Multiple Brain Markers are Linked to Age-Related Variation in Cognition

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Age-related alterations in brain structure and function have been challenging to link to cognition due to potential overlapping influences of multiple neurobiological cascades. We examined multiple brain markers associated with age-related variation in cognition. Clinically normal older humans aged 65–90 from the Harvard Aging Brain Study (*N* = 186) were characterized on a priori magnetic resonance imaging markers of gray matter thickness and volume, white matter hyperintensities, fractional anisotropy (FA), resting-state functional connectivity, positron emission tomography markers of glucose metabolism and amyloid burden, and cognitive factors of processing speed, executive function, and episodic memory. Partial correlation and mediation analyses estimated age-related variance in cognition shared with individual brain markers and unique to each marker. The largest relationships linked FA and striatum volume to processing speed and executive function, and hippocampal volume to episodic memory. Of the age-related variance in cognition, 70–80% was accounted for by combining all brain markers (but only ~20% of total variance). Age had significant indirect effects on cognition via brain markers, with significant markers varying across cognitive domains. These results suggest that most age-related variation in cognition is shared among multiple brain markers, but potential specificity between some brain markers and cognitive domains motivates additional study of age-related markers of neural health.

Keywords: aging, amyloid, executive function, memory, white matter

Introduction

Many structural and functional alterations have been documented in the aging brain, impacting different neural systems linked to one or more cognitive domains (Cabeza et al. 2004; Grady 2008; Raz and Kennedy 2009; Salthouse 2011). These results raise the possibility of early differentiation of cognitive alterations associated with aging itself from those associated with common age-related neurodegenerative disorders (Jagust 2013). One challenge is that multiple neurological cascades impacting cognition may develop independently, but likely co-occur or have synergistic effects within an individual (Buckner 2004; Hedden and Gabrieli 2004). Here, we explore how indirect markers of brain aging and neurodegeneration in isolation and in combination provide insight into cognitive alterations in healthy older adults.

An example of the complex interactions between multiple brain markers and function can be seen in that ~30% of clinically normal older adults aged 70+ may be in a preclinical stage of Alzheimer's disease (AD; Sperling et al. 2011; Jack, Knopman et al. 2013) without any cognitive symptoms (Price and Morris 1999; Bennett et al. 2006). It is likely that a conjunction of amyloid pathology and neurodegeneration is required before clinically relevant deficits in cognition emerge (Mormino et al. 2009, 2014; Rowe et al. 2010; Jack, Wiste et al. 2013). In the 70% lacking substantial amyloid burden, many nonetheless exhibit evidence of neurodegeneration (including on measures of anatomy, functional connectivity, white matter integrity, and glucose metabolism) accompanied by subtle deficits in cognition (Andrews-Hanna et al. 2007; Fjell et al. 2013, 2014; Jack, Wiste et al. 2013; Wirth et al. 2013). Likely contributing to the complexity of the patterns is that each neurological alteration resides on a continuum only partially revealed by existing techniques, and that manifestation of more than one marker in an individual may have an outsized impact (Jagust 2013).

One approach to this problem has been to separate clinically normal individuals into those with and without putative markers of preclinical neurodegenerative disease (e.g., amyloid burden associated with AD). However, this technique generally isolates one factor that may or may not be causative in an individual's progressive neurodegeneration, when in all likelihood, multiple interacting factors, both detrimental and protective, will determine the course of an individual's progression or stability. Furthermore, it does not consider that individuals who do not exceed a methodologically specific threshold on a given marker may nonetheless possess the marker at a subthreshold level, or may otherwise be on a course for clinical progression. Finally, by separating and comparing those with and without a neurodegenerative biomarker, an assumption is made that the relationship between other brain markers and cognition will be altered in the presence of the neurodegenerative biomarker.

An alternative approach, taken here, is to examine to what extent markers of neurodegenerative disease share or add to the explained age-related variation in cognition in the context of other putative brain markers of developmental aging. This approach treats individuals as simultaneously experiencing the impact of multiple facets of brain aging on their cognition, while leaving open the possibility that neurodegenerative biomarkers have a uniquely additive effect on cognitive variation or perhaps accelerate the impact of other brain markers on cognition.

Although both approaches have merits, we focus on the latter approach because it maximizes power by using the full dataset to examine our primary question of interest regarding

the relationship between brain markers and the age-related variation in cognition. There are likely to be relationships between neurodegenerative biomarkers and cognition that are independent from the age-related variation, but such relationships are not a focus of the present report.

Because many issues are raised in attempting to disentangle the age-related contributions of different brain markers to cognition, we focused on a specific question, namely: *How much of the age-related variation in cognition among clinically normal older adults is shared with one or more brain markers of structure, function, or pathology?* Our approach was to select in advance, based on prior reviews (Buckner 2004; Hedden and Gabrieli 2004; Raz and Kennedy 2009; Salat 2011; Salthouse 2011; Bennett and Madden 2013; Fjell et al. 2013; Jagust 2013), a set of brain markers that were a priori likely to relate to both age and cognition (without specific examination of these relationships in our current dataset), and covered multiple aspects of brain structure and function. We focused on brain markers that were theoretically linked to the cognitive domains of processing speed (white matter integrity), executive function (striatum volume, white matter integrity, and connectivity in a frontoparietal network), episodic memory (medial temporal lobe volume and connectivity in the default network [DN]), or to all of these domains (cortical thickness). Because a secondary goal was to examine the potential additive impact of neuropathological cascades on age-related cognitive variation, we included a set of brain markers that provide potential indices of preclinical AD (amyloid burden and glucose metabolism) or cerebrovascular disease (white

matter lesions), 2 common neurodegenerative disorders in aging hypothesized to have differential impacts across these cognitive domains. For each marker, we had hypotheses about the direction of relationships to age and cognition, and whether the marker would exhibit domain-specific or domain-general associations with cognition (hypotheses are detailed with the description of each brain marker). We examined the shared and unique age-related variance in cognition associated with each brain marker, and performed mediation analyses. We provide data relevant to alternative models and to brain–cognition relationships controlling for age, but our hypothesis-driven approach focuses on the likelihood that brain markers assessed in combination mediate age–cognition relationships (Salthouse 2011). We note that this analysis is directed at testing brain markers identified a priori as likely mediators of age-related variation in cognition whether that variation is specifically driven by developmental processes or by age-associated neuropathology, and was not designed to discover novel brain markers that may mediate additional age-related variance.

Methods

Sample Characteristics

Neuropsychological testing and neuroimaging (Fig. 1) was conducted on 186 (105 female) clinically normal, community-dwelling older adults (aged 65–90, $M = 73.8$, $SD = 6.0$). These individuals are participants in the Harvard Aging Brain Study, an on-going longitudinal study currently in the baseline assessment phase. Participants were generally well-educated (years of education: $M = 15.8$, $SD = 2.9$) with high estimated verbal intelligence ($M = 119.9$, $SD = 9.3$) and high
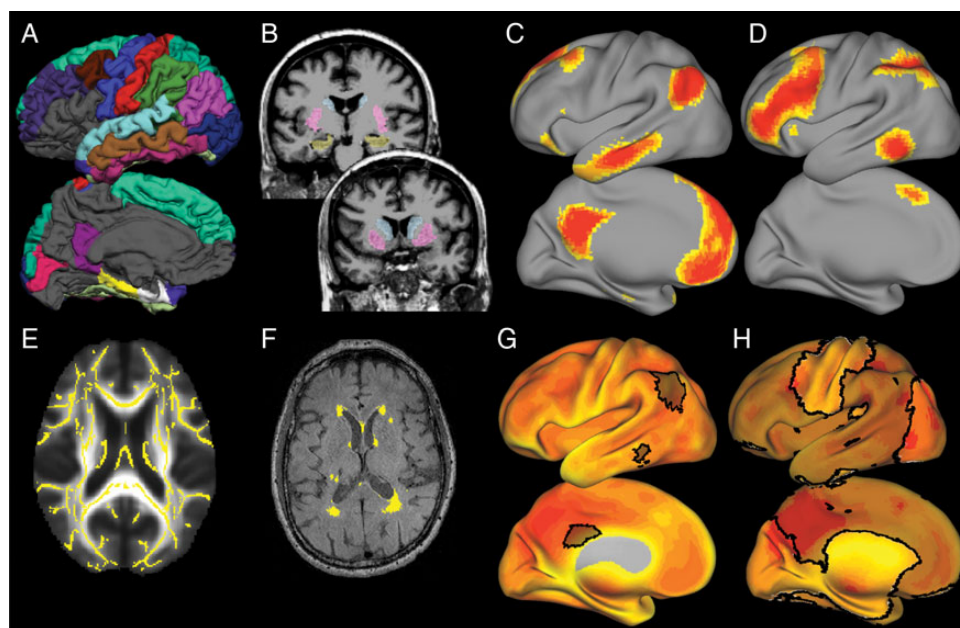

