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Structural Complexity is Negatively Associated with Brain Activity: A Novel Multimodal Test of Compensation Theories of Aging

Ian M. McDonough[a]
Christopher R. Madan[b]

Author Affiliations:
[a]Department of Psychology, The University of Alabama, BOX 870348, Tuscaloosa, AL 35487, USA
[b]School of Psychology, University of Nottingham, Nottingham, UK

Corresponding Author: Ian M. McDonough, Department of Psychology, The University of Alabama, Tuscaloosa, AL 35487-0348 USA, Email: immcdonough@ua.edu, Phone: 205-348-1168

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Abstract

Fractal dimensionality (FD) measures the complexity within the folds and ridges of cortical and subcortical structures. We tested the degree that FD might provide a new perspective on the atrophy-compensation hypothesis: age or disease-related atrophy causes a compensatory neural response in the form of increased brain activity in prefrontal cortex (PFC) to maintain cognition. Brain structural and functional data were collected from 63 middle-aged and older adults and 18 young-adult controls. Two distinct patterns of FD were found that separated cortical from subcortical structures. Subcortical FD was more strongly negatively correlated with age than cortical FD and cortical FD was negatively associated with brain activity during memory retrieval in medial and lateral parietal cortices uniquely in middle-aged and older adults. Multivariate analyses revealed that the lower FD/higher brain activity pattern was associated with poorer cognition—patterns not present in young adults, consistent with compensation. Bayesian analyses provide further evidence against the modal interpretation of the atrophy-compensation hypothesis in the PFC—a key principle found in some neurocognitive theories of aging.

Keywords: Aging; Compensation; Default Mode Network; Episodic Memory; Fractal Dimensionality; fMRI

1. Introduction

As the world's aging population grows, so too does the risk for cognitive decline and age-related neurodegenerative disorders such as Alzheimer's disease. Understanding and preventing such declines in cognition is critical to increase the length of time that one leads a happy and independent life (Rowe & Kahn, 1987). Over the past three decades, neuroimaging has been used as a tool to understand how age differences in the brain might inform the causes and consequences of cognitive aging (for a brief review, see Park & McDonough, 2013). This literature has generally revealed declining brain structures (Fjell et al., 2014) alongside patterns of both higher and lower brain activity (for meta-analyses, see Li et al., 2015; Spreng et al., 2010). In the present study, we took a multimodal approach using a relatively novel measure of brain structure, fractal dimensionality (FD), to investigate the relationship between brain structure and function in the aging brain.

A prominent hypothesis arising from the past 15 years of neuroimaging research in aging is that brain atrophy, due to advanced aging or disease, causes an increased neural response in an attempt to maintain cognition (for review, see Cabeza et al., 2018). Although lower brain activity with aging also has been widely found, these patterns have been intuitively linked to a lack of brain maintenance (Nyberg et al., 2012), neural inefficiency (Logan et al., 2002), or decline in neural distinctiveness (Li, Lindenberger, & Sikström, 2001). More counterintuitive and controversial is the notion of compensation in which atrophy in aging adults, largely in the prefrontal cortex, is offset by an increase in brain activity in nearby or contralateral prefrontal cortex (PFC) and some research has extended this notion to the lateral parietal cortex (LPC) (Cabeza, 2002; Greenwood, 2007; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). The PFC often is implicated in executive control processes to flexibly adapt to ongoing task demands across many tasks (e.g., Vincent et al., 208; Power & Petersen, 2013). One of the first studies to document higher age-related PFC activity was in an episodic memory task (e.g., Cabeza et al., 2002) and subsequent research investigating compensatory activity also has used episodic memory tasks during either encoding or retrieval (Brassen et al., 2009; Cabeza et al., 2002; Düzel et al., 2011; Persson et al., 2011; Pudas et al., 2013; Rajah et al., 2011). Supporting these single studies, quantitative meta-analyses have confirmed reliably higher brain activity in the PFC in older relative to younger adults at memory encoding (Li et al., 2015; Spreng et al., 2010) and retrieval (Li et al., 2015; Spreng et al., 2010). Similar findings also have been found in Alzheimer's disease (Schwindt & Black, 2009). Together, these studies support part of the atrophy-compensation hypothesis.

However, few studies have provided specific evidence for the association between smaller brain structures (e.g., gray matter density or volume loss) and higher brain activity in the PFC or LPC among aging adults. For example, Kalpouzos et al. (2012) found that the higher brain activity in PFC and LPC in older than younger adults during memory retrieval was eliminated after controlling for gray matter density in those regions, but not in other frontal and parietal regions (i.e., left dorsomedial PFC and right LPC). This study provides both support for and against the general notion that atrophy should be associated with elevated brain activity. Similarly, Tyler et al. (2010) found that lower gray matter density in left PFC and left temporal cortex were associated with higher activation in the right homologous regions during a language comprehension task in older adults. However, because gray matter density in each of those regions also was negatively correlated with brain activity in other frontal and temporal regions, these relationships appeared to be global rather than specific to nearby or contralateral regions. Other studies purportedly providing evidence for the atrophy-compensation hypothesis a) assessed structure-function relationships only indirectly (Colcombe et al., 2005; Düzel et al., 2011; Persson et al., 2012; Thomsen et al., 2004), b) found positive (not negative) structure-function relationships (Brassen et al., 2009; Rajah et al., 2011), c) did not find a relationship between brain structure and function (Pudas et al., 2013), or d) found relationships between brain function and white matter pathways using DTI (Daselaar et al., 2013; Persson et al., 2006), the latter of which can be difficult to classify as nearby or contralateral given the long distance of the fiber bundles. The lack of empirical support for the atrophy-compensation hypothesis is surprising given its wide-spread influence across multiple neurocognitive aging theories (Cabeza, 2002; Greenwood, 2007; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008).

One possibility is that traditional measures of brain structure (e.g., gray matter density or volume loss) may not capture the type of atrophy that serves as a catalyst for neural compensation. Fractal dimensionality (FD), a measure of structural complexity, has been shown to be highly correlated with chronological age and a dementia diagnosis. FD quantifies fractal patterns, or irregularities, of cortical or subcortical surfaces similar to calculating the complexity of continental coastlines (Mandelbrot, 1967). One of the earliest studies employing this method demonstrated that FD can provide better sensitivity to dementia-related differences in brain structure than thickness and gyrification (King et al., 2009, 2010). King et al. (2010) additionally found that FD was more strongly correlated with global cognition than other structural measures. In a series of studies, Madan and Kensinger extended this method to cognitively-normal adults across the adult lifespan and also found higher correlations with chronological age and are more reliable in test-retest assessments than conventional measures (Madan & Kensinger, 2016; Madan & Kensinger, 2017b; see also Liu et al., 2020). Subsequent studies showed that these benefits can be found with improved precision in more localized regions, including cortical parcellations (Madan & Kensinger, 2018) and subcortical regions (Madan & Kensinger, 2017a; Madan, 2019).

