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Retrieval: An Fmri Analysis of Middle Aged and Older Adults

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Dementia Risk Elevates Brain Activity During Memory Retrieval: An fMRI Analysis of Middle  
Aged and Older Adults

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**Abstract**

Longitudinal research suggests that genetic, lifestyle, and environmental factors enhance one's risk for developing Alzheimer's disease and related dementias (ADRD). However, it is not known how an accumulation of such factors impact brain functioning. One barrier to this research is that increased risk for ADRD affects the cerebrovascular system and, therefore, alters the link between neural activity and the fMRI BOLD signal. To better interpret fMRI findings, several steps were taken to adjust fMRI activity thereby reducing such cerebrovascular effects. We hypothesized that as the number of ADRD risk factors increase, brain regions within the medial temporal lobes and the default mode network would exhibit altered brain activity during an episodic memory retrieval task. Middle-aged and older adults (aged 50-74) free of dementia were recruited with varying levels of risk and underwent a neuropsychological battery and fMRI. In the memory task, participants viewed a pair of pictures. In an alternative-forced-choice test, participants viewed a picture cue and had to determine which of four pictures was paired with the cue. Increased dementia risk was positively associated with brain activity in regions of interest within the default mode network, the hippocampus, and the entorhinal cortex during memory retrieval. Whole-brain analyses revealed additional positive associations in prefrontal and occipito-temporal cortices. Risk factors most contributing to these elevated levels of brain activity included hypertension, diabetes, obesity, and cholesterol. We also ruled out confounds due to in-scanner performance and premorbid ability. Cumulative risk might represent early signs of burnout in brain regions underlying episodic memory.

**Keywords:** Alzheimer's disease; default mode network; dementia; episodic memory; functional magnetic resonance imaging; medial temporal lobe; minority health; risk factors

### *Introduction*

Alzheimer's disease and related dementias (ADRD) are characterized by a long trajectory of cognitive decline, leading to the 6<sup>th</sup> most frequent cause of death for those age 65 and older in the United States [1]. ADRD not only impact the person affected with the disease, but also place a large toll on the caregivers and/or family of the person. Because of the large burden that ADRD place on society, significant effort has been put into understanding the origins of these diseases. Specifically, neuroimaging has been touted as an effective way to detect early pathology *in vivo*, such as the accumulation of beta-amyloid or tau and to reveal early alterations in how the brain functions decades before symptoms ever manifest [2,3]. By understanding the neural origins of ADRD, lifestyle interventions that strengthen vulnerable brain regions can be implemented to potentially delay the progress of the diseases [4]. In addition, such brain targets can be used for pharmaceutical treatments once they become available [5].

Much of the histopathological and neuroimaging research has focused specifically on Alzheimer's disease (AD) as opposed to other types of dementias (e.g., frontotemporal, semantic, vascular) likely because AD is the most common form of the disease. Studies on AD have discovered a clear topographical profile as to what brain regions initially develop beta-amyloid and tau pathology. Specifically, beta-amyloid begins to accumulate in the neocortex [6], especially in midline prefrontal and parietal regions—many of which overlap with the default mode network (DMN). In contrast, tau tangles begin to accumulate in the medial temporal lobes starting in the entorhinal cortex [6]. These regional distributions also overlap with brain regions exhibiting hypometabolism [7,8] and brain shrinkage [9,10] in AD. This topological convergence might be due to the high level of energy consumption of these regions that has been proposed to

lead to an overworked neural system in some individuals and, in turn, an enhanced vulnerability to AD [4,11,12].

Whether these same brain regions are systematically related to alterations in brain function in ADRD is less clear. Mormino et al. [13] found that higher levels of beta-amyloid were associated with greater brain activity within the hippocampus during successful memory encoding, but other studies have not found similar results [14-17]. Nevertheless, changes in brain function might serve as one of the earliest biomarkers of ADRD [18]. A recent study revealed that pathology-related alterations in hippocampal functioning may be more easily detectable in the young-old (e.g., ages 60-75) than in the old-old (e.g., older than 76) [19]. This evidence suggests that investigating adults earlier in the adult lifespan bordering on what is classically defined as old age could shed additional insight into the processes giving rise to ADRD.

Epidemiological studies already have begun investigating genetic, dispositional, and lifestyle factors starting in midlife that predict conversion to late-life ADRD. Other than age, two of the most well-known risks for AD are the presence of a first-degree relative, which doubles the risk of dementia [20,21], and the presence of the apolipoprotein  $\epsilon 4$  allele, which can increase the risk of dementia by up to 12 times [22]. Other factors, with considerably lower public awareness, also have been identified [23]. Deckers et al. [24] conducted a systematic review on modifiable risk factors and found 11 that were well-documented and were consistent with knowledge from medical professionals. Some of these factors overlapped with previous research on middle-age adults such as hypertension, high cholesterol, obesity, and education (via level of cognitive activity) [25]. Other factors identified included diabetes, smoking, coronary heart disease, depression, low consumption of a Mediterranean diet, and high alcohol intake. Likely related to some of these factors, investigations into both prevalence and incidence rates provide

strong evidence that ethnic minorities also are at higher risk for developing ADRD [26-28]. Deckers et al. [24] note that many of these factors are interrelated and likely form clusters of ADRD risk (e.g., metabolic syndrome). Because of this inter-relatedness, some studies have used dementia risk scores to assess levels of clustered risk when investigating cognitive or diagnosis outcomes [29-32].

Neuroimaging studies investigating risk factors for dementia have mostly focused on genetic risk or cognitively normal adults harboring elevated levels of pathology. A recent review on family history and genetic risk factors of AD suggests that alterations in brain activity can be found most consistently in medial temporal lobe and parietal regions, although the direction (i.e., positive or negative association with increased risk) were highly variable [33]. Interestingly, most of these studies focused on brain activity during episodic memory encoding, thus emphasizing a need for more studies focusing on memory retrieval processes. We reasoned that because memory retrieval is the product of both encoding-specific and retrieval-specific processes, investigating brain activity at retrieval might evidence the most pronounced alterations with increased risk. Of the handful of studies that have investigated retrieval, most have investigated differences between carriers and non-carriers of the apolipoprotein  $\epsilon 4$  allele. Greater activity in the medial temporal lobes, the prefrontal cortex, and the parietal cortex have been found in older adults with the  $\epsilon 4$  allele than those without the  $\epsilon 4$  allele [34-36]. Braskie et al. [37] also found increased activity in the medial temporal lobe, prefrontal cortex, and the parietal cortex in older adults with elevated vascular risk (high systolic blood pressure and a high body mass index). Other studies, not related to memory retrieval, have found evidence that having diabetes is associated with less deactivation of the DMN [38-40] and less activation in the frontal cortex [39,40].

We argue that previous studies investigating adults with risks for AD RD cannot be taken at face value. Under most circumstances, increases in the blood oxygen level dependent (BOLD) signal can be roughly interpreted as increases in populations of neural activity that is most closely aligned with local field potentials [41,42]. However, both older age and risk factors that alter the cerebrovascular system also alter the coupling between the BOLD signal and neural activity [43,44]. For example, Mohtasib et al. [45] found that age-related increases in the BOLD signal in the frontal cortex was due to a reduction in cerebral metabolic rate of oxygen consumption rather than an increase in neural activity. Instead, they concluded that aging was associated with a *reduction* in neural activity despite the apparent increases in the BOLD signal. Therefore, without taking into account cerebrovascular-related alterations in the BOLD signal, previous studies that have found an association between risks for AD RD and brain activity suffer challenges in interpretation of the BOLD signal, possibly leading to an overestimation of such associations [46,47].