Figure 1. Neuroimaging methods. (*A*) Cortical thickness measures extracted from FreeSurfer-defined regions for parahippocampal gyrus (yellow), entorhinal cortex (white), and a set of cortical regions (all other colors) chosen from a prior study (Fjell et al. 2013). Regions are overlaid on an example subject's surface map. (*B*) Volume measures extracted from FreeSurfer-defined regions for hippocampus (green), and striatum averaged across caudate (blue) and putamen (pink). Volume measures were corrected for estimated total intracranial volume, and are overlaid on an example subject's brain. (*C*) Functional connectivity measure for the DN. (*D*) Functional connectivity measure for the frontoparietal network. Connectivity measures were averaged across all voxels in each displayed network template defined from an independent dataset, and are displayed on a surface map in atlas space. (*E*) Diffusion tensor imaging measure of FA extracted from a mask of the mean FA skeleton (yellow), overlaid on the group average FA map. (*F*) White matter hyperintensity volumes extracted using an automated algorithm in each individual subject. Regions labeled as hyperintensities (yellow) are displayed for an example subject. (*G*) Fluorodeoxyglucose (FDG) SUVR values extracted from a composite set of regions (gray) defined from a previous study (Landau et al. 2011). Regions are overlaid on data from an example subject and projected to a surface map in atlas space. (*H*) Pittsburgh Compound-B (PIB) DVR values extracted from a composite set of regions (gray) defined in previous studies using independent datasets (Hedden et al. 2009; Hedden, Van Dijk et al. 2012). Regions are overlaid on data from an example subject and projected to a surface map in atlas space.

socioeconomic status ($M = 29.0$, SD = 15.5—the scale ranges from 11–77 with lower scores indicating higher status (Hollingshead 1957). All participants had a Clinical Dementia Rating (CDR) of 0 (Morris 1993), performed no worse than 1.5 SD units below the age- and education-corrected norm on the Logical Memory IIa subtest of the Wechsler Memory Scale-Revised (Wechsler 1987), and scored 26 or above on the Mini-Mental State Examination (Folstein et al. 1975). Participants were excluded if previously diagnosed with a neurological or psychiatric condition or if they scored >11 on the Geriatric Depression Scale (Yesavage et al. 1983). Participants provided informed consent in accordance with protocols approved by the Partners Healthcare Inc. Institutional Review Board. Because of the staged nature of the visits (all baseline visits must be completed within 6 months), only subjects with completed imaging data from all modalities were included. All cognitive and imaging variables were screened for normality of the distribution prior to analysis and transformed (as described below) if necessary. This is a superset of the Harvard Aging Brain sample reported previously (Hedden, Mormino et al. 2012).

Neuropsychological Factors
A description of neuropsychological tests and the derivation of factor scores have been previously published (Hedden, Mormino et al. 2012). The factor weightings from that report were used to compute cognitive factor scores for executive function, episodic memory, and processing speed. Factor scores were not computed for processing speed for 2 participants and for executive function for 1 participant due to missing data. Subfactors of executive function were not examined to limit the number of tests conducted on correlated factors.

Volume and Cortical Thickness Analyses
Magnetic resonance imaging (MRI) scans were conducted on a Siemens TrioTIM 3-Tesla scanner (Siemens, Erlangen, Germany) equipped with the vendor-supplied 12-channel phased-array whole-head coil. High-resolution 3D T_1-weighted multiecho magnetization prepared rapid acquisition gradient-echo anatomical images were collected with the following parameters: time repetition (TR) = 2200 ms, multiecho time echoes (TEs) = 1.54, 3.36, 5.18, and 7 ms, flip angle = 7°, 4× acceleration, $1.2 \times 1.2 \times 1.2$ mm voxels and processed with FreeSurfer 5.1 (http://surfer.nmr.mgh.harvard.edu) using the default processing stream, from which standardized estimates of regional cortical thickness, volume of subcortical structures, and estimated total intracranial volume were computed. Volume measures were hypothesized to be negatively associated with age and positively associated with cognition. Because of the importance of medial temporal lobe structures to memory, we selected a priori measures of volume of the hippocampus and thickness from entorhinal cortex and parahippocampal cortex. Volume of the striatum (average of putamen and caudate) was selected for its association with age (Raz et al. 2003), and the potential link of these structures to processing speed and executive function (Kennedy and Raz 2005; de Jong et al. 2012). Volume measures were averaged across left and right hemisphere estimates and corrected for estimated total intracranial volume via regression before entry into the statistical models (Buckner et al. 2004). Thickness in cortical regions was computed using the standard FreeSurfer parcellation (Desikan et al. 2006). All cortical regions reported in Tables 2 and 3 from Fjell et al. (2013) as simultaneously having a significant cross-sectional age correlation from the 60–94-year-old sample ($N = 367$, their Table 3), having a significant longitudinal annual atrophy estimate ($N = 207$, their Table 3), and not exhibiting a significant nonlinear age trajectory (their Table 2) were selected. Mean thickness was computed for each subject from the aggregate of these regions. Included regions were left and right hemisphere for the isthmus of the cingulate gyrus, superior frontal gyrus, caudal middle frontal gyrus, rostral middle frontal gyrus, precentral gyrus, postcentral gyrus, supramarginal gyrus, superior parietal lobule, inferior parietal lobule, temporal pole, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, banks of the superior temporal sulcus, fusiform gyrus, lateral occipital cortex, and the cuneus. Although the parahippocampal gyrus met these criteria, it was examined as a separate region because of its role in the medial temporal lobe memory system (along with entorhinal cortex and the hippocampus). Because cortical thickness in large neocortical regions

is highly related to mean cortical thickness, we did not examine separate associations of specific neocortical regions. Cortical thickness was hypothesized to be negatively associated with age and positively associated with cognition. Because this measure of cortical thickness covers much of the neocortex, we hypothesized an association with cognition that was not domain-specific.

Functional Connectivity Analyses
Data for functional connectivity analysis were acquired using a gradient-echo echo-planar pulse sequence sensitive to blood oxygen level-dependent contrast using the following parameters: TR = 3000 ms, TE = 30 ms, flip angle = 85°, $3.0 \times 3.0 \times 3.0$ mm voxels. Forty-seven transverse slices aligned to the anterior commissure-posterior commissure plane covered the whole brain, and were acquired for 124 timepoints in each of 2 runs. Participants were instructed to lie still and remain awake with eyes open during each run. The first 4 timepoints of each run were discarded to allow for T_1-equilibration effects. Resting-state data were processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/; version r4290). Each run was slice-time corrected, realigned to the first volume of each run with INRIAlign (http://www-sop.inria.fr/epidaure/software/INRIAlign/; Freire and Mangin 2001), normalized to the MNI 152 EPI template (Montreal Neurological Institute, Montreal, Canada), and smoothed with a 6-mm full-width at half-maximum Gaussian kernel. Following these standard preprocessing steps, additional processing known to be beneficial for functional connectivity MRI (fcMRI) analysis was conducted including (1) regression of realignment parameters (plus first derivatives) to reduce movement artifacts on connectivity and (2) temporal band-pass filtering (second order Butterworth filter) to focus the analysis on frequencies in the 0.01–0.08 Hz band. Runs were discarded from further analysis if any one of the following quality assessment conditions were met: lower than a threshold of 115 for signal-to-noise ratio, higher than a threshold of 0.2 mm for mean movement, or >20 outlier volumes (defined as a change in the global signal > 2.5 SD attributable to the volume, a change in position >0.75 mm or a change in rotation >1.5° from the previous volume). Ten (5.4%) of the included participants had one run discarded for these reasons.

Functional connectivity estimates were derived using the Template Based Rotation method (detailed in Schultz et al. 2014). Briefly, this method maps the variance in each functional run onto a set of network templates derived from a reference dataset (here, the 675 participant dataset described in Schultz et al., 2014, resulting in 20 component templates including global, white matter, cerebrospinal fluid, and other nuisance components). This method has the advantage of allowing computation of individual estimates of connectivity within a set of networks whose topography has been defined in advance on a reference dataset. On an a priori theoretical basis, we examined only those network templates corresponding to the DN and the frontoparietal control network (FPCN). In the reference dataset, the FPCN is represented by 2 templates, consisting of the left and right hemisphere regions of the FPCN. We averaged the resulting estimates from these 2 FPCN templates to compute a single estimate of FPCN connectivity. For the DN and FPCN, connectivity estimates were derived corresponding to the average correlation of all voxels identified as associated with that network in the reference dataset; this measure represents an individual's overall connectivity within a network template. To account for remaining differences due to data quality, functional connectivity estimates from each network were corrected for associations with the across-run average for signal-to-noise ratio, mean movement, and number of outlier volumes via regression before entry into the statistical models. Connectivity measures were hypothesized to be negatively related to age and positively related to cognition. We hypothesized that connectivity in the FPCN would be preferentially related to executive function and connectivity in the DN would be preferentially related to episodic memory. However, because connectivity strength has been found to be related to multiple cognitive domains (Andrews-Hanna et al. 2007), we anticipated that domain-general effects may also be evident.