The present study had three primary goals. The first goal was to provide a novel test for the basic premise of the atrophy-compensation hypothesis that lower brain integrity is associated with higher brain activity in a sample of middle-aged and older adults. We used FD as a proxy for brain integrity and task-related fMRI during encoding and retrieval in a paired association task to assess potential negative associations with brain activity. According to the atrophy-compensation hypothesis, lower FD should be associated with higher task-related brain activity in PFC and LPC. We also predicted that any such negative associations would be stronger at retrieval than encoding due to the greater task demands during this phase (Manzia et al., 2004; McDonough, Wong, & Gallo, 2013). All fMRI analyses attempted to minimize vascular confounds to the BOLD signal by using a subject-specific hemodynamic response function (Handwerker et al., 2004; Huettel et al., 2001) and scaling the contrasts using resting state fluctuation analyses (Kalcher et al., 2013; Kannurpatti et al., 2011). We conducted additional control analyses to ensure that potential negative structure-function relationships did not also occur in a sample of healthy younger adults—a sample in which atrophy does not yet occur. The second goal was to test whether individual differences in FD would be associated with higher risk for dementia using a cumulative dementia risk score in middle-aged and older adults (McDonough, Letang, & Stinson, 2019). Given the previous associations with FD and Alzheimer’s disease (King et al., 2009, 2010), we predicted that higher dementia risk would be associated with lower FD in the medial temporal lobe and regions within the default mode network, consistent with previously found patterns of atrophy in Alzheimer’s disease (e.g., Buckner et al., 2005). The third goal was to link the structure-function patterns to cognition. Although finding a positive correlation between higher brain activity and better cognitive performance intuitively captures the notion of successful compensation (Cabeza et al., 2018), some perspectives suggest between-subject correlations are not necessary, especially in the cases of *attempted* rather than successful compensation (Dennis & Cabeza, 2012). To the extent that such relationships with cognition are indeed compensatory, then similar relationships should not also be present in a healthy young adult sample—a possibility that we tested.

2. Materials and Methods

2.1 Participants

Sixty-seven participants aged 50-74 were drawn from the Alabama Brain Study on Risk for Dementia. Of these, four participants were not included in the FD analysis for the following reasons: (1) no functional data to correct for movement, (2) poor quality structural scans, and (1) cognitive data were unavailable. Additionally, three more participants were not included in the task fMRI analysis due to residual movement artifact. Details from the study can be found in our earlier publication (McDonough et al., 2019). All participants were excluded if they had contra-indicators for MRI, were left-handed, had a prior diagnosis of any neurological condition, stroke, traumatic brain injury, claustrophobia, history of substance abuse. Potential participants were included if they were free of dementia as measured by the St. Louis University Mental Status (SLUMS; Tariq et al., 2006), spoke English fluently, were right handed, and had at least one of the following self-reported risks for dementia: subjective memory complaints, less than a high school education, African American or Hispanic ethnoracial category, mild head trauma, family history of AD, 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^2 (Livingston et al., 2017; Perkins, 1997). An additional control group of 18 younger adults from age 20-30 was used to test key aspects of the atrophy-compensation hypothesis. This group had similar inclusion and exclusion criteria with the exception that dementia risk nor the SLUMS were assessed. 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. Demographic characteristics can be found in Table 1.

2.2 Procedures

2.2.1 Overall Study

Across two to three sessions, participants completed a cognitive and MRI battery. From the cognitive battery, we used the scaled word reading subtest from the Wide Range Achievement Test-4 (WRAT-4) to estimate premorbid IQ. The MRI session included scans in the following order: resting-state, memory encoding, T1-structural scan, resting-state, memory retrieval, and a visual-motor checkerboard task. The analyses here focus on the structural and task-related functional data.

2.2.2 Cognitive Assessment

2.2.2.1 Saint Louis University Mental Status Exam (SLUMS).

The SLUMS was used to characterize global cognition in the middle-aged and older adult sample (Tariq et al., 2006). The assessment consisted of 11 questions that measured a variety of cognitive domains including orientation, memory, attention, and executive functioning. The maximum number of points possible was 30. The SLUMS outperforms other common global measures of cognition such as the Mini-Mental Status Examination (Folstein et al., 1975).

2.2.2.2 Premorbid Intelligence

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 (Wechsler, 1944). Each score was scaled using age norms.

2.2.3 fMRI Memory Task

The encoding phase consisted of 64 pairs of pictures of either a face-object or face-scene pair for 3 seconds followed by a judgment of learning for 2.16 seconds. The inter-trial interval ranged from 1.72 to 17.20 seconds. The encoding phase was divided into two runs lasting for about 8 minutes each. The memory test consisted of 64 trials lasting 5.16 seconds in a five-alternative-choice test. A previously viewed face was presented with two previously viewed objects, two previously viewed scenes, and a "never seen" option. Of the four possible picture choices, one was the target and three were lures. Because all options should have been familiar to participants, accurate responses relied on recollection processes. The "never seen" option specifically referred to not remembering the face, thus precluding participants from making a correct response without complete guessing. The intertrial intervals ranged from 1.72 to 10.32 seconds. The retrieval phase was divided into two runs lasting for about 5 minutes each.

2.2.4 fMRI Checkerboard Task

The purpose of this task was to obtain a measure of each participant's hemodynamic response function (HRF) in the occipital cortex that was time-locked to the onset of the visual stimulation. A reversing checkerboard was presented for 1 s in each of 20 repetitions over 2 minutes. 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 8 s and 16 s with an average of 12 s, during which the participant viewed a fixation cross.

2.2.5 Resting State Scans

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

2.3 MRI acquisition and preprocessing

A 3T Siemens PRISMA scanner at the UAB Civitan International Neuroimaging Laboratory was used to collect MRI scans. High resolution T1-weighted structural MPRAGE scans were acquired using (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°, flip angle 2 = 5°, FOV = 256 mm, matrix = 240 × 256 mm^2 , in-plane resolution = 1.0 × 1.0 mm^2). Structural images were processed using a surface-based processing stream provided by FreeSurfer v6.0 (Fischl, 2012; http://surfer.nmr.mgh.harvard.edu), including bias-field correction, intensity normalization, skull-stripping (Dale et al., 1999; Segonne et al., 2004). Following these steps, FreeSurfer segments of gray/white matter and pial surfaces were used to estimate distance between boundaries, which were checked for accuracy using Mindcontrol (Keshavan et al., 2018). Edits were made by extending white matter boundaries or removing non-brain tissue. Cortical regions of interest were defined using the Desikan-Killiany-Tourville (DKT) atlas (Klein & Tourville, 2012). Subcortical ROIs were defined using the FreeSurfer aseg atlas.

The aseg and DKT files from FreeSurfer were then submitted to the calcFD toolbox (Madan & Kensinger, 2016, 2017a; http://cmadan.github.io/calcFD) in Matlab. This toolbox calculates the FD of a three-dimensional structures, including both cortical and subcortical structures. In fractal geometry, several approaches have been proposed to quantify the complexity of natural structures; the approach here calculates the Minkowski–Bouligand or Hausdorff dimension in 3D space (Kennedy & Lin, 1986; Mandelbrot, 1967). This analysis has been validated and found to be reliable even following head-motion (Madan & Kensinger, 2017b; Madan, 2018). Briefly, fractal dimensionality is a scale-invariant measure of how complex a natural structure is and is particularly sensitive to shape information, rather than the ‘size’ of a structure, as is the case with volumetric measures—i.e., volume, thickness, and surface area. In other words, two structures can be the same size, but differ in fractal dimensionality due to variations in the folding structure, texture (‘bumpiness’), or compactness (see Madan, 2019). Conversely, two structures could be different in size and still have the same fractal dimensionality. See Madan and Kensinger (2016) for visualisations of cortical surfaces that are relatively high and low in fractal dimensionality.