In the present study, we moved beyond investigating single risk factors investigated in previous studies and propose that the accumulation of multiple risk factors provides a new window into early brain function alterations that put the brain at risk for developing pathology found in AD RD [4,48]. Towards this aim we calculated a dementia risk score and tested how increases in this measure were associated with brain function during episodic memory retrieval. Specifically, we used a paired associates memory task that relied on the retrieval of specific details, or recollections, that have been previously shown to engage regions in the medial temporal lobe, frontal cortex, and parietal cortex [49]. Critically, we also took steps to calibrate the BOLD signal to minimize cerebrovascular reactivity changes. First, we estimated the shape and timing of the BOLD response (i.e., the hemodynamic response function; HRF) using an

independent task for each individual [50-52]. Then, we calibrated the memory-related fMRI results using resting state fluctuation amplitude (RSFA) analyses [53-55]. This analysis measures the standard deviation of the BOLD signal and has been shown to reduce age-related vascular effects on the BOLD signal while leaving the majority of neuronal-related activity intact [47,56]. We predicted that higher dementia risk would be associated with alterations in brain function within the medial temporal lobes (e.g., the hippocampus and entorhinal cortex) and the DMN due to the known associations with the episodic memory retrieval [49] and decline in AD [9,11,12,18]. However, it is unclear whether the direction of the effects would be in the form of increased or decreased brain activity because nearly all previous studies investigating various risks for ADRD (including older adults with elevated beta-amyloid or tau as measured by PET or CSF) failed to calibrate the BOLD signal (for an exception, see [19]). Lastly, we reduced the likelihood of other confounding explanations by controlling for inter-individual differences in the in-scanner memory performance and premorbid intellectual ability. To the extent that the brain regions implicated with dementia risk overlapped with those associated with cognition, one might consider this a confound due to different levels of retrieval success or effort.

### *Materials and Methods*

#### *Participants*

Data were collected as a part of the Alabama Brain Study on Risk for Dementia to investigate the influence of cumulative risk factors on brain structure and brain function in adults free of dementia. In contrast to most samples used in cognitive aging research that consist of very healthy adults, participants in this study were enriched with varying levels of risk factors for dementia accrued throughout their lifetime [24,25,48,57,58]. Inclusion criteria included being right-handed, having a St. Louis University Mental Status (SLUMS) score above 19 (after

adjusting for education) [59], the ability to understand and comprehend English, and at least one of the following self-reported risks for dementia that were assessed by the initial phone screener: subjective memory complaints, less than a high school education, African American or Hispanic ethnographic category, mild head trauma, family history of Alzheimer's disease, current diagnosis of hypertension or systolic blood pressure greater than 140 mmHg, current diagnosis or a family history of heart disease, current diagnosis of high total cholesterol, history or current use of smoking tobacco, current diagnosis or family history of diabetes, and body mass index greater than 30 kg/m<sup>2</sup>. Exclusion criteria included being pregnant, having a prior diagnosis of dementia or another neurological condition, a medical history of stroke or traumatic brain injury, claustrophobia, history of substance abuse, or having metallic implants that are incompatible with MRI. All participants gave informed consent using methods approved by the institutional review board at The University of Alabama. Vision was normal or corrected to normal using MR-compatible glasses or contact lenses. All participants were monetarily reimbursed for their time and participation in this study.

This study included 67 participants aged 50-74 years. Of these, 3 participants stopped scanning early due to: claustrophobia (2) and feeling sick (1). The HRF could not be calculated for 1 participant and an additional 3 participants were removed due to movement (see *fMRI Acquisition and Preprocessing* section for details), resulting in a total sample of 60 participants. All participants were recruited from the Tuscaloosa and Birmingham areas within Alabama through word of mouth, flyers, Facebook ads, and newsletters. Demographic characteristics of the final sample can be found in Table 1. Participants had an education ranging from 6 to 18 years and had a moderate to high level of cognitive functioning as measured by the SLUMS;  $M = 26.49$ , Range = 21 to 30).

## ***Procedures***

### ***Overall Study***

The study was distributed across two to three in-person sessions. The first session consisted of a cognitive battery and an assessment of health metrics. Following the cognitive session, participants were provided with an online survey to fill out several questionnaires. If needed, we offered a computer for participants to take the survey in a separate session. The last session consisted of the MRI scan that included a structural scan and several functional scans: two resting-state, a paired-associates memory encoding task, a memory recognition task, and a visual-motor checkerboard task. The analyses here focus on the memory recognition task.

### ***Cognitive Assessment***

#### *Saint Louis University Mental Status Exam (SLUMS)*

The SLUMS was used to screen out severe cognitive deficits (e.g., possible dementia) [59]. The assessment consisted of 11 questions that measured a variety of cognitive domains including an individual's orientation, memory, attention, and executive functioning. The maximum number of points possible was 30. Cut off scores for dementia depended on the participants education level such that participants were categorized as having possible dementia if they scored below 21 with a high school education or below 20 without a high school education. The SLUMS can distinguish between dementia and mild cognitive problems with a sensitivity of .96-1.00 and a specificity of .98-1.00 and outperforms other common global measures of cognition such as the Mini-Mental Status Exam [60]. Participants who scored in the dementia range based on their education level were discontinued from the research study and where provided information on nearby memory clinics if concerned.

*Wide Range Achievement Test - 4 (WRAT-4)*

The WRAT-4 Word Reading subtest was administered to measure participants' reading skills via pronunciation ability of increasingly more difficult words. Pronunciation ability is commonly used to assess one's cognitive ability level prior to potential aging or pathologically related declines in ability [61]. Each score was scaled using age norms. Additional cognitive assessments were administered to participants following the WRAT-4 but were not used for this study.

*fMRI Scans**Checkerboard Task*

The purpose of this task was to obtain a measure of each participant's HRF in the occipital cortex that was time-locked to the onset of the visual stimulation. A reversing checkerboard (changing 8 times over 1 second) was presented for 1s in each of 20 repetitions. When the checkerboard was presented, the participant was instructed to view the image and tap a button on the MR-compatible box that was provided to them. Inter-trial intervals varied between 8s and 16s with an average of 12s, during which the participant viewed a fixation cross. A total of 73 volumes were collected over a 2min span.

*Paired Associates Memory Task*

In the scanner, participants were asked to view a picture of an emotionally neutral face above a picture of either an object or scene for 3s either on the left or right side of the screen. To assist their memory, participants were told to imagine the person interacting with the object or within the scene. After viewing the pair of pictures, participants were asked how likely they think they would remember the face-object or face-scene pair and rate their prediction on a three-point scale: likely to remember, possibly will remember, or unlikely to remember. Trials were

separated by a fixation cross of jittered duration (1.72–17.20 s). Stimuli were divided into two runs with each run consisting of 32 pairs of pictures and lasting for 8 min, totaling 558 volumes.

An 11 min delay occurred between the end of the last encoding run and the beginning of the first retrieval run. During the alternative-forced-choice retrieval test, participants were presented with a previously seen face and asked to choose the correct object or scene pairing from five options. The options included pictures of two objects, two scenes, and a “never seen” option that could be chosen if participants believed they never saw the face. All four of the picture options were previously seen during the encoding phase. However, two of the pictures were always in the object category and two were always in the scene category, but only one was previously paired with the face during the encoding session. Each of the picture options were seen multiple times such that a given picture might be a lure on one memory trial, but a correct answer on a different memory trial. Because the lures were familiar to participants, to answer correctly, recollection of the face-item association must be used. Thus, accuracy on this task is best understood as a recollection memory score. Note that despite being provided with a “never seen” option, all faces were previously seen in the scanner. The location of the pair (left or right side of the screen) also was provided to participants for half of the trials to help cue their memory. The test was divided into two runs with each run consisting of 32 memory trials and lasting for 5 min.

The face stimuli were taken from the Chicago Face Database Version 2.0.3 [62]. This database contains high-quality photos of male and female faces from different ethnoracial categories ranging in age from 18 to 50 years old. From this database half of the faces chosen to be included were of men and half were of women. Within each sex, half were African Americans and half were non-Hispanic White. The ethnoracial categories were chosen to represent the local

demographics. Pictures of the objects and scenes were taken from <http://cvcl.mit.edu/MM/stimuli.html> and have been used in several studies to assess memory [63-65].

The order of items and fixations was maximized for event-related fMRI using optseq2 program (<https://surfer.nmr.mgh.harvard.edu/fswiki/optseq2>). One order was created for each memory task run, totaling 4 runs (2 encoding and 2 retrieval). These four orders were rotated across retrieval cue type (left, right, no cue) across participants.

### *Resting State Scans*

Two resting state scans were collected that each consisted of 175 volumes over a 5min span. Participants were told to close their eyes but not fall asleep.

### *Data Analyses*

#### *Dementia Risk Score Calculation*

We used a dementia risk score to assess the cumulative risk that participants have accrued throughout their lifetime [24,25,48,57,58]. This score was calculated by summing the following self-reported risk factors: memory problems, a family history of Alzheimer's disease, less than a high school level of education, hypertension, current or family history of heart disease, current or family history of diabetes, obesity, high total cholesterol, mild head trauma, of African American or Hispanic background, current or history of tobacco use. These risk factors were chosen because of their consistent association with progression to dementia in either middle or old age and were easily approximated via self-report. Although we had a relatively small age range, we conducted a second dementia risk score in which adults 65 and older were given an extra risk point, given that aging is the largest risk factor for ADRD.