Diffusion Tensor Imaging Analyses
Diffusion tensor imaging (DTI) data were collected with the following parameters: TR = 8040 ms, TE = 84 ms, time to inversion (TI) = 2100

ms, $2 \times 2 \times 2$ mm voxels, 64 transverse slices, b-value $= 700$ s/mm^2, 30 diffusion directions, 2× acceleration, and processed using TBSS (Tract-Based Spatial Statistics; Smith et al. 2006), including eddy-current correction, computation of fractional anisotropy (FA) images by fitting a tensor model, and alignment into standard space ($1 \times 1 \times 1$ mm MNI152) with nonlinear registration. After alignment to standard space, the average FA value was extracted from the full mask of the standard FSL FMRIB58 white matter skeleton (Fig. 1E), a high-resolution average of 58 good quality FA images from healthy male and female subjects aged between 20 and 50, applied to each subject. FA was hypothesized to be negatively related to age and positively related to cognition. Although this mask represents a global measure of FA, based on meta-analytic data (Gunning-Dixon and Raz 2000; Oosterman et al. 2004), we hypothesized that it would be primarily related to processing speed and executive function.

White Matter Hyperintensity Analyses

Fluid attenuation inversion recovery (FLAIR) images for visualization of white matter lesions were collected with the following parameters: TR = 6000 ms, TE = 454 ms, TI = 2100 ms, $1 \times 1 \times 1.5$ mm voxels, 2× acceleration. White matter hyperintensities (WMH) were identified from each individual's FLAIR image with an automated fuzzy-connected algorithm previously validated against a visual grading system (Wu et al. 2006) and using methods detailed previously (Hedden, Mormino et al. 2012; Hedden, Van Dijk et al. 2012). From the resulting WMH segmentation, we extracted the total WMH volume in cubic millimeters within a mask defined by the Johns Hopkins University White Matter Atlas (Wakana et al. 2004), which was reverse normalized to the native space of each individual's FLAIR image. Because of the skewed distribution of WMH values, WMH volumes were log-transformed (resulting in a normal distribution) and treated as a continuous variable in all analyses, with higher values indicating greater WMH burden. WMH volume was hypothesized to be positively related to age and negatively related to cognition. Based on prior data (Hedden, Mormino et al. 2012; Hedden, Van Dijk et al. 2012), we expected a relationship to cognition across domains.

Fluorodeoxyglucose Imaging Acquisition and Analysis

Fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging was completed at Massachusetts General Hospital. Before injection, 10-min transmission scans for attenuation correction were collected. 5.0–10.0 mCi was intravenously injected, and after a 45-min uptake period, FDG-PET images were acquired for 30 min in 3D acquisition mode.

FDG-PET data were realigned, summed, and normalized to a standard template using SPM8. Average FDG uptake was extracted from a MetaROI reflecting regions known to be vulnerable in AD (Landau et al. 2011) (lateral parietal, lateral inferior temporal, and posterior cingulate cortex; the MetaROI can be downloaded at http://adni.loni.usc.edu/methods/research-tools/). We used the identical pons/vermis reference region previously used and normalized average MetaROI values by the mean value from the top 50% of voxels from this pons/vermis reference region (Landau et al. 2011). Glucose metabolism in this MetaROI was hypothesized to be negatively related to age and positively related to cognition. Because this measure was defined from differences between healthy controls and AD patients, we hypothesized that this measure would be primarily related to episodic memory, but could have more general relationships given deficits in executive function associated with AD (Dickerson et al. 2007; Ewers et al. 2013).

Amyloid Imaging Acquisition and Analysis

Amyloid burden was measured with N-methyl-[^{11}C]-2-(4-methylaminophenyl)-6-hydroxybenzothiazole (Pittsburgh Compound B; PIB), which binds to fibrillar amyloid, and was prepared at Massachusetts General Hospital as described previously (Mathis et al. 2003; Klunk et al. 2004). Data collection and analysis methods have been previously described (Gomperts et al. 2008; Hedden et al. 2009; Hedden, Mormino et al. 2012). Briefly, 8.5–15 mCi [^{11}C]-PIB was injected as a bolus and followed immediately by a 60-min dynamic acquisition. PET data were parameterized by the distribution volume ratio (DVR) computed using the Logan graphical analysis technique (Logan et al.

1990) applied to the frame data acquired 40–60 min after injection. Time–activity curves were measured in each brain region under analysis (region of interest or voxel) and in a reference region in cerebellar cortex known to contain low levels of fibrillar amyloid. For each participant, an index of PIB binding in cortical regions was calculated using the dynamic data via Logan graphical modeling within a large aggregate cortical region of interest (ROI) consisting of frontal, lateral parietal and temporal, and retrosplenial cortices (the FLR region). PIB retention in the FLR region is substantial in patients with diagnosed AD and has been used as a summary measure of PIB retention in previous studies (Johnson et al. 2007; Gomperts et al. 2008; Hedden et al. 2009; Hedden, Mormino et al. 2012).

Because of the bimodal distribution of PIB-PET data, we log-transformed the data and then, following a published approach, employed a 2-distribution Gaussian mixture model approach to assign each individual a probability of belonging to the high and low Aβ distribution (Mormino et al. 2014; see e-supplement at http://www.neurology.org/content/82/20/1760/suppl/DC1). This procedure results in a distribution of probabilities that represents the bimodal distribution of amyloid burden (measured by PIB-PET) and can be applied to different amyloid platforms (different tracers or assays, or dynamic versus static measurements) to produce measurements on a common scale in a data-driven way without relying on any method-specific threshold (Mormino, et al. 2014). The probability that each participant is assigned to the high Aβ distribution was entered as a variable in our regression and correlation models. This probability (ranging from 0–1, higher values indicate greater likelihood of high Aβ) acts as a pseudo-dummy variable, with the vast majority of values clustered near 0 and 1, thereby weighting more highly those individuals with PIB binding patterns most consistent with either low or high Aβ while still allowing individuals with uncertainty as to their classification as low or high Aβ to be included in the analysis. PIB binding was hypothesized to be positively related to age and negatively related to cognition. Based on meta-analytic data, we hypothesized that PIB binding would be primarily related to episodic memory (Hedden et al. 2013).

Statistical Analyses

The primary analyses focused on the potential mediating effects of brain variables on the relationship between age and cognition (executive function, episodic memory, and processing speed). Correlation and regression analyses were conducted in SPSS v21 (IBM, Armonk, New York). Estimates of the proportion of age-related variance shared with brain markers were computed from partial correlation analyses, using the formula: $(r^2_{A-C} - r^2_{A-C \cdot B_k})/r^2_{A-C}$, where each kth brain marker (B) was partialled from the correlation between age (A) and each cognitive factor (C). Estimates of the unique age-related variance shared with each brain marker (B_k) were computed by the formula: $(r^2_{A-C \cdot B \in !k} - r^2_{A-C \cdot B \in k})/r^2_{A-C}$, where (B∈$k$) is the set of all brain markers and (B∈!k) is the set of all brain markers excluding the kth marker. Mediation effects were examined using the INDIRECT SPSS macro designed for use with multiple mediator variables, which estimates path effects using ordinary least squares regression (Preacher and Hayes 2008). Because each marker was expected to have a specific directional effect, significance of indirect effects were assessed with a 90% confidence interval (CI), corresponding to $P < 0.05$ one-tailed, using 10 000 bootstrap iterations and accepted if the interval did not overlap zero. All brain markers were simultaneously entered into the primary mediation models. Because these models simultaneously control all variables in the model, no correction for multiple comparisons was applied. Standardized coefficients (achieved by z-scoring all variables prior to entry in the model) are reported to aid in comparison across models and across brain markers within each model.

To avoid tuning potential associations to the current dataset, all of the brain markers used in this report were selected on the basis of theoretical importance and prior reports of associations with age or cognition from reviews or other datasets. Although multiple studies have been conducted using the same population (Hedden et al. 2009; Sperling et al. 2009; Rentz et al. 2010, 2011; Becker et al. 2011; Rentz et al. ; Hedden, Van Dijk et al. 2012; Vannini et al. 2012, 2013) and we have examined amyloid, white matter lesions, and functional connectivity in subsamples specific to the current dataset (Amariglio et al.

2011; Hedden, Mormino et al. 2012; Huijbers et al. 2014; Mormino et al. 2014), no brain marker was specifically examined for associations with age or cognition in the current sample prior to analysis (i.e., all brain markers were selected for inclusion blind to the results to avoid bias and inflation of measured relations).

Results

Age Effects on Cognition

As expected and corresponding to our prior report (Hedden, Mormino et al. 2012), age was negatively associated with the cognitive domain factor scores of processing speed ($r = -0.23$), executive function ($r = -0.24$), and episodic memory ($r = -0.30$). These associations provide the measured upper bound for the amount of age-related variance in cognition that can be shared with any brain variables in the current dataset, as examined in subsequent analyses.

Brain Marker Associations with Age and Cognition

For any brain marker to be likely to share age-associated variation in cognition, it must be correlated with age and/or with cognition. The brain markers of cortical thickness, entorhinal thickness, hippocampal volume, striatum volume, DTI FA, WMH, FDG, and PIB binding were significantly related to age, whereas parahippocampal thickness, DN functional connectivity, and FPCN functional connectivity were not (Table 1, Fig. 2). All brain markers had a significant correlation with at least one cognitive factor (Table 1).

