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A Review of the Brain Structure Correlates of Successful Cognitive Aging

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Abstract

Unimpaired cognition is an important feature of successful aging. Differences in cognitive performance among healthy older adults may be related to differences in brain structure. We reviewed the literature to examine the relationship between brain structure size and cognitive performance in older adults. Eighty-three percent of studies found at least one positive relationship between these factors; however, findings were variable. Positive relationships emerged most consistently between the hippocampal formation and global cognition and memory and between frontal measures and executive function. Additional longitudinal study is needed to further evaluate structure-cognition relationships in older adulthood and across the adult lifespan.

Keywords

Brain structure; successful aging; healthy aging; cognition; magnetic resonance imaging

Introduction

Much effort has been devoted to the study of both “normal” age-related cognitive decline and age-related pathology affecting cognition, such as Alzheimer’s disease. However, Rowe and Kahn{1} argued that the distinction between normal and pathological is insufficient to describe aging processes, given the heterogeneity found among healthy older adults in various domains, including cognition. Instead, they suggested we further distinguish between “usual” and “successful” aging. Definitions of successful aging vary widely and have included factors such as physical health, cognitive health, life satisfaction and/or well-being, and productivity and/or social activity.{2} While physical health is commonly included in researcher-defined criteria of successful aging, relatively few older adults who view themselves as aging “successfully” actually meet this criteria{3}. In contrast, unimpaired cognition is a common feature of most researcher-defined criteria of successful

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aging{2} and a contributing factor named by older adults as important to overall success in aging.{4} Determining factors that promote successful cognitive aging could lead to improvements in the quality of life of older adults.

Research often focuses on what happens “on average” across a group of individuals, while overlooking variability among individuals. When examining cognitive aging, an “on average” approach may result in overly simplistic conclusions. Wilson et al.,{5} a longitudinal study of cognitive function among older adults, illustrates this phenomenon. They found that, as a group, older adults declined in their cognitive performance over time; however, there was great variability among individuals. Whereas some individuals showed steep declines in performance, some showed only gradual declines, some others’ cognitive performance remained stable, and the rest even displayed improvements. This pattern of results exemplifies the heterogeneity in cognitive performance among aging individuals, and highlights the importance of examining different trajectories of aging.

Individual differences in cognitive performance among older adults may, at least in part, be explained by neurobiological factors, such as the size and integrity of brain structures. Some aspects of the relationship between brain structure and cognition in adulthood have been well researched and summarized. Studies examining structural correlates of intelligence in adults have largely shown that larger brain volumes are associated with higher intelligence scores.{6-8} There is also evidence to suggest that relationships between brain volume and intelligence are genetically determined.{9} Whereas this line of research provides important information regarding volumetric contributions to cognition, age effects are not emphasized. Much is also known about the relationship between brain structure and cognition among older adults with age-related pathology. For example, Alzheimer’s disease has been shown to be associated with volume loss in several brain areas, including the hippocampus, parahippocampal gyrus, entorhinal cortex, and the amygdala.{10} Although such evidence suggests that smaller volumes are associated with poorer cognitive functioning in impaired older adult populations, it remains to be seen whether similar relationships are observed as consistently among healthy older adults.

Careful examination of brain-behavior relationships in aging will prove useful in several ways. First, given the heterogeneity in cognitive performance among older adults, at least some of the variability is likely due to differences in brain structure. Determining structures predictive of superior cognitive performance may suggest neuroanatomical correlates of successful cognitive aging. Finally, knowing the relationship between age, brain structure, and cognition in healthy adults might suggest ways in which these factors interact in impaired populations.