#### *fMRI Acquisition and Preprocessing*

MRI data were collected using a 3T Siemens PRISMA scanner at the UAB Civitan International Neuroimaging Laboratory. Structural scans were acquired using high resolution T1-weighted structural MPRAGE (parallel acquisition acceleration type= GRAPPA; acceleration factor= 3, TR = 5000 ms, TE = 2.93 ms, TI 1 = 700 ms, TI 2 = 2030 ms, flip angle 1 = 4 degrees, flip angle 2 = 5 degrees FOV = 256 mm, matrix = 240 x 256 mm<sup>2</sup>, in-plane resolution = 1.0 x 1.0 mm<sup>2</sup>). For all functional scans, T2\*-weighted images were used to estimate neural activity via the BOLD signal (56 interleaved axial slices, 2.5 mm thickness) using an EPI sequence (TR = 1720 ms, TE = 35.8 ms, flip angle = 73 degrees, FOV = 260 mm, matrix = 104 x 104 mm, in-plane resolution = 2.5 x 2.5 mm<sup>2</sup>, multi-band acceleration factor=4). Data were preprocessed using Statistical Parametric Mapping 12 (SPM12). Preprocessing steps included calculating and correcting for head movement, coregistering the structural images to the functional images, segmenting the structure into gray matter, white matter, and cerebral spinal fluid, normalizing to the MNI template (2 mm cubic voxels), and spatial smoothing (8 mm FWHM kernel). Artifact Detection Tools (ART) was used to detect outliers due to movement or signal intensity spikes [66].

Following preprocessing, the memory retrieval runs were further processed to remove artifacts. Specifically, the BOLD signal from these runs was decomposed into its spatiotemporal components using MELODIC [67]. Components were flagged if they were believed to be potential artifacts (e.g., signal around the edge of the brain, centered in ventricles, characterized by temporal spikes). The identified components were then regressed from the BOLD signal also using MELODIC. Thus, task-data motion (and other sources of artifact) was taken into account in two ways. First, time points of movement outliers (from ART) were dummy coded in the first level analysis and MELODIC was used to regress out artifact. Indeed, the number of framewise-

displacement scans that were greater than .20 mm were reduced from a mean of 70.52 per person to 0.03 per person after implementing MELODIC. The maximum range of translational movement across all runs and participants was 0.06 mm and the maximum average root mean squared realignment average was 0.04 mm, both of which were well below recommended thresholds for movement [68,69]. Despite the lack of objective residual movement, when the final data sets were visually inspected, some runs continued to exhibit residual artifact (e.g., banding across the brain), thus leading to 11 runs across 8 participants being removed from further analyses.

The two resting-state scans were further processed in preparation for the RSFA analyses [53]. `Afni_proc.py` [70] was used to despike the time series, remove the first 3 TRs, bandpass filter the time series between .01 and .08 Hz, demean the time series, and to regress out motion parameters, their derivatives, and white matter signal from the time series. RSFA analyses calculate the standard deviation of the BOLD signal. These analyses were implemented separately for each run and averaged together.

### *Statistical Analyses*

To estimate each participants' HRF, a finite impulse response function was used to model task-evoked brain activity in response to the flashing checkerboard. In this general linear model (GLM), 12 basis functions were modeled across a 21s window and outliers were entered as nuisance regressors. At the first level, an  $F$ -test was calculated across the 12 time points at a liberal threshold of  $p = .05$  using an inclusive mask of the occipital cortex. At the peak voxel within this mask, parameter estimates were extracted, which were used to represent each participant's new HRF.

For the memory retrieval task, we first conducted first level analyses under the assumptions of the GLM using a stick function (setting duration to 0s) and the canonical HRF. Two trial types of interest were included as regressors in this analysis: trials for which participants correctly remembered the picture pair and trials for which the participants did not correctly remember the picture pair. Other regressors of non-interest included outliers and session effects. We next conducted a first level analysis in which we substituted the canonical HRF (in the variable SPM.xBF.bf of the SPM.mat) with each participants' own HRF. Each of the contrast images were then scaled to account for cerebrovascular reactivity differences within the BOLD signal. This scaling process was done by dividing the contrast images by the mean RSFA image from the resting-state scans.

At the second level, we conducted two sets of analyses: a region of interest (ROI) and a whole-brain approach. ROIs were chosen based on the *a priori* predictions [4] that the medial temporal lobe and regions with the DMN would be the earliest affected by an accumulation of risk factors. Thus, we chose the left and right hippocampus and the left and right entorhinal cortex using masks derived from FreeSurfer v6.0 (<http://surfer.nmr.mgh.harvard.edu>), and a mask of the DMN available from previous studies [71]. As a control region, we used a medial occipital network mask [71]. Other researchers have used a similar control ROI to assess the specificity of the results [72]. Regression analyses were used to assess the relationship between the dementia risk score and mean BOLD signal from the contrast of correct retrieval > baseline, consistent with prior studies [34,35]. For these ROIs, the alpha was set to  $p < .05$ . For the whole-brain analyses, we first assessed which brain regions were sensitive to our fMRI task by conducting a one-sample *t*-test for the contrast of correct retrieval > baseline. Next, we conducted a similar regression analysis to test the association between dementia risk score and

correct retrieval > baseline activity. All regression analyses controlled for inter-individual differences in episodic memory performance and lifelong differences in premorbid ability using the word pronunciation score from the WRAT.

All analyses excluded voxels with low signal-to-noise in the fMRI signal due to susceptibility artifact in the nasal passages and ear canals. Note that the premorbid ability score was lost for one participant. This missing value was imputed using a regression equation derived from the other participants similar to other studies [73]. Specifically, the following factors were used to predict the premorbid ability score: dementia risk, age, sex, years of education, whether non-Hispanic White, and fMRI memory accuracy. The resulting model was significant,  $F(6,52) = 11.24, p < .001$ , and explained 56.46% of the variance in premorbid ability. The beta-coefficients from this model were then used to predict the missing value for the participant. This strategy allowed us to include all available fMRI data for all analyses. For the whole-brain analyses, an alpha was set to .005 with 50 contiguous voxels. For comparison purposes, we also present the results at the different stages of corrections on the BOLD signal: canonical HRF, after using the participants' own HRF, and after scaling the contrasts by the participants' mean RSFA images.

To better understand which risk factors contributed the most weight to the brain effects that were found, we conducted a partial least squares (PLS) regression analysis using the ExPosition package in R [74]. We chose this method because risk factors often are highly related to one another and PLS capitalizes on the shared variance across factors to explain the majority of the covariance in the data. For this analysis, two matrices were created: one that represented each risk (including age) for each participant and one that represented extracted beta-coefficients in each brain region from the fMRI results for each participant. The cross product of these two

matrices were decomposed into mutually orthogonal latent variables using singular value decomposition. The latent variable scores represented the weights of risk factor that contributed to increases or decreases in the BOLD signal for each brain region.

## ***Results***

### ***Participant Demographics***

The four participants that were removed from the analyses had lower premorbid ability scores (84.25 vs. 103.91,  $p = .037$ ), and were more likely to be an ethnic minority (100% vs. 33%,  $p = .007$ ) compared with participants that were retained in the study. Demographic information for the final set of participants can be found in Table 1. Participants had a dementia risk score that ranged from 1 to 8. Greater dementia risk was associated with poorer memory performance in the fMRI task ( $r(58) = -.28, p = .028$ ), consistent with prior work suggesting that the chosen risk factors are associated with cognitive decline. However, greater risk was not associated with older age ( $r(58) = .03, p = .82$ ) and age was not associated with memory performance ( $r(58) = -.19, p = .14$ ). When modifying the dementia risk score to include age 65 or above as an additional risk, this second dementia risk score was marginally related to age ( $r(58) = .23, p = .081$ ) and continued to be associated with memory performance ( $r(58) = -.28, p = .031$ ).

### ***Region of Interest Analyses***

In separate regression analyses, we tested the association between accumulated dementia risk on mean BOLD signal in five ROIs (Table 2, Figure 1). We found a significant positive association between dementia risk and mean BOLD signal in the DMN ( $p = .042$ ), left entorhinal cortex ( $p = .036$ ), and left hippocampus ( $p = .029$ ). The left hippocampal association was strongest for voxels in posterior regions of the hippocampus (Figure 2). No significant

association was found in the right lateral ROIs nor the medial occipital network that served as a control (all  $p$ 's > .25). When adjusting the risk score to include an extra risk if aged 65 or older, the patterns of correlations remained the same.