Estimates of Age-Related Variance Shared with Brain Markers

Each brain marker was examined in univariate partial correlation analyses to estimate the percentage of age-related variation in cognition shared with that brain marker. For processing speed (Table 2), DTI FA shared 77% of the age-related variance, followed by WMH (36%), hippocampal volume (32%), striatum volume (31%), and FDG (30%). For executive function (Table 3), DTI FA shared 71% of the age-related variance, followed by WMH (43%), FDG (34%), hippocampal volume (32%), striatum volume (26%), and cortical thickness (24%). For episodic memory (Table 4), hippocampal volume shared 52% of the age-related variance, followed by DTI FA (41%), WMH (38%), FDG (27%), cortical thickness (25%), and striatum volume (20%). Although not among the brain markers with the largest share of age-related variance, PIB binding shared 16% of the age-related variance in episodic memory and <5% in processing speed or executive function, potentially indicating specificity (Hedden et al. 2013). Entorhinal thickness, parahippocampal thickness, and DN and FPCN connectivity had a lower share (maximum 18%) of the age-related variance across cognitive domains. These analyses indicate that a similar set of brain markers share the largest proportion of age-related variance across the 3 examined cognitive factors (DTI FA, WMH, hippocampal volume, striatum volume, FDG, and cortical thickness). These analyses of individual markers were followed by a multivariate analysis simultaneously partialling all brain variables from the age–cognition relation for each cognitive factor. All brain variables together accounted for 83% of the age-related variation in processing speed (Table 2), 75% in executive function (Table 3), and 74% in episodic memory (Table 4).

Estimates of Age-Related Variance Unique to Each Brain Marker

The above analyses indicate that several brain markers shared a substantial portion of the age-related variation in cognition when examined individually, but multivariate analysis indicates that much of this shared age-related variance is likely to be overlapping among 2 or more brain markers. To estimate the proportion of age-related variance in cognition uniquely shared with each brain marker, each brain marker was systematically removed from the partial correlation analysis. For processing speed (Table 2, Fig. 3), DTI FA uniquely shared 17% of the age-related variance (compared with 77% in the univariate analysis), followed by striatum volume (11%). For executive function (Table 3, Fig. 4), DTI FA uniquely shared 14% of the age-related variance (compared with 71% in the univariate analysis), followed by striatum volume (8%). For episodic memory (Table 4, Fig. 5), hippocampal volume uniquely shared 8% of the age-related variance (compared with 52% in the univariate analysis), followed by PIB binding (3%), WMH (2%), and entorhinal thickness (2%). All other variables uniquely shared <2% of the age-related variance across all cognitive factors

Table 1
Correlations

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Age														
2. Processing speed	**−0.23**													
3. Executive function	**−0.24**	**0.85**												
4. Episodic memory	**−0.30**	**0.54**	**0.68**											
5. Cortical thickness	**−0.22**	0.12	**0.18**	**0.24**										
6. Entorhinal thickness	**−0.21**	0.13	0.13	**0.15**	**0.39**									
7. Parahippocampal thickness	−0.13	0.14	**0.21**	**0.25**	**0.36**	**0.30**								
8. Hippocampal volume	**−0.43**	0.14	**0.15**	**0.28**	**0.29**	**0.38**	**0.16**							
9. Striatum volume	**−0.30**	**0.17**	**0.15**	**0.16**	**0.29**	**0.18**	**0.17**	**0.36**						
10. DN fcMRI	−0.10	**0.20**	0.14	**0.15**	−0.01	**0.22**	0.06	0.14	0.04					
11. FPCN fcMRI	−0.08	**0.23**	**0.25**	**0.16**	−0.03	0.14	0.07	0.13	0.02	**0.71**				
12. DTI FA	**−0.41**	**0.32**	**0.31**	**0.23**	0.16	**0.37**	**0.28**	**0.44**	0.08	**0.24**	**0.28**			
13. WMH	**0.40**	**−0.16**	**−0.20**	**−0.22**	**−0.29**	**−0.29**	**−0.29**	**−0.26**	0.00	−0.05	−0.12	**−0.55**		
14. FDG	**−0.23**	**0.20**	**0.24**	**0.26**	**0.20**	**0.30**	**0.30**	**0.27**	**0.18**	0.10	0.07	**0.34**	**−0.33**	
15. PIB	**0.24**	−0.05	−0.02	**−0.15**	−0.12	**−0.24**	**−0.16**	**−0.22**	−0.12	−0.05	0.02	−0.08	**0.20**	−0.14

Note: For display purposes, bold values indicate significance at $P \leq 0.05$, two-tailed. All variables were included in the primary analyses on an a priori basis.

(Tables 2–4). Estimates with a negative value indicate potential variance suppression effects, in which inclusion of that brain marker alters the portion of age-related variance available to be shared among other brain markers; such effects likely indicate substantial colinearity with one or more other markers in the model. One can also estimate the portion of age-related variance in cognition unique to any brain marker when controlling for any other single brain marker, or the portion of age-related variance in cognition shared between any 2 brain markers (Table 5).
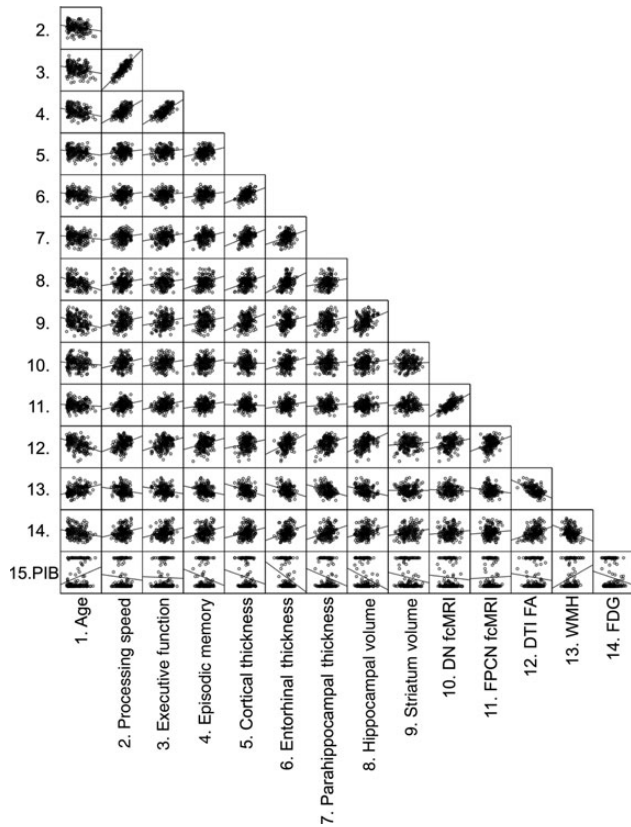

Figure 2. Pairwise correlations between age, cognition, and brain markers. Scatterplots for each correlation reported in Table 1 are displayed for descriptive purposes.

Brain Markers as Mediators of Age–Cognition Relations

As suggested by the above analyses, a substantial proportion of the age-related variation in cognition is likely to be mediated by one or more of the examined brain markers. For each cognitive factor, a multiple mediator model was conducted, in which all brain variables were simultaneously entered as potential mediators. Results demonstrated that for processing speed (Table 6, Fig. 6) and executive function (Table 7, Fig. 7), full mediation was achieved (as shown by a nonsignificant Age′ direct effect, $P = 0.28$ and $P = 0.14$, and significant bootstrapped indirect total effects, 90% CI: −0.18, −0.03, and −0.19, −0.01). For episodic memory (Table 8, Fig. 8), partial mediation was achieved (significant Age′ direct effect, $P = 0.04$, and a significant bootstrapped indirect total effect, 90% CI: −0.18, −0.02).

The numerous nonsignificant indirect age-to-brain-to-cognition relationships in Tables 6–8 indicate that not all brain markers will be necessary to achieve the maximally observed mediation of the age–cognition relationships. We therefore pursued a reduced model for each cognitive domain, beginning with those variables having the largest indirect effect in the multivariate models (i.e., DTI FA for processing speed and executive function, and hippocampal volume for episodic memory) and attempting to minimize the number of variables required to obtain the largest total indirect effect from age to cognition and the largest model R^2, while also requiring each brain marker to have a significant indirect effect. For processing speed, a model containing DTI FA and striatum volume met these criteria (Fig. 6). No other brain marker had a significant indirect effect when added to this model. For executive function, a model containing cortical thickness, DTI FA, and FDG met these criteria (Fig. 7). When added to this model, no other brain markers had a significant indirect effect. For episodic memory, a model containing hippocampal volume, parahippocampal thickness, and FDG met these criteria (Fig. 8), with no other markers having a significant indirect effect when added to this model. We note that (as suggested by the full model results) a model including only cortical thickness, parahippocampal thickness, and FDG resulted in all included markers having a significant indirect effect, but the total indirect effect (−0.06, 90% CI: −0.10, −0.02) and model fit ($R^2 = 0.17$) were not better than the accepted model. Note that