Whether brain-behavior relationships change or remain stable across adulthood has not been well studied. Stability in these relationships from younger to older adulthood would support the concept of neural reserve (as described by Stern et al.{11}), in that individual differences would seem to persist throughout adulthood, and the more “reserve” an individual has, the greater his/her cognitive abilities. On the other hand, if brain-behavior relationships differ substantially between older and younger adults, this would provide evidence for neural compensation (also described by Stern et al.{11}). For example, if a particular brain area is unassociated with a cognitive ability in young adulthood but becomes strongly associated with the ability in older adulthood, one could argue that new brain areas are being used to achieve the same cognitive function in the face of other negative effects of aging.

In the following review, we sought to examine the brain structural correlates of successful cognition among healthy older adults. We chose to examine cognitive success, in particular, rather than other aspects of successful aging, as cognition is the most widely studied aspect

of successful aging in relation to brain structure. We hypothesized that brain structure size would be positively associated with performance in relevant cognitive domains (e.g., hippocampal size and memory performance). In addition, we wished to evaluate whether the relationship between brain structure and cognition differed between younger and older adults. While existing reviews{12,13} comment on some of these issues, they do not focus exclusively on them. Thus, we aimed to address these issues in a more detailed and comprehensive manner.

Methods

We conducted a literature review to identify papers in which the relationship between successful cognitive aging and brain structure was examined. A search of PubMed was performed using the following search terms: successful aging OR normal aging OR cognitive reserve AND imaging OR magnetic resonance imaging (MRI) OR computed tomography (CT). Relevant references cited in papers found via this search were also reviewed. This literature search was limited to papers published (or at least readily available *in press*) prior to April 1, 2008.

Inclusion Criteria

For inclusion in this review, studies were required to measure age, brain structure, and cognition in healthy older adults. Although factors other than cognition likely contribute to successful aging, we chose to examine successful aging in terms of good cognitive performance (i.e. successful cognitive aging) for the purposes of this review. We included studies that sampled a wide age range (age > 18 years), which extended into older adulthood, and studies whose samples consisted entirely of adults over 50 years of age. In order to best capture successful aging, only studies of healthy individuals were reviewed, with the definition of “healthy” being left at the discretion of the study authors. Studies of patient populations were also reviewed if a healthy control group was included, and results specific to that control group were reported.

The studies reviewed below had conducted a variety of brain structure analyses (ranging from whole brain measurements to measures of specific regions or structures) using MRI or CT. We included studies measuring the volume, thickness, and surface area of brain structures. However, we chose to exclude studies of white matter integrity and white matter hyperintensities, believing that their inclusion would result in an overly complicated review and given that a thorough review had recently been conducted including these studies.{14} If a study examined both an included and an excluded brain structure measure (e.g. volume and hyperintensities), we included it in our review but only report findings related to the included measure. There were no specific inclusion/exclusion criteria for measures of cognition.

Review Process

Using the above combination of search terms, 485 articles were initially found. We then reviewed the titles and abstracts of these articles and identified a subgroup of 34 papers that met our inclusion criteria (listed above) for further review. Sixteen additional articles were obtained from the references cited in these papers. In total, 50 papers met the above criteria and were reviewed. Descriptions of the results from each study are based on the study authors’ interpretations of their statistical analyses. We aimed to summarize the relationship of brain structure to cognition among older adults. In addition, we aimed to discuss the available, but limited, evidence concerning whether this relationship is different in younger and older adults. We also report age effects on brain structure. We did not, however, directly

examine age effects on cognitive performance, as our focus was on the structural brain correlates of cognition in aging.

Results

Summary information for each study is presented in Table 1 (with 39 cross-sectional studies) and Table 2 (with 11 longitudinal studies). Table 3 contains the demographic characteristics of the samples studied, aggregated across all 50 reviewed papers and across the 35 reviewed papers that specifically addressed structure-cognition relationships in older adulthood .