### ***Whole-Brain Analyses***

A whole-brain analysis on correct retrieval trials revealed large clusters of brain activity in lateral prefrontal cortex, dorsolateral parietal cortex, occipital cortex, ventral temporal cortex, and the medial temporal lobes (see Figure 3). Deactivations were found in medial prefrontal cortex, posterior cingulate cortex, ventrolateral parietal cortex, and lateral temporal cortex.

### ***Association Between Dementia Risk and Brain Activity***

To test how cumulative risk for dementia was associated with brain function, a regression analysis was conducted with the dementia risk score (regardless of age) as the predictor variable in a whole-brain analysis on the BOLD signal during correct memory trials at retrieval (see Figure 4, Figure 5, and Table 3). Across the three different stages of the analyses (canonical HRF, using the participant's own HRF, and the RSFA scaling), only positive associations were found between dementia risk and BOLD signal largely in frontal and occipital cortices. In relation to the stages of the BOLD signal correction, using the participants' HRF increased the sensitivity to find significant clusters compared to when the canonical HRF was used. After scaling the BOLD signal using RSFA, many of the previously significant clusters were no longer significant. Brain regions that remained significant after full calibration of the BOLD signal included right dorsal anterior cingulate gyrus (BA 32), left mid cingulate gyrus (BA 24), right ventral striatum, and right lingual gyrus (BA 19). No brain regions exhibited reversals in the direction of brain activity (e.g., positive associations in one analysis and negative associations in

the same region in another analysis). These brain regions were primarily right lateralized and associated with executive control and visual object recognition [71,75].

### ***Associations Between Dementia Risk, Brain Activity, and Age***

When adjusting the risk score to include an extra risk if aged 65 or older, only positive associations between dementia risk and BOLD signal were found, which largely overlapped with the previous analysis, but also included several new clusters (Figure 6A). These clusters included right middle frontal gyrus (BA 10), right superior medial frontal gyrus (BA 8), left ventral striatum, left fusiform gyrus (BA 37), right inferior occipital cortex (BA 18), and right superior occipital cortex (BA 19). These new regions spanned both the left and right hemispheres and included brain areas underlying attention and visual processing [71,75].

To clarify whether this second dementia risk score that included age revealed brain regions associated with “pure” age effects or whether the effects might represent differences in physiology that led to compounded risks, we also assessed the effects of age while controlling for dementia risk (not including age), memory performance, and premorbid ability (Table 4, Figure 6B, and Figure 7). This analysis revealed only positive associations with age, but no clusters were significant that overlapped with the dementia risk score that included age. These age-specific effects were found in right precentral gyrus (BA 3/4), left postcentral gyrus (BA 3/4), right supramarginal gyrus (BA 40), bilateral inferior parietal cortex (BA 40), left middle occipital cortex (BA 19), and the left cerebellum. These regions have been implicated in somatosensory processing, motor processing, and attention [71,75]. These age-related increases also have been found in lifespan samples of middle-aged and older adults [76].

### ***Contributions of Specific Risk Factors for Dementia***

PLS analyses were next conducted on each brain region found to be significantly associated with either of the dementia risk scores using the fully calibrated BOLD signal (Figure 8). The first latent variable explained 70.81% of the covariance and described overall increases in the BOLD signal across all brain regions with the posterior brain regions having the greatest weight. These increases in BOLD signal were most highly associated with the presence of hypertension, diabetes, obesity, heart disease, and high cholesterol (in order of contribution to the model). The second latent variable explained 14.50% of the covariance and expressed a more subtle pattern. Individuals who self-reported being a minority, had diabetes, low education, and smoked exhibited increased BOLD signal in prefrontal brain regions and decreased BOLD signal in occipital and medial temporal brain regions. In contrast, individuals who reported having a family history of ADRD and were obese showed increased BOLD signal in occipital and medial temporal brain regions and decreased BOLD signal in prefrontal regions.

### ***Discussion***

Recent advances in neuroimaging now allow scientists and clinicians to detect ADRD pathology *in vivo* among cognitively normal adults [7,77]. Longitudinal studies conducted in older adults with elevated biomarkers of pathology using these measures have indicated a high likelihood of subsequent cognitive decline [78,79] and conversion to AD [80] relative to those without elevated biomarkers. Models of AD progression propose that an overburdened neural system might bring about the accumulation of AD-related pathology [4,11,12]. However, such neuroimaging research has not uncovered which individuals are most vulnerable to an overburdened neural system and subsequently accumulate pathology in the first place. Building from epidemiological research on risk factors for dementia starting in midlife, we tested the extent that greater dementia risk might set the stage for a toxic brain environment that fosters

such pathologic processes in high-risk brain regions spanning the medial temporal lobe and the DMN [4]. Consistent with these theoretical ideas, we found that greater risk for dementia was associated with inter-individual differences in brain activity in the hippocampus and entorhinal cortex in the medial temporal lobe and the DMN. We also found increases in prefrontal and occipital cortices with greater dementia risk. These regions were significant while controlling for memory performance and premorbid intellectual abilities, suggesting that these findings were not likely due to differential levels of cognitive ability or effort.

### ***Dementia Risk is Associated with Elevated Brain Activity***

We found that increases in dementia risk were exclusively associated with increases in brain activity. Previous studies investigating memory retrieval-related differences in brain activity comparing risk groups (e.g., the presence of the apolipoprotein  $\epsilon 4$  allele, vascular risk, diabetes) also found risk-related increases across the brain [34-37]. However, none of these previous studies calibrated the BOLD signal for differences in cerebrovascular reactivity that likely differentially affect adults with greater risk for ADRD. When not calibrating the BOLD signal, we found more brain regions that showed similar increases including the insula, cerebellum, occipital cortex, precentral gyrus, and middle frontal gyrus. This additional activity suggests that many previous studies might have overestimated the number of brain regions that are associated with risk and/or reported stronger relationships than reality. Although somewhat encouraging, we did not find that the direction of any of the BOLD signal effects completely reversed direction [45].

Although we found increased BOLD signal in medial temporal regions and the DMN as we hypothesized, the effects in these regions were much weaker than those found in the prefrontal and occipital cortices. In fact, none of the regions from our ROI analysis survived the

more stringent threshold in the whole-brain analysis. Part of the reason is the heterogeneity of the direction of the effects within these ROIs as exemplified by the left hippocampus (Figure 2). Whereas the posterior hippocampus showed positive associations with dementia risk, mid-hippocampal voxels showed a numerically negative association. Although this negative effect was not significant, this finding might hint at a cause for some of the mixed effects found in the literature [33]. Nonetheless, we were successful in garnering some evidence that increased dementia risk would selectively target hub regions. Notably, we found additional unexpected brain regions associated with dementia risk. These additional brain regions associated with dementia risk might reflect different mechanisms of brain alterations. We found that the dorsal anterior cingulate cortex, lingual gyrus, and occipital cortex also showed associations with dementia risk. On the one hand, the anterior cingulate cortex might be classified as a critical region because it has been shown to be reliably activated across a variety of tasks as indicated by a large-scale meta-analysis [81]. On the other hand, these regions might have been significant because they were most sensitive to our task demands due to the high level of cognitive control needed and the necessity of recollection-based processes that reactivate sensory regions during the memory test to reject familiar lures [82,83].

An alternative explanation for these widespread effects is that the risk factors may represent different profiles of dementia risk. The risk factors assessed in the current study do not distinguish between different types of dementia (e.g., AD, vascular dementia, frontotemporal dementia). Some individuals might be at higher risk for dementias that target the frontal cortex (e.g., frontotemporal dementia) whereas others might be more at risk for dementias that target the medial temporal lobe (e.g., AD). A hint of this possibility is found from the PLS analysis. Individuals who were identified as an ethnic minority, had diabetes and low education, and

smoked exhibited a stronger increase in prefrontal brain activity whereas those who were obese and had a family history of AD exhibited stronger increases in occipital and medial temporal activity. Following these two potential groups of participants longitudinally and characterizing differential cognitive trajectories would confirm such heterogenous effects.