Table 2
Processing speed

B_k	A − C	A − C · B_k	A − C · B∈!k	A − B_k	A − B_k · C	B_k − C	B_k − C · A	Shared %	Unique %
Cortical thickness	**−0.225**	**−0.206**	−0.096	**−0.217**	**−0.197**	0.119	0.074	16.2	0.8
Entorhinal thickness	**−0.225**	**−0.204**	−0.097	**−0.212**	**−0.189**	0.128	0.085	17.8	1.1
Parahippocampal thickness	**−0.225**	**−0.211**	−0.092	−0.126	−0.097	0.144	0.120	12.1	−0.7
Hippocampal volume	**−0.225**	**−0.186**	−0.077	**−0.429**	**−0.413**	0.136	0.044	31.7	−5.7
Striatum volume	**−0.225**	**−0.187**	0.119	**−0.295**	**−0.268**	0.167	0.108	30.9	10.5
DN fcMRI	**−0.225**	**−0.211**	−0.095	−0.100	−0.059	**0.195**	**0.178**	12.1	0.4
FPCN fcMRI	**−0.225**	**−0.213**	−0.088	−0.080	−0.030	**0.229**	**0.217**	10.4	−2.2
DTI FA	**−0.225**	−0.108	−0.132	**−0.413**	**−0.370**	**0.320**	**0.255**	77.0	17.0
WMH	**−0.225**	**−0.180**	−0.083	**0.395**	**0.374**	−0.157	−0.076	36.0	−3.8
FDG	**−0.225**	**−0.188**	−0.094	**−0.229**	**−0.192**	**0.202**	0.159	30.2	0.0
PIB	**−0.225**	**−0.220**	−0.097	**0.242**	**0.237**	−0.051	0.004	4.4	1.1
All brain markers (B∈k)	**−0.225**	**−0.094**[a]						82.5	

Note: Correlations and partial correlations between age (A), cognition (C; here, processing speed), and brain markers in each row (B_k); B∈k = the set of all brain markers; B∈!k = the set of all brain markers excluding the kth marker; Shared = percentage of variance in the age–cognition relation shared with the brain marker; Unique = percentage of variance in the age–cognition relation that is uniquely shared with the brain marker when partialling all other brain markers. Negative values for shared or unique indicate potential variance suppression effects. Bold partial correlations indicate significance for a one-tailed test, corrected for multiple comparisons ($P ≤ 0.009$).
[a]Value is given for A − C · B∈k.

because age-related variance in cognition shared with each brain marker includes the portions uniquely attributable to the marker and shared with other markers, there is no requirement that markers with unique age-related variance identified in the previous analysis will also be most important for mediating age-related variance, although they are likely candidates.

Discussion

These results provide both hope and caution regarding our ability to address the portion of age-related variation in cognition among clinically normal older adults shared with multiple brain markers of structure, function, or pathology. First, examined individually, all brain markers shared some portion of the age-related variance in one or more cognitive domains, and all observed relationships were in the hypothesized direction. Second, multivariate analyses controlling for the simultaneous relationships among brain markers found that white matter integrity (DTI FA) and striatum volume were associated with

unique age-related variance in processing speed and executive function; relationships that accord with prior findings from reviews or meta-analyses (Gunning-Dixon and Raz 2000; Oosterman et al. 2004; Salthouse 2011). Brain markers of hippocampal volume, amyloid burden, white matter lesions, and parahippocampal thickness were associated with unique age-related variance in episodic memory; again these relationships accord with prior findings (Mormino et al. 2009; Hedden, Mormino et al. 2012; Jack et al. 2012; Hedden et al. 2013). Third, mediation analyses found that all significant age-related variance in processing speed was mediated by white matter integrity and striatum volume, all significant age-related variance in executive function was mediated by white matter integrity, cortical thickness, and glucose metabolism, and a significant portion of the age-related variance in episodic memory was mediated by hippocampal volume, parahippocampal thickness, and glucose metabolism. Notably, despite the unique variance attributable to a small subset of brain markers, a majority (>50%) of the age-related variance in
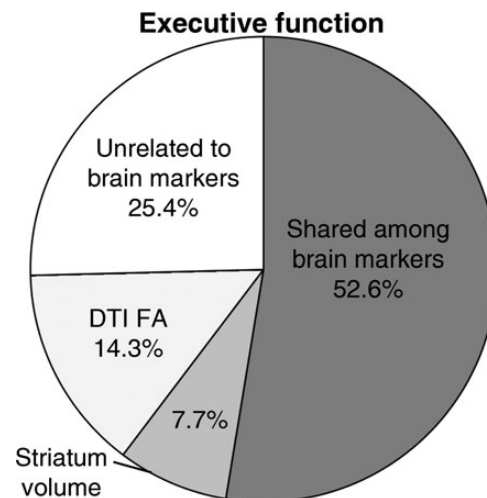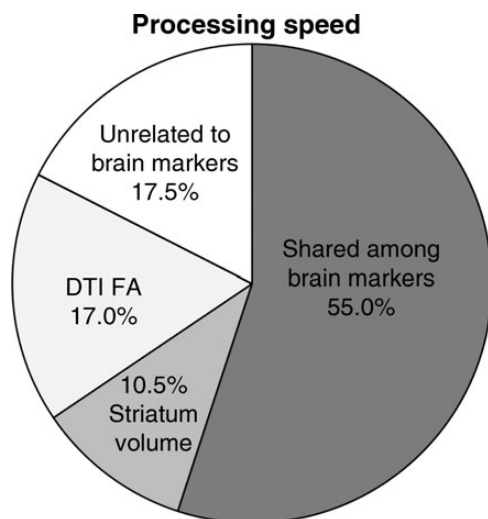

Figure 3. Age-related variance in processing speed shared with and unique to brain markers. Pie sections indicate the percentage of age-related variance in processing speed that is unrelated to any brain marker examined, unique to individual brain markers, or shared among any 2 or more brain markers. Only variables uniquely sharing >2% of age-related variance in processing speed are indicated.

Figure 4. Age-related variance in executive function shared with and unique to brain markers. Pie sections indicate the percentage of age-related variance in executive function that is unrelated to any brain marker examined, unique to individual brain markers, or shared among any 2 or more brain markers. Only variables uniquely sharing >2% of age-related variance in executive function are indicated.

Table 3
Executive function

B_k	$A - C$	$A - C \cdot B_k$	$A - C \cdot B \in !k$	$A - B_k$	$A - B_k \cdot C$	$B_k - C$	$B_k - C \cdot A$	Shared %	Unique %
Cortical thickness	**−0.238**	**−0.208**	−0.124	**−0.217**	**−0.183**	**0.177**	0.132	23.6	1.7
Entorhinal thickness	**−0.238**	**−0.218**	−0.124	**−0.212**	**−0.188**	0.127	0.081	16.1	1.7
Parahippocampal thickness	**−0.238**	**−0.219**	−0.114	−0.126	−0.082	**0.206**	**0.182**	15.3	−2.5
Hippocampal volume	**−0.238**	**−0.196**	−0.109	**−0.429**	**−0.410**	0.148	0.052	32.2	−4.4
Striatum volume	**−0.238**	**−0.205**	−0.137	**−0.295**	**−0.270**	0.151	0.087	25.8	7.7
DN fcMRI	**−0.238**	**−0.227**	−0.116	−0.100	−0.069	0.141	0.122	9.0	−1.7
FPCN fcMRI	**−0.238**	**−0.226**	−0.108	−0.080	−0.022	**0.250**	**0.239**	9.8	−4.8
DTI FA	**−0.238**	−0.128	−0.150	**−0.413**	**−0.368**	**0.309**	**0.238**	71.1	14.3
WMH	**−0.238**	**−0.179**	−0.115	**0.395**	**.366**	**−0.195**	−0.113	43.4	−2.1
FDG	**−0.238**	**−0.194**	−0.120	**−0.229**	**−0.182**	**0.241**	**0.197**	33.6	0.0
PIB	**−0.238**	**−0.241**	−0.117	**0.242**	**0.245**	−0.018	0.042	−2.5	−1.3
All brain markers ($B \in k$)	**−0.238**	−0.120[a]						74.6	

Note: Correlations and partial correlations between age (A), cognition (C; here executive function), and brain markers in each row (B_k); $B \in k$ = the set of all brain markers; $B \in !k$ = the set of all brain markers excluding the kth marker; Shared = percentage of variance in the age–cognition relation shared with the brain marker; Unique = percentage of variance in the age–cognition relation that is uniquely shared with the brain marker when partialling all other brain markers. Negative values for shared or unique indicate potential variance suppression effects. Bold partial correlations indicate significance for a one-tailed test, corrected for multiple comparisons ($P \leq 0.009$). [a]Value is given for $A - C \cdot B \in k$.