All functional scans used T2*-weighted EPI sequences (56 interleaved axial slices, 2.5 mm thickness, TR = 1720 ms, TE = 35.8 ms, flip angle = 73°, FOV = 260 mm, matrix = 104 × 104 mm, in-plane resolution = 2.5 × 2.5 mm^2 , multi-band acceleration factor = 4). The functional data were unwarped, coregistered to the structural scan, and spatially smoothed (8-mm FWHM kernel) using Statistical Parametric Mapping 12 (SPM12). The blood oxygen level dependent (BOLD) signal was then denoised using Multivariate Exploratory Linear Optimized

Decomposition into Independent Components (MELODIC) (Beckmann & Smith, 2004). The resulting spatiotemporal components were flagged using an in-house script that applied machine learning to frequency and temporal elements indicative of potential artifacts. The flagged components were then regressed from the BOLD signal, also using MELODIC. The denoised data were then warped into a study template using Advanced Neuroimaging Tools (ANTs) (Avants & Gee, 2004). For the resting state data, additional preprocessing steps were used to prepare the data for the resting-state fluctuation amplitude analyses. AFNI's proc.py (Cox, 1996) was used to despike the time series, remove the first 3 TRs, bandpass filter the time series between 0.01 and 0.08 Hz, demean the time series, and to regress out motion parameters, their derivatives, and white matter signal from the time series.

2.4 Statistical Analyses

2.4.1 Fractal Dimensionality Analysis

Movement parameters from the functional scans were calculated using Artifact Detection Tools (ART; Mazaika et al., 2005), including mean framewise displacement and mean root squared realignment parameters. Although research using a large healthy sample of adults showed very little influence of head motion on FD estimations (Madan, 2018), a growing body of research has shown that in-scanner movement can have large effects on brain size estimates, in general (Alexander-Bloch et al., 2016; Savalia et al., 2017). Thus, we checked to see if this was the case in our data set. Preliminary correlations between FD and movement (framewise displacement and root mean squared estimates) ranged from -.43 to .10 across ROIs, suggesting that more movement was related to smaller estimates of FD values. In light of this relationship, we regressed out these movement parameters from all ROIs before further analyses.

Next, we aimed to reduce the data set by conducting a factor analysis on the 76 ROIs (62 neocortical and 14 subcortical). To determine the optimal number of factors, we conducted a parallel analysis (Valle et al., 1999). A factor analysis was then conducted using oblimin rotation. Subsequent regression analyses were then conducted using these factor scores. Specifically, we investigated linear and quadratic effects of age, dementia risk, and their interaction separately for each FD factor. The dementia risk score consisted of a sum of 11 possible self-reported risk factors that could be identifiable by participants (see Participants section). A backwards stepwise regression method was used to eliminate higher order interaction terms to preclude saturating the model using a p-value threshold of .10. In the second set of regression analyses, we investigated the extent that each factor, age, dementia risk, and their interactions predicted cognition. In these latter analyses, we included premorbid IQ as a covariate to control for lifelong cognition.

2.4.2 Task fMRI Analysis

All fMRI analyses were analyzed under the assumptions of the general linear model (GLM). We first estimated each subject's HRF using a finite impulse response function to model task-evoked brain activity in response to the flashing checkerboard using SPM. In this GLM, 12 basis functions were modeled across a 21 s window and outliers derived from ART 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 subject's HRF. These new HRF's were then entered into GLM analyses using SPM separately for encoding and retrieval using a stick function (setting duration to 0 s). For both memory encoding and retrieval, two trial types of interest were included as regressors: trials subsequently remembered (or correctly remembered) and trials subsequently forgotten (or inaccurately remembered). Other regressors of non-interest included six motion parameters, binary flags for outlying trials derived from ART, and two binary constants for mean session effects. A high-pass filter of 128 s was used. The encoding contrast (subsequently remembered > subsequently forgotten) and the retrieval contrast (correctly remembered > incorrectly remembered) 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. RSFA analyses calculate the standard deviation of the BOLD signal. These analyses were implemented separately for each run and averaged together. Whole brain contrasts can be found in Supplemental Materials.

2.4.3 Structure-Function Group Analysis

Because our group analyses were concerned with the potential effects of atrophy on brain activity, our analyses focused on middle-aged and older adults only. To test our primary hypothesis, regression analyses were conducted using both FD Factors as predictors of the whole-brain beta maps in the same model, but separately for the encoding and retrieval contrasts. Regression analyses were conducted using FSL's randomise function (Winkler et al., 2014). Randomise uses a nonparametric approach and generates 5,000 permutations to create a null distribution from which to make inferences. Data was demeaned prior to conducting the analyses. Threshold-free cluster enhancement (TFCE) was used to correct for the family-wise error rate at the .05 level for each regression analysis. This method of significance testing has been argued to be more sensitive than cluster-based and voxel-based thresholding (Smith & Nichols, 2009). In exploratory analyses, we also tested non-linear effects by including four regressors in a new model (linear and quadratic effects of each FD factor). To strengthen the inferences from any null results found in the PFC (the site of our primary hypothesis), we conducted additional analyses using Bayesian Correlation Pairs under the hypothesis that a negative correlation would be found between FD and brain activity. Specifically, mean values for brain activity (correct > incorrect) were calculated for each of the 22 PFC ROIs from the DKT atlas and paired with either the FD value in the same hemisphere (i.e., left brain activity with left FD) or in the contralateral hemisphere (i.e., left brain activity with right FD). Bayes factor values closer to 0 indicate stronger evidence that the structure-function correlations are not negatively correlated. Lastly, we conducted the same analyses in the young control group to ensure that the same relationships were not found.

To better understand how the FD factors and the associated functional clusters from the above regression related to cognition, partial least squares regression (PLS-R) was conducted using the ExPosition package in R (Beaton et al., 2014). We chose this method because it permits a single analysis that captures the shared variance across the inputted measures to explain the majority of the covariance in the data. For this analysis, two matrices were created: one that represented each brain measure (the FD factors and clusters of brain activity) and one that represented cognition (global cognition via the SLUMS, memory accuracy, and premorbid IQ). 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 the brain factors that contributed to higher or lower cognition for each test. Correlations between the latent variable scores from each X and Y matrix were used to determine significance. Additional analyses were carried out including age group (younger vs. middle-aged/older) in the model to test that these relationships did not also occur for younger adults.

3. Results

3.1 Factor Analysis of Fractal Dimensionality Across All Regions of Interest

Among the middle-aged and older adults, a parallel factor analysis suggested two factors, which explained 29.0% and 13.0% of the variance for each factor. Factor loadings can be found in Figure 1 and Supplemental Table 1. Similar loadings were found in the young adult control group was included (Supplemental Table 2). For more details on the analyses, see Supplemental Material. The first factor loaded on neocortical brain regions with the highest loadings consisting of lateral frontal and parietal regions. The second factor loaded subcortical brain regions with the highest loadings consisting of the pallidum, caudate, and putamen. Occipital and orbitofrontal cortices had the lowest loadings across the two factors, which are sometimes found to be spared with age using other structural measures (e.g., Fjell et al., 2009; Raz et al., 2005). No clear pattern of laterality was observed. The two factors were moderately correlated with one another, r (61) = .37, p = .003).