### ***Implications for Understanding the Trajectory of AD***

Overall, the findings are consistent with the observation by Sperling and colleagues in which preclinical AD and early mild cognitive impairment are characterized by increases in brain activity, and it is only in late mild cognitive impairment and diagnosed AD in which decreases in brain activity are seen in the medial temporal lobes in the shape of an inverted-U [3,84, 85]. The main difference in those observations and the data reported here is that our participants were generally younger (starting at 50 years of age) and many would not be classified as being in preclinical AD because the accumulation of pathology and beginning of neurodegeneration is often found in later decades of life [86]. Notably, some of these positive associations were found in the posterior hippocampus, which has been implicated in the retrieval and/or representation of detailed spatiotemporal information from past events (i.e., recollections) [49,83,87]. Recollection deficits might occur earlier in the AD trajectory than other types of memory deficits such as familiarity or gist processing [88,89]. Thus, the present findings suggest that these abnormal increases in brain activity can occur before one is in the preclinical stages of the disease and might target recollection processes.

In a new model of neurocognitive disorders, we have proposed that the many dispositional and lifestyle factors that have developed over one's lifetime in addition to the exposure to environmental demands and stressors affect the balance of neuroprotection vs. toxicity of the brain's microenvironment [4]. The general idea is that these factors might make

the brain more prone to burnout and thus more vulnerable to pathogenesis. Specifically, such a burnout might compromise the neuronal processes that help to restore and maintain normal brain functioning. We hypothesized that candidate regions that would be most vulnerable would be those that have a high energy consumption and high interconnectivity with other brain regions, including the DMN and the medial temporal lobes [11,12]. We found preliminary support for this model and found associations with brain regions associated with executive control and visual object processing [71,75]. Lastly, the present results offer some clues as to which risk factors might have the most negative impact on the balance of neuroprotection vs. toxicity. Factors that directly impact the cardiovascular system (e.g., hypertension), the glucose metabolic system (e.g., diabetes), and the lipid metabolism system (e.g., obesity, cholesterol) had the largest impact on overall increases in brain activity [73,90]. Future studies including a greater number of risk factors and/or weighting the relative importance of risk factors might increase the sensitivity to find more brain regions that vary with dementia risk.

### ***Limitations***

The present study also has several limitations. First, while this study is one of the first to investigate the associations with brain function and cumulative risk factors for dementia, not all risk factors were included in our dementia risk score. We did not include genetic information, eating habits, levels of depression, alcohol intake, among others. For this study, we included factors that were relatively reliable as a self-report measure and were simple to assess. Another limitation is that we did not have any biomarker data to assess the presence of AD-related pathology such as beta-amyloid or tau. Excluding participants with AD-related pathology would confirm that these elevations in brain activity begin occurring before preclinical stages and might even be a casual contributor to the development of pathology [4,12].

The present study also did not address protective factors that are proposed to be critical in offsetting the toxic effects of risk factors on the brain [4]. A recent attempt at redefining “reserve” describes it as an accumulation of genetic and environmental factors that mitigate neural decline by aging or age-related diseases [91]. This new definition fits well with our model. One prediction from both our notion of neuroprotective effects and reserve are that the increases in brain activity associated with dementia risk (as shown here) should be reduced when factoring in protective factors. Consistent with this idea, studies have found that higher IQ and education can be associated with lower brain activity [92]. Similarly, an experimental manipulation of lifestyle engagement found that older adults who engaged in challenging cognitive activities (e.g., digital photography), and thereby potentially increasing reserve, evidenced reduced brain activity during low task demands [93].

### ***Conclusion***

The present study found evidence that middle-aged and older adults with an accumulation of risk factors for dementia exhibit early alterations in brain function. Because many risk factors for dementia also affect the cerebrovascular system such as hypertension, diabetes, high cholesterol, and smoking, fMRI BOLD activity has the potential to be confounded by non-neuronal factors. Importantly, multiple steps were taken to minimize such non-neuronal influences in the fMRI analyses. While such precautions are still infrequently implemented in studies of aging and disease, they are critical to appropriately interpret fMRI findings in older adults and other at-risk populations. Indeed, the present study found that not calibrating the BOLD signal would lead to an overestimation of the breadth of these effects. Nevertheless, for a subset of brain regions, convergence was found with previous studies as to which brain regions

are affected by elevated risk for dementia and offer consistent brain regions to target in lifestyle interventions or future pharmaceutical treatments.

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***Conflict of Interest/Disclosure Statement***

The authors have no conflict of interest to report.

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**Table 1. Participant Characteristics in Final Sample**

Factor	M (SD) or N (%)
N	60
Age	60.67 (7.06)
Sex (F/M)	37 (62%) / 23 (38%)
Race	
Non-Hispanic White	40 (67%)
African American	18 (30%)
Other	2 (3%)
Years of Education	14.27 (2.69)
Less than High School Education	2 (3%)
SLUMS*	26.49 (2.88)
fMRI Memory Accuracy	.35 (.12)
Word Pronunciation Scaled*	102.69 (16.92)
Memory Problems	23 (38%)
Family History of Alzheimer's Disease	30 (50%)
Hypertension	25 (42%)
Current or Family History of Heart Disease	39 (65%)
Current or Family History of Diabetes	38 (63%)
Current or History of Tobacco Use	28 (47%)
Obese	21 (35%)
High Total Cholesterol	28 (47%)
Mild Head Trauma	14 (23%)
Dementia Risk Score Mean	4.47 (1.78)
Dementia Risk Score with Age Mean	4.78 (1.89)

\*Missing score for one participant.

**Table 2. Region of Interest Multiple Regression Analyses for the Association Between Dementia Risk Score and Brain Activity During Memory Retrieval**

	DMN (ICN 13)	L HC	R HC	L ENT	R ENT	Medial Occipital (ICN12)
Factor	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)
Intercept	.029*** (.004)	.044 (.006)***	.053 (.007)***	.017 (.007)*	.031 (.008)***	.012 (.009)***
Dementia Risk Score	.005* (.002)	.008 (.004)*	.0001 (.004)	.008 (.004)*	-.002 (.005)	.006 (.005)
Memory Accuracy	.001* (.0004)	.001 (.001)*	.0007 (.0007)	.001 (.0006)	.001 (.0008)	.001 (.0009)
Premorbid Ability	-.0001 (.0003)	-.0004 (.0004)	-.00007 (.0004)	.0004 (.0004)	-.0006 (.0005)	-.00002 (.0006)

Notes. \*\*\* $p < .001$ ; \*\* $p < .01$ ; \* $p < .05$ ; DMN = Default Mode Network; ICN = Intrinsic

Connectivity Network from Laird et al. (2011); B = unstandardized beta coefficient; SE = standard error.

**Table 3. MNI Coordinates for Association Between Dementia Risk Score and Brain Activity During Memory Retrieval**

MNI Coordinates			Region	BA	T-value	Cluster size (voxels)
x	y	z				
Positive Dementia Risk Score Effect						
6	22	30	Right dorsal anterior cingulate gyrus	32	4.16	78
-8	-4	38	Left mid cingulate gyrus	24	4.05	50
6	34	42	<i>Right superior medial frontal gyrus</i>	8	4.04	94
14	6	-10	Right ventral striatum	-	4.03	55
-18	8	-16	<i>Left ventral striatum</i>	-	3.92	52
26	-56	-4	Right lingual gyrus	19	3.66	64
12	-90	30	<i>Right superior occipital gyrus</i>	19	3.41	144
22	-86	-4	<i>Right inferior occipital gyrus</i>	18	3.34	89
40	52	4	<i>Right middle frontal gyrus</i>	10	3.15	52
-20	-48	-12	<i>Left fusiform gyrus</i>	37	3.00	50

Notes. MNI = Montreal Neurological Institute; BA = Brodmann Area. Clusters are labeled in order of statistical magnitude and italicized clusters are the additional clusters found when including old age as an additional risk for dementia.

**Table 4. MNI Coordinates for Association Between Age and Brain Activity During Memory Retrieval**

MNI Coordinates			Region	BA	T-value	Cluster size (voxels)
x	y	z				
Positive Age Effect						
54	-8	50	Right precentral gyrus	3/4	4.72	582
-36	-78	36	Left middle occipital gyrus	19	3.94	134
-10	-62	-44	Left cerebellum	-	3.89	61
64	-22	46	Right supramarginal gyrus	40	3.74	59
-56	-14	50	Left postcentral gyrus	3/4	3.59	62
36	-52	50	Right inferior parietal cortex	40	3.55	90
-52	-28	38	Left inferior parietal cortex	2/40	3.22	93

Notes. MNI = Montreal Neurological Institute; BA = Brodmann Area. Clusters are labeled in order of statistical magnitude.

