3.51	0.0611
Cornu Ammonis (CA1–3)	1.387 (0.173)	1.404 (0.130)	0.05	1.84	0.1751
Dentate Gyrus (with CA4)	0.762 (0.105)	0.778 (0.089)	0.08	3.18	0.0744
Subiculum	0.368 (0.054)	0.364 (0.050)	0.03	0.01	0.9380
Entorhinal Cortex	0.486 (0.066)	0.463 (0.050)	0.18	2.27	0.1320
Perirhinal Cortex	1.780 (0.242)	1.870 (0.284)	0.17	3.97	0.0454
• BA35	0.395 (0.069)	0.393 (0.054)	0.02	0.80	0.3721
• BA36	1.385 (0.196)	1.477 (0.256)	0.21	4.20	0.0404

Medial temporal lobe volumes examined were the mean volume across hemispheres, presented in milliliters. Effect size determined using Cohen's d. Models with 72 df tested for group differences while controlling for age, sex, medical morbidity (Cumulative Illness Rating Scale score) and total intracranial volume.

Table 3.

Differences in left hemisphere perirhinal cortex volumes by age of depression onset

Region	Volumes			Statistical Group Comparisons		
	EOD (N=45)	LOD (N=14)	ND (N=21)	EOD – LOD	EOD – ND	LOD – ND
Left	1.82	1.76	1.95	ES = 0.19	ES = 0.42	ES = 0.61
Perirhinal	(0.30)	(0.25)	(0.34)	Wald $\chi^2 = 0.02$	Wald $\chi^2 = 6.13$	Wald $\chi^2 = 3.41$
Cortex				p = 0.9005	p = 0.0133	p = 0.0647
Left BA35	0.40	0.36	0.40	ES = 0.53	ES = 0	ES = 0.53
	(0.07)	(0.08)	(0.08)	Wald $\chi^2 = 2.46$	Wald $\chi^2 = 0.12$	Wald $\chi^2 = 2.91$
				p = 0.1169	p = 0.7323	p = 0.0883
Left BA36	1.41	1.39	1.55	ES = 0.07	ES = 0.50	ES = 0.57
	(0.26)	(0.20)	(0.32)	Wald $\chi^2 = 0.34$	Wald $\chi^2 = 7.05$	Wald $\chi^2 = 2.48$
				p = 0.5618	p = 0.0079	p = 0.1157

Groups abbreviated as EOD (early onset depression), LOD (late-onset depression), and ND (nondepressed). Volumes displayed as adjusted group mean (standard deviation) measured in milliliters. Statistical comparisons presented were post-hoc group comparisons, presenting effect sizes (ES) calculated using Cohen's d and testing for group differences using general linear models with 73 degrees of freedom, controlling for age, sex, medical morbidity, and intracranial volume.

Table 4.

Interactive effects of age and diagnosis on medial temporal lobe morphology

	Left Hemisphere Regions			Right Hemisphere Regions		
	Correlation with Age		Interaction	Correlation with Age		Interaction
	Depressed	ND		Depressed	ND	
Hippocampus	$r_s = -0.35$ $p = 0.0060$	$r_s = -0.19$ $p = 0.4030$	Wald $\chi^2 = 2.05$ $p = 0.1522$	$r_s = -0.39$ $p = 0.0021$	$r_s = -0.25$ $p = 0.2744$	Wald $\chi^2 = 4.21$ $p = 0.0401$
Cornu Ammonis (CA1–3)	$r_s = -0.34$ $p = 0.0090$	$r_s = -0.28$ $p = 0.2178$	Wald $\chi^2 = 1.47$ $p = 0.2247$	$r_s = -0.41$ $p = 0.0011$	$r_s = -0.14$ $p = 0.5402$	Wald $\chi^2 = 5.05$ $p = 0.0246$
Dentate Gyrus (with CA4)	$r_s = -0.27$ $p = 0.0416$	$r_s = -0.04$ $p = 0.8484$	Wald $\chi^2 = 2.00$ $p = 0.1572$	$r_s = -0.31$ $p = 0.0159$	$r_s = -0.17$ $p = 0.4680$	Wald $\chi^2 = 2.78$ $p = 0.0955$
Subiculum	$r_s = -0.35$ $p = 0.0070$	$r_s = -0.25$ $p = 0.2697$	Wald $\chi^2 = 0.88$ $p = 0.3492$	$r_s = -0.30$ $p = 0.0230$	$r_s = -0.33$ $p = 0.1496$	Wald $\chi^2 = 0.34$ $p = 0.5627$
Entorhinal Cortex	$r_s = -0.29$ $p = 0.0278$	$r_s = -0.12$ $p = 0.5922$	Wald $\chi^2 = 1.04$ $p = 0.3070$	$r_s = -0.21$ $p = 0.1036$	$r_s = 0.32$ $p = 0.1642$	Wald $\chi^2 = 5.97$ $p = 0.0145$
Perirhinal Cortex	$r_s = -0.28$ $p = 0.0303$	$r_s = -0.14$ $p = 0.5516$	Wald $\chi^2 = 0.28$ $p = 0.5938$	$r_s = -0.37$ $p = 0.0043$	$r_s = 0.05$ $p = 0.8331$	Wald $\chi^2 = 4.65$ $p = 0.0310$
• BA35	$r_s = -0.23$ $p = 0.0858$	$r_s = 0.07$ $p = 0.7592$	Wald $\chi^2 = 3.66$ $p = 0.0557$	$r_s = -0.40$ $p = 0.0015$	$r_s = -0.29$ $p = 0.2088$	Wald $\chi^2 = 1.90$ $p = 0.1677$
• BA36	$r_s = -0.27$ $p = 0.0377$	$r_s = -0.19$ $p = 0.4112$	Wald $\chi^2 = 0.00$ $p = 0.9477$	$r_s = -0.27$ $p = 0.0351$	$r_s = 0.12$ $p = 0.6180$	Wald $\chi^2 = 4.32$ $p = 0.0377$

Table displays group differences in the correlation between age and regional medial temporal volume. Correlations between age and volume are presented for each diagnostic group (depressed or nondepressed, ND) using the Spearman's rank correlation coefficient (r_s). Results from the statistical interaction between diagnostic group and age are presented from models examining regional volumes as the dependent variable and the age-diagnosis interaction term as an independent variable. Additional independent variables in those models included primary effects for age and diagnostic group, along with sex, medical morbidity by CIRS score, and total intracranial volume.