3.2 Associations Between Fractal Dimensionality, Age, and Dementia Risk

For Factor 1 (neocortical structures), the Age x Dementia Risk interaction (p = .31) was not significant and so was removed from the analysis. In the next model, neither Age (p = .47) nor Dementia Risk (p = .36) were significant. None of the quadratic effects of Age, Dementia Risk, or their interaction were significant (*p's* > .48). When the young adult control group was included, age (b = -.029, SE = .006, p < .001) but not age^2 (p = .75) was significant. For Factor 2 (subcortical structures), the Age x Dementia Risk interaction (p = .46) was not significant and so was removed from the analysis. In the next model, Age was negatively related to FD (b = -.060, *SE* = .022, p = 0.0082), but Dementia Risk was not (p = .19). None of the quadratic effects of Age, Dementia Risk, or their interaction were significant (*p's* > .54). Steiger's Z-test revealed that the strengths of these two linear age effects were marginally different from one another (Z = 1.36, p = 0.091). When the young adult control group was included, age (b = -.033, SE = .006, p < .001) but not age^2 (p = .49) was significant. Together, the findings show that older age is associated with much lower cortical and subcortical FD than younger adults but when focusing on middle-aged and older adults, differences are only found for subcortical structures accompanied by no effects of AD risk (see Figure 2).

3.3 Associations Between Fractal Dimensionality and Brain Activity During Memory

To the extent that FD can be interpreted as a proxy for brain atrophy, lower FD should be associated with higher frontoparietal brain activity. In contrast to this prediction, neither Factor 1 nor Factor 2 were associated with frontoparietal brain regions during successful memory encoding. However, FD in the neocortex (Factor 1) was negatively associated with brain activity during memory retrieval in several posterior brain regions, including bilateral precuneus, right supplemental motor area, right paracentral lobule, and left inferior parietal lobule (see Table 2 and Figure 3). Of these regions, the largest cluster was in the precuneus, which is a major hub within the default mode network. No significant associations were found with FD in subcortical regions (Factor 2) nor were associations found for quadratic associations between FD and brain activity. Correlations between brain activity and cortical FD in young adults revealed no significant relationships (all *p*'s > .08, uncorrected) with three of the four clusters showing numerically positive relationships (ranging from *r*=.04 to .41). These non-significant relationships in the young control sample bolster the idea that the negative structure-function relationships are unique to middle-aged and older adults in which atrophy has started in some individuals.

Given the above null effects in the PFC among middle-aged and older adults, we conducted additional analyses to provide evidence for the null hypothesis using a Bayesian approach (see Figure 4). For structure-function relationships in the same hemisphere ROIs, the Bayes factor scores ranged from 0.052 to 1.19. Across both encoding and retrieval, 29 of the 44 (66%) ROIs showed moderate to strong evidence for the null hypothesis, 13 (30%) showed anecdotal evidence for the null hypothesis, and two showed anecdotal evidence for a negative structure-function relationship. The two regions that showed anecdotal evidence in favor of a negative structure-function relationship were the left pars triangularis during encoding (BF = 1.19) and the right pars opercularis during retrieval (BF = 1.07). For structure-function relationships in the contralateral hemisphere ROIs, the Bayes factor scores ranged from 0.064 to 0.92. Across both encoding and retrieval, 35 of the 44 (80%) ROIs showed moderate to strong evidence for the null hypothesis and 9 (20%) showed anecdotal evidence for the null hypothesis. These findings provide additional evidence against the atrophy-compensation hypothesis.

3.4 Associations Between Fractal Dimensionality, Brain Activity, and Cognition

Among middle-aged and older adults, the partial least squares analysis revealed two significant components (see Figure 5). The first latent variable explained 93.69% of the covariance among the variables, *r*(58)=.31, *p* =.017. This first latent variable revealed that that lower FD and higher brain activity during retrieval was associated with worse cognition across all of the cognitive measures. The second latent variable explained 4.91% of the covariance among the variables, $r(58)=.36$, $p=.0049$. This latent variable revealed that individuals with better word reading (premorbid IQ) revealed lower brain activity in the left inferior parietal lobule during retrieval. Note that removing the FD factors from the analysis (thereby removing the redundancy from the previous structure-function analysis) results in the same two factors. For nonlinear effects on cognition, see Supplemental Material. These results provide evidence that higher FD and the related lower levels of brain activity are associated with better cognition, with stronger effects for neocortical FD than subcortical FD in middle-aged and older adults. In contrast, the young adult group revealed only one significant latent variable that explained 86.25% of the covariance among the variables, $r(16)=.60$, $p=.009$, such that higher cortical FD and higher brain activity associated with better cognition with the caveat that brain activity overall did not strongly contribute to the model at all (see Supplemental Material). Given that the brain-activity-cognition relationships were largely in the opposite direction than that found in the older sample, these relationships are likely not due to natural individual differences that occur throughout the lifespan but are unique to the older sample.

Given this negative relationship with brain activity and cognition in the first latent variable in the older sample, we tested whether Simpson's Paradox might be at play (Cabeza et al., 2018). Assuming the atrophy-compensation hypothesis were correct, this paradox would predict that higher brain activity would be associated with higher cognition, but only for individuals with the greatest brain atrophy. In contrast, there might be no relationship (or a negative relationship) between brain activity and cognitive performance for those with the least atrophy. We tested this paradox by conducting a brain activity x brain atrophy interaction on cognitive performance. Of the three cognitive measures, only the word reading (i.e., premorbid IQ) evidenced interactions in the right paracentral lobule (interaction $p = .011$) and the right supplemental motor area (interaction $p = .024$). However, the interaction was in the opposite direction than that predicted by Simpson's Paradox (see Figure 6). In individuals with the most brain atrophy (lower cortical FD), higher brain activity was associated with poorer word reading scores. In individuals with the lowest brain atrophy (higher cortical FD), higher brain activity was associated with higher word reading scores.

4. Discussion

The present study revealed two separable patterns of FD, a measure of structural complexity. One pattern was more strongly associated with cortical structures and the other more strongly associated with subcortical structures. Replicating previous research, lower FD factor values were associated with advanced age (Madan & Kensinger, 2017a; Madan, 2019). However, we also found that among middle-aged and older adults, only subcortical FD was associated with age, indicating that cortical FD decreases earlier in the lifespan (i.e., middle age) whereas subcortical FD continues to decline into old age. In contrast to these age effects, no relationship between FD and dementia risk was found. Beyond characterizing these basic relationships with FD, we critically provided a novel test for the atrophy-compensation hypothesis, which serves as a key principle found in some current neurocognitive theories of aging (Cabeza, 2002; Greenwood, 2007; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). This hypothesis proposes that brain atrophy causes a compensatory neural response in the form of increased brain activity in PFC and LPC likely stemming from the recruitment of executive control functions during other cognitive tasks, including episodic memory. Although we did find support for the general notion that lower brain structure is associated with more brain activity uniquely in our older sample, most of these associations were not found within PFC and LPC. Instead, the majority of these negative associations were found in the medial parietal cortex, particularly in bilateral precuneus. Lastly, we found that this atrophy-compensation pattern was most dominantly associated with poorer cognition in middle-aged and older adults. Young adults did not reveal a strong relationship between brain activity and cognition in the same brain regions. We elaborate on the major findings in more detail below.