**Figure Captions**

**Figure 1.** Scatterplots for region of interest analyses assessing the relationship between accumulation of dementia risk and mean brain activity controlling for memory performance and premorbid ability. Significant positive relationships were found in the Default Mode Network (DMN), left hippocampus, and left entorhinal cortex. No significant relationships were found in the right hippocampus, right entorhinal cortex, or the medial occipital network, the latter of which served as a control. Data points are jittered to prevent masking of overlapping data.

**Figure 2.** Bootstrapped regression analyses were conducted to assess the relationship between dementia risk and mean brain activity in voxels along cross-sections of the y-axis of the left hippocampus. Significant positive associations were found in the posterior hippocampus whereas numerically negative (but non-significant) associations were found in the mid-hippocampus. These analyses used 10,000 bootstraps with bias-corrected acceleration and controlled for fMRI memory performance and verbal ability. L = Left.

**Figure 3.** Whole-brain analysis of correct retrieval trials > baseline in warm colors and baseline > correct retrieval trials in cool colors. L = left, R = right.

**Figure 4.** Clusters of brain activity in whole-brain regression analyses associated with dementia risk (without age included in the risk score) when using the canonical hemodynamic response function (left), when using the participant-specific hemodynamic response function (middle), and when also scaling the data using resting state fluctuation amplitude analyses (right). Only positive associations were found in all three analysis steps.

**Figure 5.** Scatterplots from extracted beta-coefficients found in significant clusters of brain activity in the whole-brain regression analyses using the fully calibrated BOLD data and the dementia risk score that did not include age. Data points are jittered to prevent masking of overlapping data.

**Figure 6.** Clusters of brain activity in whole-brain regression analyses. Panel A represents brain maps associated with dementia risk (with age included in the risk score) for the fully calibrated BOLD data. Panel B represents brain maps associated with chronological age for the fully calibrated BOLD data. Despite the fact that adults older than 65 get an extra risk point, this dementia risk score did not show overlapping clusters of brain regions associated with age.

**Figure 7.** Scatterplots from extracted beta-coefficients found in significant clusters of brain activity in the whole-brain regression analyses using the fully calibrated BOLD data and the dementia risk score that included age. Data points are jittered to prevent masking of overlapping data.

**Figure 8.** Scatterplots showing the results of the partial least squares regression analyses assessing the association between the individual risk factors and brain regions associated with dementia risk. The top panel shows how the risk factors are expressed across the first latent variable (x-axis) and the second latent variable (y-axis). The axes represent the weights each of latent variable such that increasing weights move further away from the center of the axis (0,0). The diameters of the circles are proportionate to the amount of total covariance explained by that

factor. The bottom panel shows how the brain regions are expressed across the first latent variable (x-axis) and the second latent variable (y-axis). Latent variable 1 describes the association between having hypertension, diabetes, obesity, and high cholesterol (the largest contributors) and increases in the BOLD signal in occipital, temporal, and frontal brain regions. Latent variable 2 describes the association between being an ethnic minority, having diabetes, having less than a high school education, and smoking and increases in prefrontal activity, but decreases in occipital and temporal activity. Individuals with a family history of Alzheimer's disease and who are obese show the opposite pattern (increases in occipito-temporal activity and decreases in frontal activity). HT = hypertension; Diab = diabetes; Heart = heart disease; Chol = High cholesterol; ADFam = family history of Alzheimer's disease; Compl = subjective memory complaints; Tobac = tobacco user; Trma = mild head trauma; LessHS = less than a high school education; Minor = ethnic minority; iOcc = inferior occipital gyrus; sOcc = superior occipital gyrus; Hippo = hippocampus, lLing = left lingual gyrus; rLing = right lingual gyrus; DMN = default mode network; vStriat = ventral striatum; dACC = dorsal anterior cingulate cortex; mCing = middle cingulate gyrus; rMFG = right middle gyrus.

Figure 1.

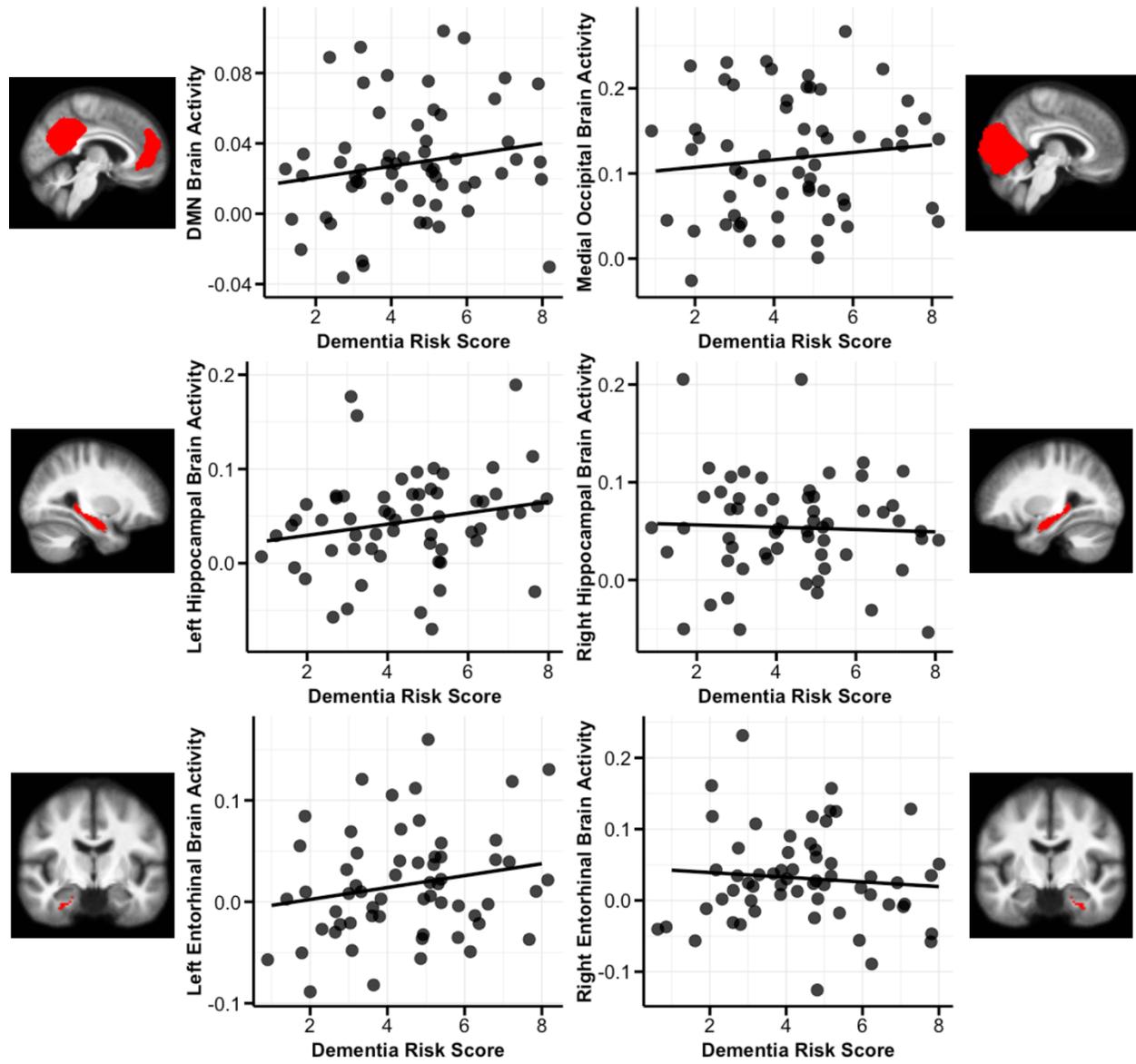


Figure 2.