Table 4
Episodic memory

B_k	A−C	A−C·B_k	A−C·B∈!k	A−B_k	A−B_k·C	B_k−C	B_k−C·A	Shared %	Unique %
Cortical thickness	**−0.297**	**−0.258**	−0.156	**−0.217**	−0.157	**0.239**	**0.187**	24.5	1.4
Entorhinal thickness	**−0.297**	**−0.274**	−0.158	**−0.212**	**−0.177**	**0.151**	0.094	14.9	2.1
Parahippocampal thickness	**−0.297**	**−0.276**	−0.140	−0.126	−0.058	**0.245**	**0.219**	13.6	−4.0
Hippocampal volume	**−0.297**	**−0.205**	−0.173	**−0.429**	**−0.379**	**0.276**	**0.173**	52.4	7.7
Striatum volume	**−0.297**	**−0.266**	−0.152	**−0.295**	**−0.264**	0.156	.075	19.8	0.0
DN fcMRI	**−0.297**	**−0.287**	−0.153	−0.100	−0.060	0.146	0.122	6.6	0.3
FPCN fcMRI	**−0.297**	**−0.288**	−0.147	−0.080	−0.034	0.163	0.147	6.0	−1.7
DTI FA	**−0.297**	**−0.229**	−0.152	**−0.413**	**−0.372**	**0.227**	0.121	40.5	0.0
WMH	**−0.297**	**−0.234**	−0.158	**0.395**	**0.354**	**−0.221**	**−0.118**	37.9	2.1
FDG	**−0.297**	**−0.253**	−0.152	**−0.229**	**−0.165**	**0.256**	**0.202**	27.4	0.0
PIB	**−0.297**	**−0.272**	−0.161	**0.242**	**0.210**	**−0.148**	−0.082	16.1	3.2
All brain markers (B∈k)	**−0.297**	−0.153[a]						73.8	

Note: Correlations and partial correlations between age (A), cognition (C; here, episodic memory), and brain markers in each row (B_k); B∈k = the set of all brain markers; B∈!k = the set of all brain markers excluding the kth marker; Shared = percentage of variance in the age–cognition relation shared with the brain marker; Unique = percentage of variance in the age–cognition relation that is uniquely shared with the brain marker when partialling all other brain markers. Negative values for shared or unique indicate potential variance suppression effects. Bold partial correlations indicate significance for a one-tailed test, corrected for multiple comparisons ($P \leq 0.009$).
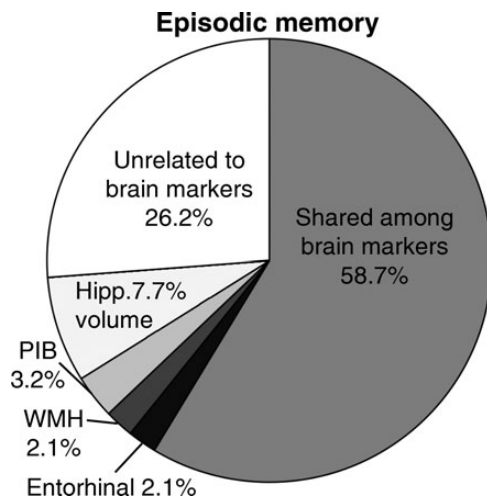[a]Value is given for A − C · B∈k.

Episodic memory

Figure 5. Age-related variance in episodic memory shared with and unique to brain markers. Pie sections indicate the percentage of age-related variance in episodic memory that is unrelated to any brain marker examined, unique to individual brain markers, or shared among any 2 or more brain markers. Only variables uniquely sharing >2% of age-related variance in episodic memory are indicated.

cognition was nonetheless shared between 2 or more brain markers. About one-quarter of the age-related variance in any cognitive domain was unrelated to any brain markers examined (Figs. 3–5). These results provide hope that with additional brain markers (e.g., in vivo tau imaging, neurotransmitter availability, etc.), we may be able to account for much of the neural underpinnings of cognitive variation within the normal range that is currently attributed to the developmental trajectory of aging.

However, the results must be interpreted in light of multiple limitations. Although our focus here was on the age-related variance, the total variance in cognition shared with the full set of brain markers was only ~20% (indicated by R^2 in the mediation models, Tables 6–8). This means that ~80% of the person-specific variation in cognition is explained by something outside of our models. Candidates include a combination of genetic factors, intellectual ability, educational training, practice effects, arousal or fatigue, medication use, emotional status, or other brain markers

that have not been sampled here. Notably, verbal intelligence, education, and socioeconomic status were not sufficiently related to age in our sample to impact our reported results. Additionally, APOE and other genetic phenotypes, or other person-specific factors, may modify that portion of the variance in cognition that is linked to brain markers but not to age.

Our ability to detect mediating influences of brain markers on age–cognition relationships may be limited by the relatively small age–cognition relations observed in our sample. Our estimates of age–cognition relations (processing speed: $r = -0.23$, executive function: $r = -0.24$, episodic memory: $r = -0.30$) are in the same general range as prior meta-analytic estimates in individuals older than 50 (processing speed: $r = -0.37$, working memory: $r = -0.24$, reasoning: $r = -0.28$, episodic memory: $r = -0.23$) (Verhaeghen and Salthouse 1997). Nonetheless, when viewed in the context of age–cognition relations observed across the entire adult lifespan, our effects are relatively small. Larger relationships are likely to be observed between cognition and the brain alterations that occur between the average 20-year-old's brain and the average 75 year-old's brain. Understanding how such brain alterations co-occur with cognitive alterations at various points throughout the lifespan may provide additional information regarding the developmental trajectories of pathology, neurodegenerative markers, and cognitive function.

The similarity of relationships between the brain markers across the cognitive domains of processing speed and executive function may result in part from the substantial correlation between these cognitive domains in our sample. Although we employed factor scores to alleviate test-specific measurement error (Salthouse 2011), exactly how cognitive function is assessed and which cognitive domains are sampled across studies may impact observed relationships between cognitive domains, age, and brain markers.

Our results indicate the importance of considering the set of brain markers available in a given study. For example, when examining individual brain markers only, a likely conclusion would be that DTI FA, hippocampal volume, striatum volume, FDG, WMH, and cortical thickness were all important indicators of the age-related variation in cognition, as they each shared substantial portions of the age-related variance across cognitive domains. However, when examined as part of a set of correlated

Table 5

Age-related variance in cognition shared between pairwise brain markers

	1	2	3	4	5	6	7	8	9	10	11
Processing speed											
1. Cortical thickness	*16.2%*	7.9%	4.0%	20.5%	21.2%	12.5%	11.8%	65.2%	25.4%	22.6%	2.4%
2. Entorhinal thickness	6.3%	*17.8%*	4.8%	16.1%	23.1%	4.8%	4.8%	59.6%	23.8%	18.9%	0.0%
3. Parahippocampal thickness	8.1%	10.5%	*12.1%*	23.9%	24.7%	10.5%	8.9%	65.3%	23.9%	21.8%	0.8%
4. Hippocampal volume	5.0%	2.2%	4.3%	*31.7%*	11.9%	3.6%	0.7%	42.2%	20.9%	12.6%	0.0%
5. Striatum volume	6.5%	10.0%	5.8%	12.7%	*30.9%*	10.0%	9.3%	59.7%	33.1%	19.1%	1.5%
6. DN fcMRI	16.6%	10.5%	10.5%	23.2%	28.8%	*12.1%*	0.0%	64.9%	32.9%	26.1%	3.3%
7. FPCN fcMRI	17.6%	12.2%	10.6%	22.0%	29.8%	1.7%	*10.4%*	63.5%	28.4%	27.0%	5.8%
8. DTI FA	4.5%	0.4%	0.4%	−3.1%	13.6%	0.0%	−3.1%	*77.0%*	−3.5%	4.1%	1.7%
9. WMH	5.6%	5.6%	0.0%	16.5%	28.0%	8.9%	2.8%	37.4%	*36.0%*	10.2%	0.7%
10. FDG	8.6%	6.5%	3.7%	14.1%	19.9%	7.9%	7.2%	50.8%	16.0%	*30.2%*	0.7%
11. PIB	14.2%	13.4%	8.5%	27.3%	28.0%	11.0%	11.8%	74.2%	32.3%	26.5%	*4.4%*
Executive function:											
1. Cortical thickness	*23.6%*	5.1%	3.6%	16.6%	14.0%	8.6%	11.3%	56.2%	27.7%	22.9%	−4.5%
2. Entorhinal thickness	12.6%	*16.1%*	6.0%	18.8%	19.5%	3.8%	4.6%	55.4%	31.7%	22.2%	−5.5%
3. Parahippocampal thickness	11.9%	6.8%	*15.3%*	22.3%	18.2%	7.6%	8.3%	56.2%	28.1%	22.9%	−7.1%
4. Hippocampal volume	8.1%	2.7%	5.4%	*32.2%*	9.3%	2.7%	1.4%	38.0%	26.5%	14.4%	−3.5%
5. Striatum volume	11.8%	9.8%	7.7%	15.7%	*25.8%*	7.1%	8.4%	58.6%	40.1%	22.6%	−3.7%
6. DN fcMRI	23.1%	10.9%	13.9%	25.9%	23.8%	*9.0%*	−2.4%	62.0%	40.5%	29.9%	−3.2%
7. FPCN fcMRI	25.1%	10.8%	13.8%	23.7%	24.4%	−3.2%	*9.8%*	57.0%	36.1%	30.4%	−0.8%
8. DTI FA	8.7%	0.5%	0.5%	−0.9%	13.3%	0.0%	−4.2%	*71.1%*	2.2%	6.0%	−1.8%
9. WMH	7.9%	4.3%	0.0%	15.2%	22.5%	6.1%	2.5%	29.9%	*43.4%*	10.8%	−4.5%
10. FDG	13.0%	4.7%	4.7%	13.0%	14.8%	5.4%	6.7%	43.5%	20.7%	*33.6%*	−5.6%
11. PIB	21.7%	13.2%	10.8%	31.2%	24.7%	8.3%	11.6%	71.8%	41.5%	30.5%	−2.5%
Episodic memory											
1. Cortical thickness	*24.5%*	3.5%	2.9%	34.1%	8.0%	6.3%	5.7%	29.7%	22.1%	17.6%	11.2%
2. Entorhinal thickness	13.1%	*14.9%*	4.9%	38.4%	14.3%	2.5%	2.5%	28.2%	27.2%	17.6%	9.6%
3. Parahippocampal thickness	13.8%	6.1%	*13.6%*	42.4%	12.6%	5.5%	4.3%	25.9%	23.2%	17.8%	10.3%
4. Hippocampal volume	6.3%	0.9%	3.6%	*52.4%*	3.2%	1.8%	0.9%	10.9%	17.2%	8.8%	5.4%
5. Striatum volume	12.7%	9.4%	6.5%	35.8%	*19.8%*	5.9%	5.3%	35.8%	37.1%	19.2%	12.2%
6. DN fcMRI	24.2%	10.7%	12.6%	47.6%	19.1%	*6.6%*	0.6%	33.9%	36.0%	24.8%	15.0%
7. FPCN fcMRI	24.3%	11.4%	12.0%	47.3%	19.2%	1.3%	*6.0%*	32.0%	33.5%	25.4%	16.2%
8. DTI FA	13.6%	2.6%	−1.0%	22.7%	15.0%	0.0%	−2.6%	*40.5%*	9.9%	7.5%	11.8%
9. WMH	8.7%	4.2%	−1.1%	31.6%	19.0%	4.7%	1.6%	12.6%	*37.9%*	8.7%	7.7%
10. FDG	14.7%	5.1%	4.0%	33.8%	11.5%	4.0%	4.0%	20.6%	19.2%	*27.4%*	10.0%
11. PIB	19.7%	8.4%	7.8%	41.6%	15.8%	5.5%	6.1%	36.2%	29.5%	21.3%	*16.1%*