4.1 Differential Sensitivity of Fractal Dimensionality in the Aging Brain and Cognition

In an attempt to simplify the FD analyses, a factor analysis was conducted to find groups of brain regions that covaried together. We found two very clear patterns that separated FD into cortical and subcortical factors. These differences might be interpreted in several ways. One methodological interpretation is that the calculation for FD on volumetric shapes systematically differs from the calculation for gyri, potentially due to the different biomechanical constraints on the relative growth/cohesion of tissue in the respective regions. Given the qualitatively different shapes of the two, it should not be a surprise that analytical properties might differ as well.

Another interpretation is that the biological significance of these two sets of regions differs in meaningful ways, at least in the current sample. Consistent with this latter perspective, chronological age had a stronger association with FD in subcortical structures than cortical structures, but brain activity during memory retrieval and cognition had a stronger association with cortical structures than subcortical structures (as summarized in Figure 4). While not directly compared in past research, prior studies have generally found stronger correlations between age and subcortical FD than cortical FD (Madan & Kensinger, 2016, 2017a; Madan, 2019). These findings suggest that FD in cortical regions should be considered separately from FD in subcortical regions when trying to understand age differences in brain morphology.

Only two other studies to-date have related FD to cognition. The first did so in older adults with mild Alzheimer's disease and healthy controls (King et al., 2010). When collapsing across both groups, lower global cognition as measured by the ADAS-Cog was associated with lower FD scores in the neocortex (i.e. a positive relationship)—though only global cortical FD was examined; no regional parcellation was considered. More recently, Liu et al. (2020) examined longitudinal changes in FD in older adults aged 70-90 years old. This study also assessed FD and global cognition. In their analyses, they found lobe-wise cortical parcellations of FD were positively associated with global cognition in the temporal lobe, occipital lobe, and several subcortical structures. They further found that FD partially mediated age-related changes in global cognition declines, with many of the effects stronger than the mediating effects of cortical thickness. Extending these previous results, the present study shows that even in young and middle-aged adults, higher cortical FD is associated with better global cognition and other cognitive domains including premorbid IQ and associative memory.

4.2 Testing the Atrophy-Compensation Hypothesis

Madan and Kensinger (2016, 2018; Madan, 2019) showed that FD is more correlated with chronological age than traditional measures of structural indices captured by T1 MRIs, including volume, cortical thickness, and gyrification. Similarly, FD can better distinguish between older adults with mild Alzheimer's disease than healthy controls compared with cortical thickness and gyrification indices (King et al., 2010). More recent studies have demonstrated age-related decreases in FD longitudinally as well (Liu et al., 2020; Madan, 2020).

With this idea in mind, we tested the extent that using FD in conjunction with measures of brain activity could provide evidence for the hypothesis that lower brain integrity causes a compensatory neural response in the form of higher brain activity in PFC and LPC (i.e., the atrophy-compensation hypothesis). We focused this analysis on middle-aged and older adults who would have the most likely of presenting with variable degrees of atrophy. Notably, the first FD factor most highly loaded onto PFC and LPC, thus providing a strong test for this hypothesis. We found no evidence for such associations during memory encoding and found only small evidence in support of this hypothesis during memory retrieval. Although several parietal regions evidenced this inverse relationship in our middle-aged and older adult sample (and not the young adult controls), only one small cluster in the LPC was negatively associated with the cortical FD factor. However, given the small size of the cluster and that most studies emphasize the role of the PFC, specifically, in such compensatory processes, this finding does not provide strong support for the atrophy-compensation hypothesis. Bayesian analyses directly targeting a negative structure-function relationship in the PFC provided moderate to strong evidence in nearly every ROI for an absence of such a relationship. Thus, the present findings add to an already mixed literature against a strict interpretation of the atrophy-compensation hypothesis (e.g., Brassen et al., 2009; Pudas et al., 2013; Rajah et al., 2011).

At least in the current paradigm, the present findings suggest that neural compensation may not always occur in the PFC and LPC. One possibility is that the PFC is less flexibly used in the presence of atrophy than expected. Intervention studies can provide causal evidence of the role that the PFC might play in compensating for cognitive abilities. McDonough et al. (2015) tested whether challenging activities over a 14-week period would increase the engagement of frontal-parietal brain regions involved in initiating and sustaining effortful cognitive processes. In contrast to predictions, only a small portion of the precentral gyrus (near the frontal eye fields) showed increased brain activity after the intervention, which did not differ from the active control groups. Instead, mid-cingulate cortex, medial parietal cortex and LPC showed reliable increases in activity after the intervention that differed from the control groups. The findings from this intervention are quite consistent with the present study and offer some preliminary evidence that lateral PFC may not always be the primary source of neural compensation.

Another possibility is that neural compensation might occur anywhere near the site of the atrophy. For example, Daselaar et al. (2013) found that older adults with poorer white matter integrity in the PFC had higher brain activity in a nearby gray matter region whereas those with poorer white matter integrity in the medial temporal lobe (MTL) had higher brain activity in a nearby gray matter region. The impact on cognition from this more generic pattern of “less wiring, more firing” was specific to the brain regions involved. They found that the stronger atrophy-compensation relationship in the PFC was associated with poorer executive function whereas the stronger atrophy-compensation in the MTL was associated with poorer memory function. These authors argued that older adults successfully compensated for the brain atrophy because brain activity was defined as correct memory relative to incorrect memory and rejected the notion that successful compensation should be defined by inter-individual differences (cf. Wang & Cabeza, 2016). Our findings are more aligned with this perspective because the cortical FD factor loaded highly on the parietal cortex, which was the site that a negative association was found. Additionally, our results can be interpreted as successful compensation for two reasons. First, lower cortical FD was associated with higher correct than incorrect brain activity, thereby associating this pattern with successful memory performance. Second, this structure-function pattern was unique to middle-aged and older adults; young adults did not demonstrate these relationships, which would be expected if older, but not younger adults needed to engage in compensatory processes. Given that lateral and medial parietal cortices often are recruited during memory retrieval (e.g., Rugg & Vilberg, 2013; Spaniol et al., 2009) in young adults, the type of compensation would be categorized as upregulation because the same regions used in younger adults are being upregulated in this sample (Cabeza et al., 2018).

Although our findings might be interpreted as successful compensation, not all researchers agree on how to characterize compensation. Many researchers believe that higher brain activity should be considered compensatory if higher activity were positively associated with individual differences in cognition (Cabeza et al., 2018). In the current study, we found that individuals who recruited more brain activity were *less* likely to remember correct associations, overall. From this inter-individual differences perspective, the present findings provide behavioral evidence for brain dysfunction such as neural inefficiency (e.g., McDonough et al., 2013) or even neural toxicity (Pasquini et al., 2019).