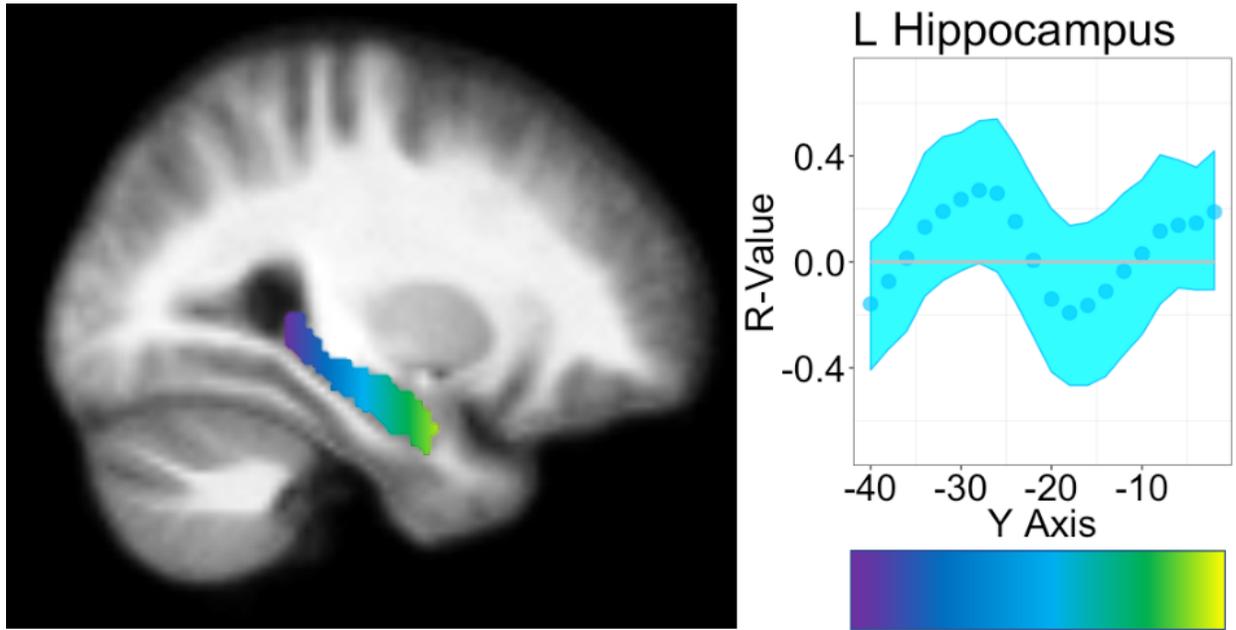


Figure 3.

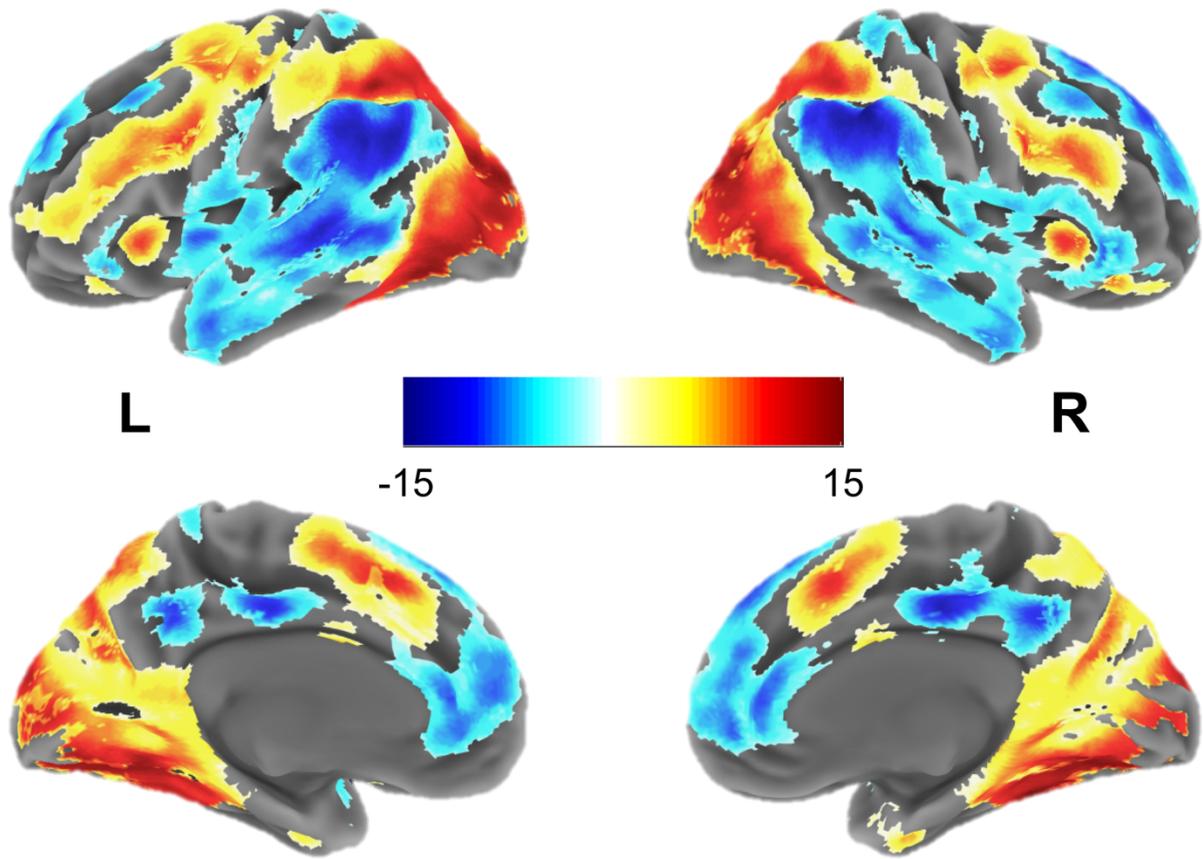


Figure 4.

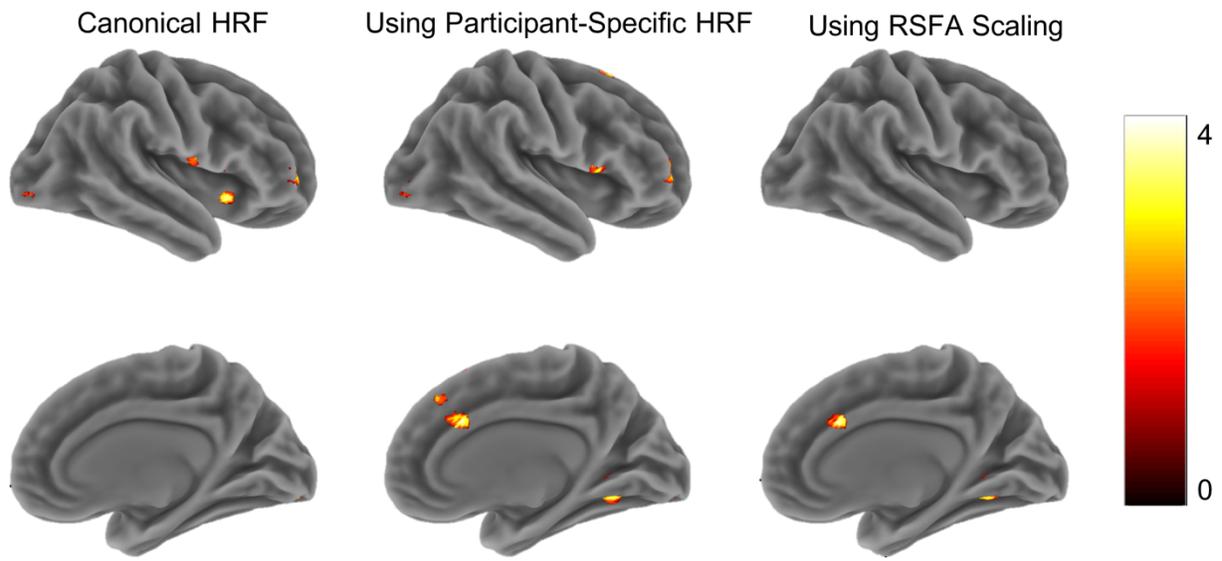


Figure 5.