Note: Each cell indicates the percentage of age-related variance in cognition shared with the column variable and unique from that shared with the row variable. *Italicized* values on the diagonal indicate the percentage of age-related variance in cognition shared with the variable (same as in Tables 2–4). The percentage of age-related variance in cognition shared with the column variable that is also shared with the row variable can be computed by subtracting the value of any cell from the italicized value in that cell's column. Negative values indicate potential variance suppression effects.

Table 6

Mediation analysis of age, brain markers, and processing speed

	$\beta(A - B_k)$	$\beta(B_k - C)$	$\beta(A - B_k - C)$
Cortical thickness	**−0.21**	0.06	−0.01
Entorhinal thickness	**−0.21**	−0.04	0.01
Parahippocampal thickness	**−0.12**	0.02	0.00
Hippocampal volume	**−0.43**	−0.08	0.03
Striatum volume	**−0.29**	0.09	**−0.03**
DN fcMRI	−0.10	0.04	0.00
FPCN fcMRI	−0.08	0.10	−0.01
DTI FA	**−0.41**	**0.22**	**−0.09**
WMH	**0.39**	0.06	0.02
FDG	**−0.23**	0.08	−0.02
PIB	**0.24**	−0.01	0.00

	$\beta(A - C)$	$\beta(A - B{\in}k - C)$
Age	**−0.17**	
Age'	−0.07	**−0.10**

Note: Mediation models were conducted by simultaneously entering all brain markers as potential mediators of the age–cognition relationship. Standardized beta estimates (β) are shown for relationships between age (A), each brain marker (B_k) or total effects ($B{\in}k$), and the cognitive outcome of processing speed (C). Sample size was $N = 184$ and model fit was $R^2 = 0.17$. Age' indicates the remaining direct effect of age on cognition after controlling for the potential mediating effects of all brain markers. Bold values indicate significance at $P < 0.05$, one-tailed, as established by T-test (direct effects) or bootstrapped 90% confidence intervals (indirect effects). Because all variables were simultaneously controlled in each model, no correction for multiple comparisons was applied.

Figure 6. Mediation model for processing speed. Results from the reduced mediation model including only brain markers with significant indirect effects from age to cognition. Solid lines indicate significant paths ($P \leq 0.05$, one-tailed), dashed lines indicate nonsignificant paths. Path values indicate standardized beta weights. *Italicized* values indicate direct (unmediated) paths from age to cognition. Indirect effects operating through each brain marker and the total indirect effect are given below the model. Values in parentheses indicate the 10 000 sample bootstrapped 90% confidence intervals for the indirect effects. All displayed confidence intervals did not include 0; results are truncated at −0.001. R^2 indicates the fit of the reduced model.

neurological alterations occurring during aging, we find that only a few of these markers carry unique age-related variance, and, as indicated by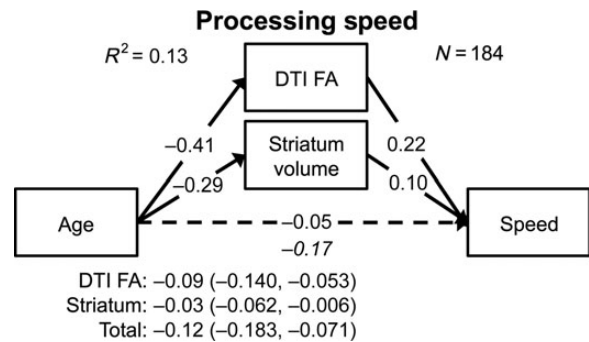 the mediation analyses, that only a small subset may be necessary for accounting for the majority of age-related variance. Notably, this subset varies across cognitive domains in a manner that is informative about relations between specific neurobiological cascades and cognition.

One question that we can begin to ask from such multivariate data is: *What is the minimal set of brain markers necessary*

Table 7
Mediation analysis of age, brain markers, and executive function

	$\beta(A - B_k)$	$\beta(B_k - C)$	$\beta(A - B_k - C)$
Cortical thickness	**−0.21**	0.10	**−0.02**
Entorhinal thickness	**−0.21**	−0.05	0.01
Parahippocampal thickness	**−0.12**	0.08	−0.01
Hippocampal volume	**−0.43**	−0.07	0.03
Striatum volume	**−0.29**	0.06	−0.02
DN fcMRI	−0.10	−0.07	0.01
FPCN fcMRI	−0.08	**0.23**	−0.02
DTI FA	**−0.41**	**0.19**	**−0.08**
WMH	**0.39**	0.05	0.02
FDG	**−0.23**	**0.12**	**−0.03**
PIB	**0.24**	0.02	0.01
		$\beta\,(A - C)$	$\beta(A - B\in k - C)$
Age		**−0.21**	
Age′		−0.11	**−0.10**

Note: Mediation models were conducted by simultaneously entering all brain markers as potential mediators of the age–cognition relationship. Standardized beta estimates (β) are shown for relationships between age (A), each brain marker (B_k) or total effects ($B\in k$), and the cognitive outcome of executive function (C). Sample size was $N = 185$ and model fit was $R^2 = 0.20$. Age′ indicates the remaining direct effect of age on cognition after controlling for the potential mediating effects of all brain markers. Bold values indicate significance at $P < 0.05$, one-tailed, as established by T-test (direct effects) or bootstrapped 90% confidence intervals (indirect effects). Because all variables were simultaneously controlled in each model, no correction for multiple comparisons was applied.

Table 8
Mediation analysis of age, brain markers, and episodic memory

	$\beta(A - B_k)$	$\beta(B_k - C)$	$\beta(A - B_k - C)$
Cortical thickness	**−0.21**	0.10	**−0.02**
Entorhinal thickness	**−0.21**	−0.07	0.01
Parahippocampal thickness	**−0.12**	**0.10**	**−0.01**
Hippocampal volume	**−0.43**	0.10	−0.04
Striatum volume	**−0.29**	−0.01	0.00
DN fcMRI	−0.10	0.03	0.00
FPCN fcMRI	−0.08	0.09	−0.01
DTI FA	**−0.41**	−0.01	0.01
WMH	**0.39**	−0.01	0.00
FDG	**−0.23**	**0.10**	**−0.02**
PIB	**0.24**	−0.04	−0.01
		$\beta\,(A - C)$	$\beta(A - B\in k - C)$
Age		**−0.23**	
Age′		−0.13	**−0.10**

Note: Mediation models were conducted by simultaneously entering all brain markers as potential mediators of the age–cognition relationship. Standardized beta estimates (β) are shown for relationships between age (A), each brain marker (B_k) or total effects ($B\in k$), and the cognitive outcome of episodic memory (C). Sample sizes was $N = 186$ and model fit was $R^2 = 0.19$. Age′ indicates the remaining direct effect of age on cognition after controlling for the potential mediating effects of all brain markers. Bold values indicate significance at $P < 0.05$, one-tailed, as established by T-test (direct effects) or bootstrapped 90% confidence intervals (indirect effects). Because all variables were simultaneously controlled in each model, no correction for multiple comparisons was applied.

Figure 7. Mediation model for executive function. Results from the reduced mediation model including only brain markers with significant indirect effects from age to cognition. Solid lines indicate significant paths ($P \leq 0.05$, one-tailed), dashed lines indicate nonsignificant paths. Path values indicate standardized beta weights. *Italicized* values indicate direct (unmediated) paths from age to cognition. Indirect effects operating through each brain marker and the total indirect effect are given below the model. Values in parentheses indicate the 10 000 sample bootstrapped 90% confidence intervals for the indirect effects. All displayed confidence intervals did not include 0; results are truncated at −0.001. R^2 indicates the fit of the reduced model.