These two perspectives might be reconciled by considering the effects of both the latent variables from the PLS-R analysis. Given that inter-individual differences often are larger and can mask intra-individual differences (Aguirre et al., 1998; Leontiev, & Buxton, 2007), one might consider the first latent variable as representing such large inter-individual differences and the second latent variable as representing the residual intra-individual differences. Thus, the present findings might be interpreted such that middle-aged and older adults with higher lifelong cognition (estimated across the three cognitive measures) have generally a) higher structural complexity and b) more efficient (i.e., lower) brain activity. This interpretation is consistent with theories of brain maintenance (Cabeza et al., 2018; Nyberg et al., 2012) in which those adults that are able to maintain high structural and functional integrity also are able to maintain high levels of cognition. A related interpretation is that these individual differences are related to traits stable across the adult lifespan. However, the second latent variable dissociates premorbid IQ and fMRI memory accuracy. Thus, in the context of the specific memory retrieval task, higher structural complexity in the neocortex and higher fMRI activity in the left inferior parietal lobule is associated with better memory performance. This positive (rather than negative) association between the three modalities (structure, function, and cognition) would be predicted by attentional theories of memory (Cabeza et al., 2008; Ciaramelli et al., 2008). Note that, in the second latent variable, brain activity in the precuneus did not contribute to fMRI performance (as inferred by the centroid being close to the center of the y-axis). In fact, the part of the precuneus implicated in this study is more dorsal than that found in many prior memory studies (e.g., Spaniol et al., 2009; Gilmore et al., 2015; Huijbers et al., 2012), and instead might be associated with other cognitive processes (Power et al., 2011; Yeo et al., 2011). Regardless of the role that this part of the precuneus might play in memory retrieval, the PLS-R analysis might be able to offer a new perspective that accounts for how structure-function relationships can be both positively and negatively related to cognition. Although the middle-aged and older adult sample provide support for this new perspective, the control analyses in younger adults only partly support this view. In younger adults, higher cortical structural complexity was associated with better cognition, but these patterns were not associated with “more efficient” brain activity, thus questioning whether the all of the individual differences in the first latent variable were due to lifelong relationships between brain activity and cognition.

4.3 Strengths and Limitations

One large difference between this study and the other studies investigating fMRI is that we calibrated the BOLD signal in each individual. Most older adults, and especially those with poorer health associated with dementia risks, have changes in brain vasculature that can cause alterations of the BOLD signal and lead to both false positives and false negatives (for review see, Wright, & Wise, 2018). We calibrated the BOLD signal in two practical ways: we used a subject-specific HRF and scaled the contrasts using RSFA analyses. At least some prior claims of higher frontally-based activity might be due to vascular alterations rather than neural differences, possibly explaining why we failed to find evidence for the atrophy-compensation hypothesis in the PFC. The present study also tested the atrophy-compensation hypothesis during both memory encoding and retrieval, which offered two different tests of the hypothesis, albeit only within an episodic memory paradigm. Lastly, the atrophy-compensation hypothesis is most relevant to aging adults who might be experiencing atrophy and so any relationships found should not also be found in healthy young adults—who would not be experiencing atrophy and therefore would not need to recruit compensatory mechanisms. We demonstrated that structure-function-cognition relationships were not found in younger adults.

These strengths were accompanied by limitations. The most pressing limitation is the cross-sectional nature of the sample that precluded longitudinal measures of atrophy. Thus, our measure of structural complexity (FD) is best considered a combination of lifelong brain complexity mixed with longitudinal changes in complexity. As FD has only recently been used to study aging, it has only very recently been examined in longitudinal studies (Liu et al., 2020; Madan, 2020), and even then, comparisons with other markers of atrophy need to be explored further. Relatedly, we cannot tease apart the causal direction of our structure-function relationships. For example, the Scaffolding Theory of Cognitive Aging (STAC; Park & Reuter-

Lorenz, 2009) initially proposed that structural changes caused functional changes, but was later revised in STAC-R (Reuter-Lorenz & Park, 2014) to have bidirectional influences, opening the possibility that earlier changes in brain function might cause structural changes. From this perspective, subtle changes in synaptic functioning as measured by fMRI might be detected earlier than the larger synaptic alterations sensitive to T1 MRI scans (Mondadori et al., 2006; Mosconi et al., 2007). Another limitation is that the sample did not contain adults 75 years of age or older, thus providing sensitivity only for early alterations in brain structure and function and cannot speak to “old-old” samples (e.g., Song et al., 2016).

We argue that the present failure to find even moderates negative structure-function relationships in the PFC is consistent with the weak existing evidence for the atrophy-compensation hypothesis using other measures of brain structure that we outlined in the Introduction. However, our test is limited by the specific episodic memory task and contrasts employed. On the one hand, many of the theoretical perspectives that include an atrophy-compensation principle are agnostic to the actual task or cognitive domain used. These theories propose that older adults need to recruit executive function processes regardless of the original task (e.g., original processes + executive function). On the other hand, had a different task been used, the specific brain regions that showed significant relationships between FD and brain activity likely would have differed, thereby revealing other relationships. Having said that, using an episodic memory task is critical because older adults consistently show poorer associative episodic memory and studies investigating age-related differences in episodic memory often invoke the notion of neural compensation, thus providing an important context in which to test these ideas.

5. Conclusions

The present study highlights an understudied analysis of brain structure, FD, that has promise to reveal new insights into morphological brain differences in the aging process. Using FD, we tested a key principle in some cognitive neuroscience theories of aging: lower brain structure should be associated with higher brain activity in nearby or contralateral brain regions, especially in the PFC. We found the predicted negative associations that were unique to middle-aged and older adults, but not in the PFC. The null results in the PFC were supported by Bayes Factor evidence values. Therefore, this study provides a growing body of evidence that contributes to the falsification of the standard atrophy-compensation hypothesis. The past decade has been accompanied by the generation of multiple neurocognitive theories of aging. Many have been quite influential in shaping the aging narrative in the field, but it has been difficult to provide falsifiable evidence for any of these theories. Indeed, the failure to find such relationships have been attributed to lacking insufficient variability or lacking statistical power (Reuter-Lorenz & Cappell, 2008). Even evidence showing the opposite than expected relationship has been attributed to Simpson's paradox, suggesting that the direction of the relationship at the population level may be different from the direction at the level of subgroup or individual (see Cabeza et al., 2018). At least in the current study, we found strong evidence against Simpson's paradox. To the extent that future studies also fail to find atrophy-compensations associated with the PFC as in the present study, these cognitive aging theories would need to be refined.

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Table 1. Participant Characteristics.

	Older	**Younger**
	M (SD) or N (%)	**M (SD) or N (%)**
N[a]	63	18
Mean Age	60.19 (6.78)	23.22 (3.04)
Sex (Female)	41 (65%)	10 (56%)
Race (Non-Hispanic White)	40 (63%)	11 (61%)
Years of Education	14.00 (2.81)	14.89 (2.19)
Dementia Risk Score	4.44 (1.80)	-
SLUMS	26.46 (2.86)	-
Premorbid Intelligence	101.30 (17.63)	107.61 (10.73)
fMRI Memory Accuracy %[a]	.34 (.12)	.57 (.08)

Notes. SLUMS = St. Louis University Mental Status; [a]fMRI data from 3 participants were unavailable due to in-scanner movement or artifact; Young adults were not asked for dementia risk information nor were given the SLUMS.

Table 2. MNI coordinates for association between fractal dimensionality and brain activity during memory retrieval (correct > incorrect)

MNI Coordinates						
x	y	z	Region	BA	T-Value	Cluster size
-28	-79	46	Left Inferior Parietal Lobule	7	4.74	11
7	-46	69	Bilateral Precuneus	7	4.44	83
8	-15	64	Right Supplemental Motor Area	6	4.22	11
11	-24	73	Right Paracentral Lobule	6	4.01	55

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

Figure 1. Factor loadings plotted on the cortical surface and subcortical parcellations.