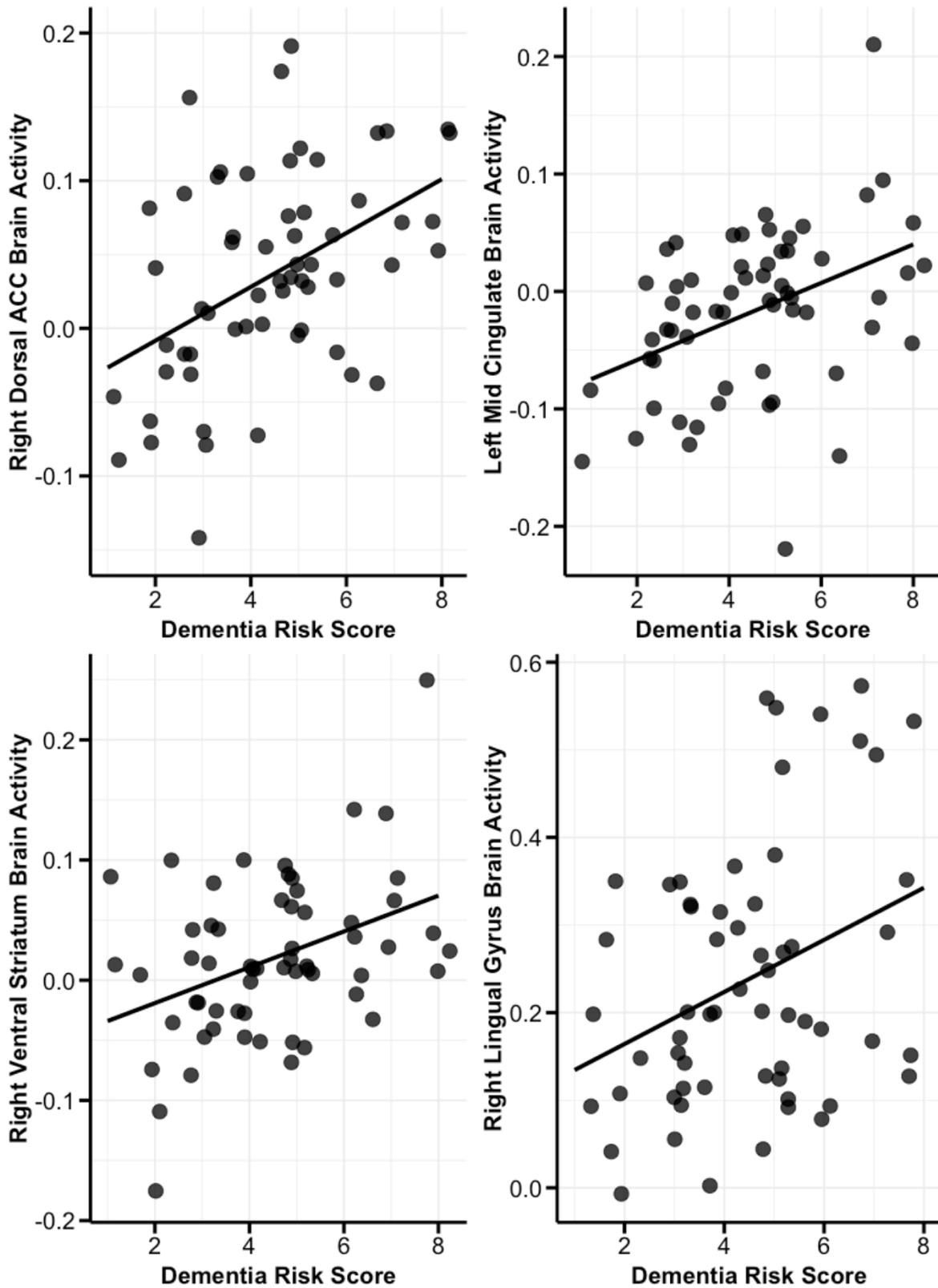


Figure 6.

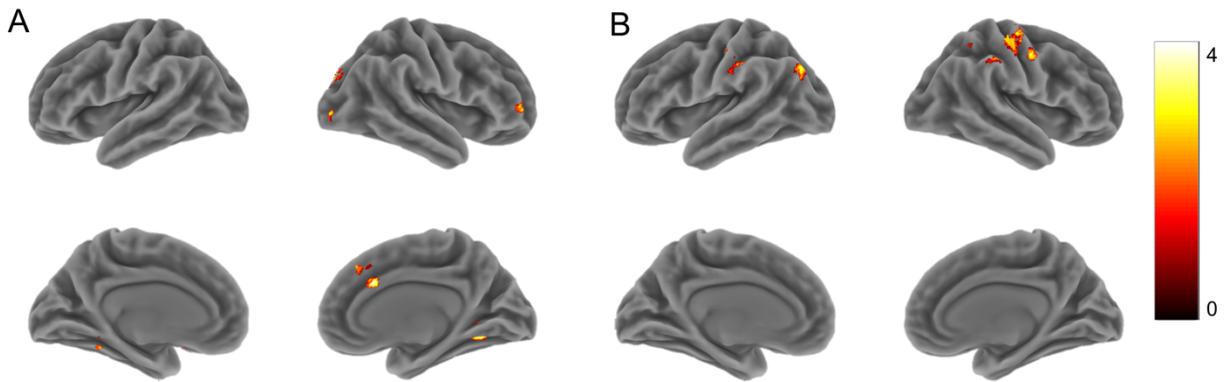


Figure 7.

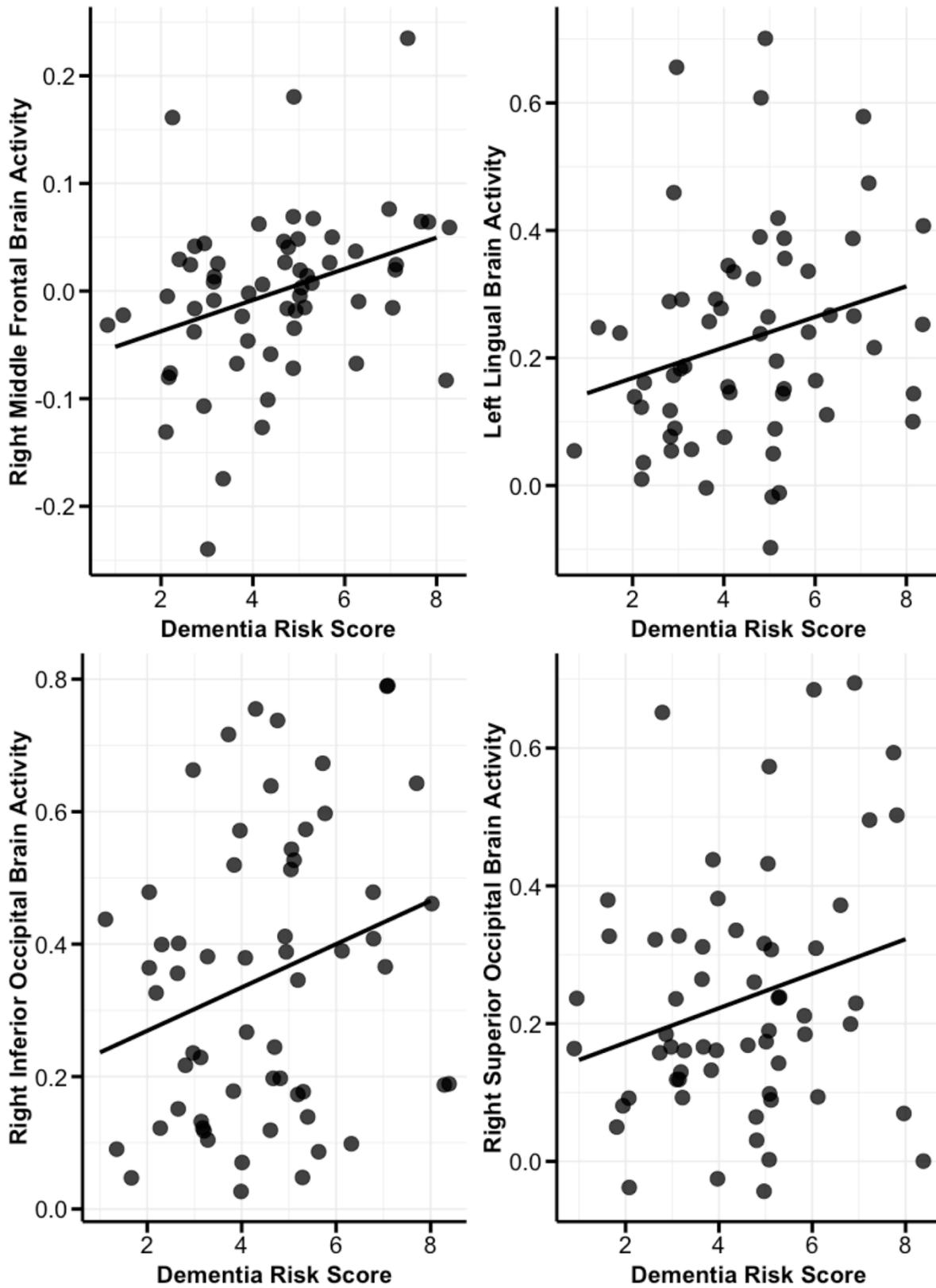


Figure 8.