Figure 8. Mediation model for episodic memory. Results from the reduced mediation model including only brain markers with significant indirect effects from age to cognition. Solid lines indicate significant paths ($P \leq 0.05$, one-tailed), dashed lines indicate nonsignificant paths. Path values indicate standardized beta weights. *Italicized* values indicate direct (unmediated) paths from age to cognition. Indirect effects operating through each brain marker and the total indirect effect are given below the model. Values in parentheses indicate the 10 000 sample bootstrapped 90% confidence intervals for the indirect effects. All displayed confidence intervals did not include 0; results are truncated at −0.001. R^2 indicates the fit of the reduced model. Hipp = hippocampal; Parahipp = parahippocampal gyrus.

to account for the majority of age-related variation in cognition? One answer to this question is the set of markers listed as mediators in Figures 6–8. But what if one wishes to minimize radiation exposure or limit the testing to a single MRI session? If FDG were unavailable, no other variable meets our criteria as a mediator in the reduced model for episodic memory, but the removal of FDG also only results in a change in the total indirect effect of 0.012 and a change in the $R^2 = 0.014$. For executive function, removal of FDG from the reduced mediator model results in a change in the total indirect effect of 0.010 and in the $R^2 = 0.015$, indicating that the unique information derived from adding an FDG scan is minimal. However, an
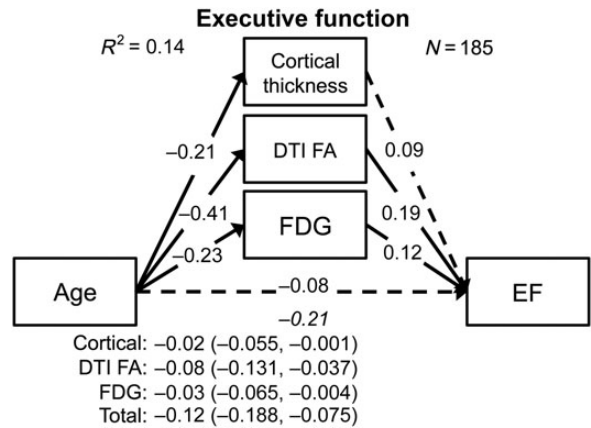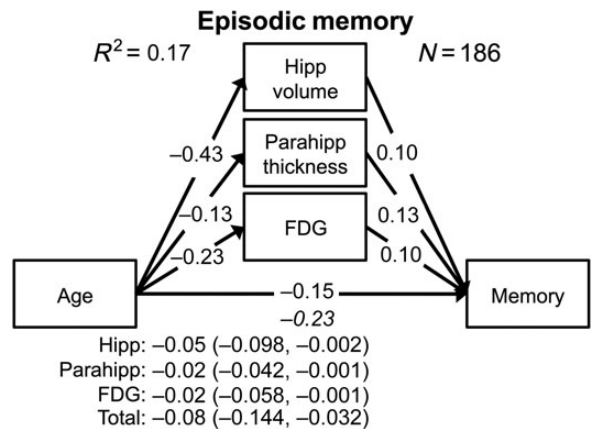
FDG scan may prove to be uniquely valuable to a clinician if the individual also exhibited subtle symptoms indicative of potential preclinical AD, as our summary measurement is impoverished relative to inspection of the map-wise information in an FDG scan. In contrast, if FDG and DTI FA were unavailable, a model with cortical thickness, WMH, and striatum volume reduces the direct effect of age to executive function so that it is no longer significant ($\beta = -0.13$, $P = 0.07$), but the total indirect effect drops to −0.08 (vs. −0.14) and the model ($R^2 = 0.09$) has lower fit than a model with cortical thickness, DTI FA, and striatum volume ($R^2 = 0.13$). This shows that related markers (e.g., DTI FA and WMH were correlated at $r =$

−0.55) can be substituted for one another to some extent, but also indicates that if an MRI is already to be obtained, the addition of a 6-min DTI scan to standard clinical sequences (plus the postprocessing and analysis time) could provide a nontrivial boost (here ∼4.3%) in variance in cognition shared with the brain markers. The results in Table 5 provide additional information about the interrelationships between each pair of markers that could be used to focus on a set of brain markers that best mediate age-related variation in cognition.

Because of our choices in defining our brain markers and cognitive factors, it is possible that our findings will not generalize beyond our sample. However, we took care to define our variables in advance without reference to the sample-dependent relationships of the brain markers with age and cognition. Our expectation is that choosing the variables in advance without reference to the sample will increase the likelihood of generalization to other samples, at the expense of lower specificity than could have been obtained through tailoring to our data. This does not mean that other regionally specific variables from one or more of the modalities are not potentially important. Because we used an a priori selection of brain markers, the most sensitive measures within each modality may have been missed. In particular, our measures of DN and FPCN connectivity were not significantly related to age in our data after controlling for motion and data quality. However, these measures were significantly related to cognition, indicating that their variance shared with cognition is not age-related. In addition, we did not examine thickness in specific neocortical regions. While additional domain-specific relationships may be present at the regional level, the correlations among neocortical regions would likely make such relationships difficult to detect in a multivariate analysis; hence, we chose an aggregate measure that nonetheless demonstrated shared age-related variance. Our results therefore likely present a conservative picture of the shared variance between brain markers and age–cognition relationships. In this investigation, we chose a wide-angle approach that primarily relies on global metrics (with the exception of some well-characterized regional markers of volume that had strong a priori theoretical justifications). With our findings in mind, future research may be fruitfully focused on regionally specific markers within those modalities that appear most promising for sharing age-related variance in cognition. Rather than conducting such exploratory analyses which would require split-sample approaches or verification in independent samples, we chose to implement only previously studied and widely available analysis techniques, as replication and standardization across large-scale studies will be crucial for establishing robust brain–cognition relationships.

Because our data are cross-sectional, it is important to examine alternative models that may explain the relationships between age, brain markers, and cognition. The data presented in Tables 2–4 allow comparison of a model in which brain markers mediate age–cognition relationships to models where age acts on both brain markers and cognition, or cognition mediates age–brain relationships (Salthouse 2011). Although our strongest effects (e.g., DTI FA to processing speed and executive function) are not consistent with these alternatives, the overarching pattern cannot rule out such alternatives. A model in which age acts independently on brain markers and cognition is particularly difficult to refute from these data. One assumption of the mediation approach is that the relationships between age and its mediators to cognition are invariant across the age range examined. One could also hypothesize alteration of the brain–cognition relationships as a function of age (referred to as moderation) or other factors (e.g., education, socioeconomic status, tau or amyloid burden, or genetic factors). Because moderating effects may be relatively subtle and the range of potential moderating relationships is complex when examining many brain markers, their observation may require a larger age range, a sample including both patients and clinically normal adults, or a larger sample size (e.g., Kennedy and Raz 2009; Salthouse 2011; Steffener et al. 2014; Tschanz et al. 2013; Zimmerman et al. 2006). Moderation of brain–cognition relationships may be especially likely when comparing younger-to-older age groups, or when comparing across patient groups or risk groups within the older age range. The causal chain is likely multidimensional, and will only be fully understood through longitudinal data confirmed across multiple large-sample studies (Raz and Lindenberger 2011).

Even though we were able to attribute unique age-related variance in each cognitive domain to specific theoretically motivated brain markers, the majority of age-related variance in all cognitive domains was shared between 2 or more brain markers. This indicates the importance of multivariate analytic frameworks that account for the interrelationships among different physiological mediators. Although the mediation models presented here include multivariate information, they do not explore the potentially complex hierarchy of relationships between the various brain markers. For example, one might use such data to examine whether alterations in measures of white matter integrity explain the age-related variability in cognition associated with gray matter measures or glucose metabolism, or vice versa. Such explorations of multivariate models are currently rare in the literature because their complexity is likely to require very large-sample sizes, replication across multiple datasets, and verification with longitudinal data.

In conclusion, our results demonstrate that a large portion of the age-related variation in cognition is shared among multiple brain markers, but that some unique age-related variance is attributable to specific markers of brain aging or preclinical neuropathology. These results focus specifically on the age-related portion of the variance in cognition, and do not address the contribution of these markers on the cognitive variation that is independent of age. In particular, although the markers of neuropathology examined here tend to be more prominent in aging adults, such markers likely have specific detrimental effects on cognition not related to age. We emphasize that our approach takes a wide-angle view of the relationship between brain markers and the age-related variation in cognition, and does not preclude the likelihood of more complex interrelationships between brain markers (e.g., mediation of one marker's impact on cognition by another), the potential for other important regional markers, or of additional brain markers we may have neglected to include. We hope that our findings will be taken as an impetus for further exploration of multivariate relationships between brain markers and cognition. It will be important to replicate these relationships in other datasets and to confirm their existence in longitudinal data, as the brain markers that predict change within an individual may differ from those that predict concurrent differences across individuals. Only with such convergent data can the causal sequence between brain and cognition be

confirmed, and can recommendations be made for the brain markers most likely to disambiguate age-related change from pathology-driven change in cognition.

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Notes

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