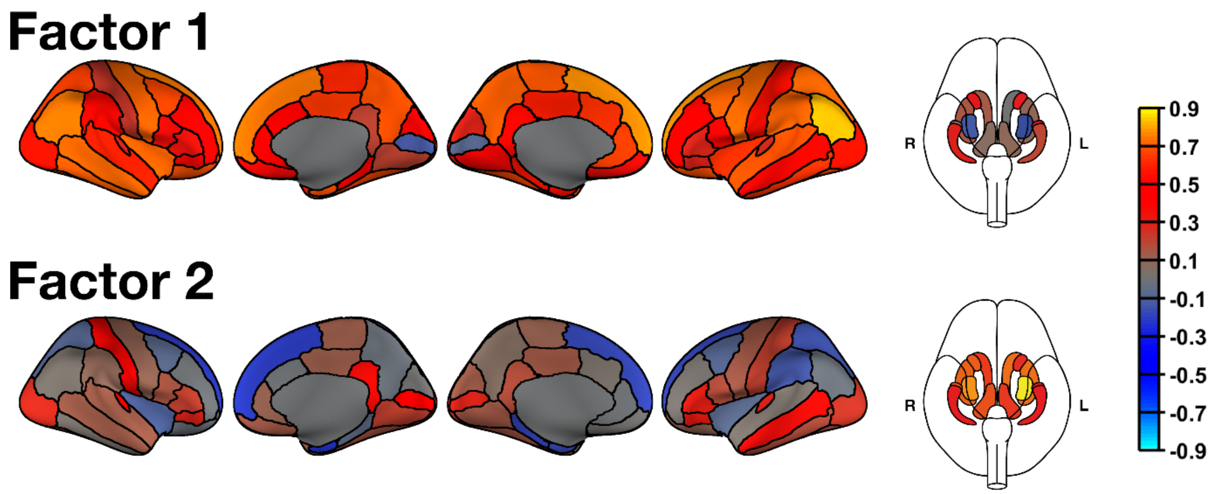

Figure 2. Scatterplots illustrating the relationship between chronological age (x-axis) and fractal dimensionality (y-axis) for the first factor that represented fractal dimensionality in neocortex structures (upper panel) and the second factor that represented fractal dimensionality in subcortical structures (lower panel). In the middle-aged and older adult sample, only Factor 2 revealed a significant relationship with age (*r* = -.29, 95% CI [-0.54, -0.05]). However, when young adults were included in the models, both showed strong associations with age (*r* = -.49, 95% CI [-0.69, -0.30] for Factor 1 and *r* = -.56, 95% CI [-0.74, -0.37] for Factor 2). Blue lines represent a linear fit and the purple lines represent a non-linear fit with 95% confidence intervals in gray.

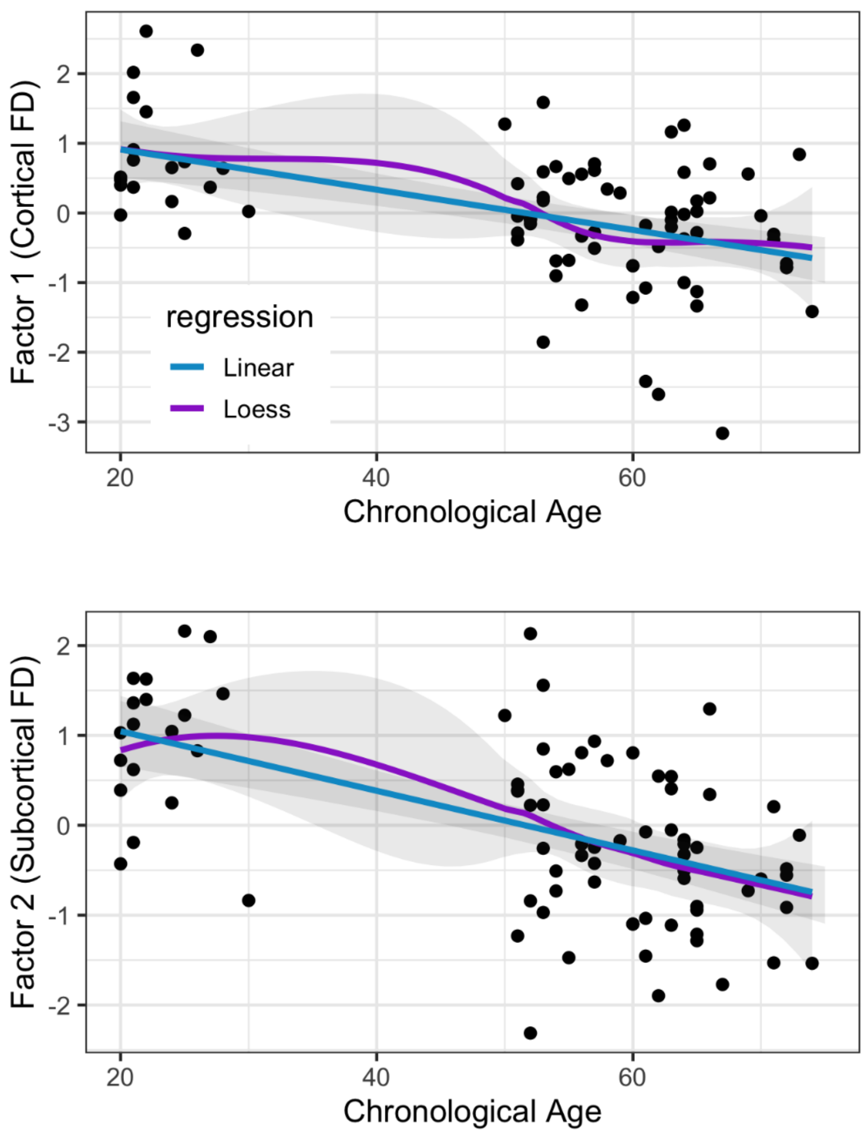

Figure 3. Depiction of the negative association between fractal dimensionality in the neocortex (Factor 1) and successful memory retrieval on the cortical surface. Scatterplots are shown in either side of the images with cortical FD on the x-axis and change in BOLD signal on the y-axis. The scatterplot inset in the upper left corner for the left inferior parietal lobule shows plot without the circled outlier (*r* = -0.43 , p-value = 0.00060). Note that the left inferior parietal lobule was significant, but is not clearly shown in the surface rendering. FD = fractal dimensionality; L = left; R = right.

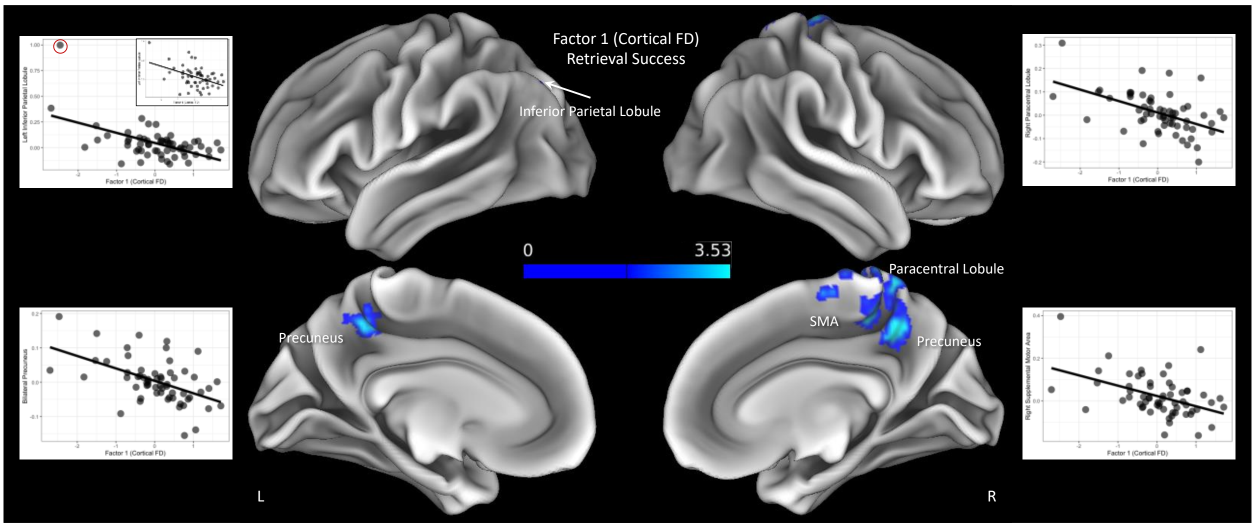

Figure 4. Results from the Bayes correlation analysis between FD and brain activity showing a brain map of Bayes factor scores within prefrontal cortex regions of interest (ROIs) for memory encoding (left) and memory retrieval (right) in the same hemisphere (top) and the contralateral hemisphere (bottom). Bayes factor scores approaching 0 (from gray to red to yellow) indicate evidence for the null hypothesis (a negative structure-function relationship does not exist) whereas values greater than 1 (in blue) show anecdotal (i.e., weak) evidence for a negative association. The majority of the ROIs showed moderate to strong evidence for the null hypothesis whereas one-quarter of the ROIs showed anecdotal evidence for the null hypothesis and only 2% of the ROIs showed anecdotal evidence for a negative-structure function relationship.

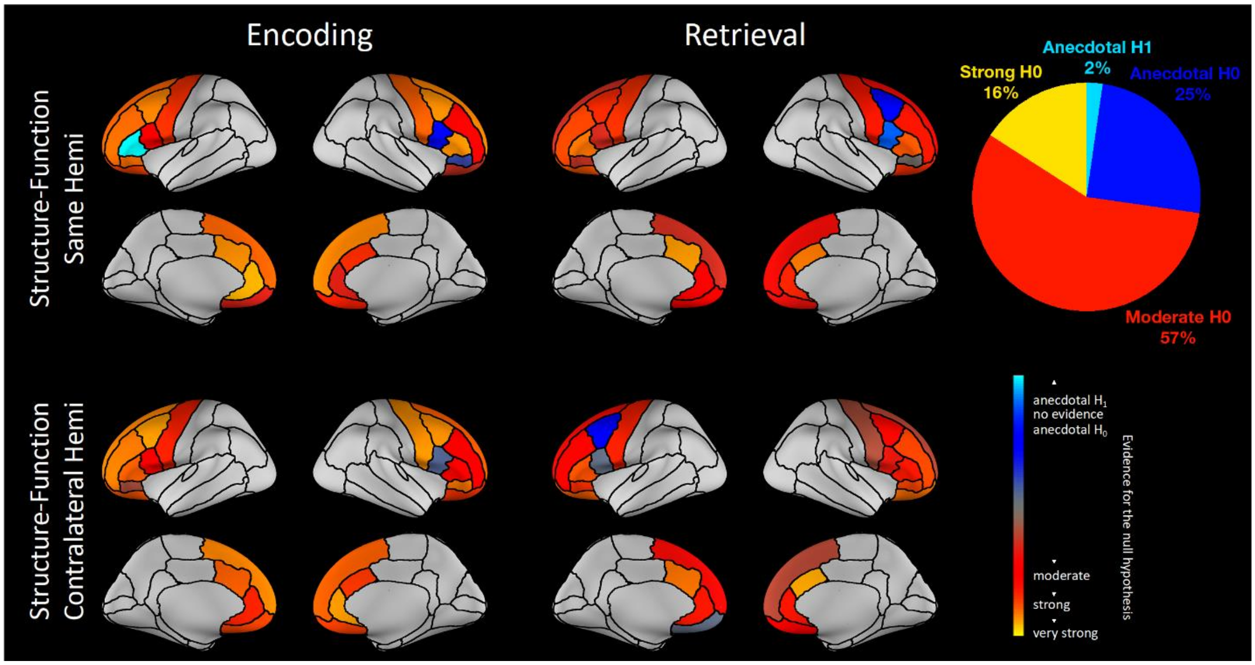

Figure 5. Scatterplots showing the results of the partial least squares regression analyses assessing the association between brain measures and cognitive measures. The left panel shows how the brain measures are expressed across the first latent variable (x-axis) and the second latent variable (y-axis). 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 right panel shows how the cognitive measures are expressed across the first latent variable (x-axis) and the second latent variable (y- axis). Latent variable 1 shows that lower FD values and higher retrieval-related activity were associated with poorer cognition. Latent variable 2 shows that lower brain activity in the left parietal cortex was associated with better word reading ability (i.e., premorbid IQ) and lower memory accuracy. RSMA = right supplemental motor area; RPARACEN = right paracentral lobule; RPREC = right precuneus; LIPL = left inferior parietal lobule; SLUMS = St. Louis University Mental Status.

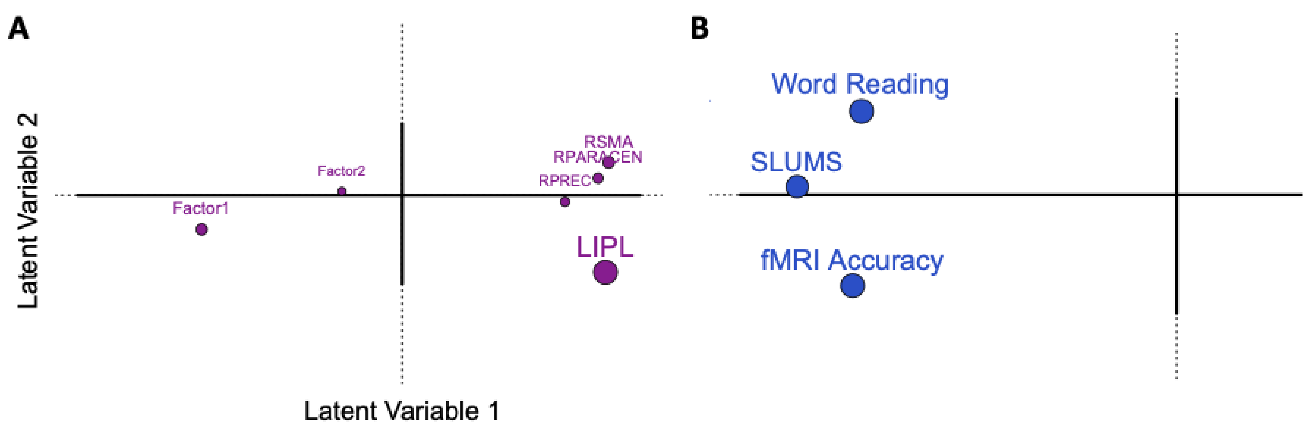

Figure 6. Marginal means plots testing whether brain activity-cognition relationships differed between those with low atrophy (high fractal dimensionality) in blue, average atrophy in green, and high atrophy (low fractal dimensionality) in red. The left panel shows the significant brain structure x brain activity interaction in the right paracentral lobule and the right panel shows the significant interaction in the right supplemental motor area. For both regions, higher brain activity was associated with poorer word reading (i.e., premorbid IQ) in adults with higher atrophy whereas higher brain activity was associated with better word reading in adults with lower atrophy. The gray areas represent 95% confidence intervals.