It was not possible to conduct a meta-analysis of the reviewed studies because of the great methodological variations among them. For example, operationalized definitions of "healthy" used by each study varied from relatively lenient (e.g., no major medical conditions){15} to relatively strict (e.g., no neurological, psychiatric, or medical conditions; no dementia or signs of MCI in cognitive performance; no evidence of cerebrovascular disease or lesions on MRI; no head trauma with loss of consciousness greater than 5 minutes; not taking any antidepressant, anxiolytic, or antiseziure medications; Mini-Mental State Exam not less than 26).{16} Domains mentioned as criteria for "health" consisted of following: 1) physical health, 2) cognitive health, 3) psychological health (e.g., no depression or anxiety), and 4) absence of substance abuse/dependence.

Neuroimaging methods and analysis techniques also differed across studies. The vast majority of studies (n=47) collected imaging data via MRI, whereas 4 used CT scans. In 28 studies, image analysis was done manually, such as hand tracing of a region of interest (ROI), whereas eight studies used automated analysis methods, and 13 utilized a combination of automated and manual methods. (One study did not report the analysis methods used). Five investigations conducted both whole-brain and ROI analyses, one exclusively used a whole-brain approach, and the remaining studies employed an ROI approach.

The studies reviewed here examined a wide range of brain measures and cognitive domains. Volume was by far the most common brain measure, collected in 49 studies. Two studies examined cortical thickness, and one measured surface area. Three studies utilized voxel-based morphometry (VBM). Gray matter (GM) regions in the temporal lobe, including the hippocampus, were the most common brain areas measured, followed by frontal brain measures. Although the reviewed studies assessed a wide variety of cognitive domains, memory, attention/working memory, and executive function were emphasized.

Relationship between Brain Structure and Cognition among Older Adults

Findings from all 50 reviewed studies can be found in Tables 1 and 2. In this section, we describe findings pertaining to the relationship between brain structure and cognition among older adults, as summarized in Table 4.

Global Brain Measures—Two of the reviewed cross-sectional studies examined relationships between overall brain size and global cognition among older adults: One found a positive association{17} while the other found no relationship.{18} Findings from the only longitudinal study of these factors{19} were consistent with a positive structure-cognition association. When relationships between overall brain size and individual cognitive domains were examined, positive relationships were found with a "frontal" cognitive factor,{20} while no associations were found with memory.{18-20}

Available findings suggest that global GM is positively associated with global cognition, both cross-sectionally{21} and longitudinally.{22} Global GM was also positively associated with the individual cognitive domains of abstract reasoning and processing speed, {21} and older adults who demonstrated better "fluid" cognitive ability had thicker cortex in several regions.{23} In contrast, global GM was unassociated with memory.{21} Unlike global GM, the evidence suggests that global white matter (WM) is unassociated with global cognition cross-sectionally{21} and longitudinally.{22} However, like global GM, global WM was positively associated with abstract reasoning and processing speed and unassociated with memory.{21}

Only one study examined the relationship between cerebrospinal fluid (CSF) and global cognition. In this longitudinal study, greater CSF predicted global cognitive decline.{22} Studies more commonly focused on associations between CSF and memory, yielding mixed results. One cross-sectional study found that less CSF was associated with better memory, {24} while another found no relationship between these factors.{25} Similarly, one longitudinal study, McArdle et al.,{26} found an inverse relationship, while another found no relationship.{27}

Frontal Measures—Among studies examining potential relationships between frontal brain measures and cognition among older adults (all cross-sectional), executive function was the domain most often studied. Most evidence supports a positive relationship between the size of frontal structures and executive function. Specifically, positive associations were found for total frontal lobe volume,{28} prefrontal cortical (PFC) volume,{29} and lateral frontal GM volume.{30} Other studies hinted at positive relationships. Namely, Fjell et al. {23} found that "high"-performing older adults did not differ from "average"-performing older adults in regards to cortical thickness, except in a small area in the right middle frontal gyrus. In MacLullich et al.,{17} greater frontal volume predicted better abstract reasoning, but only prior to adjustment for intracranial volume. In contrast, three studies found no relationship between frontal brain structures and executive function, specifically for measures of frontal cortical GM,{31} the superior, middle, and inferior frontal gyri,{20} and medial and orbital frontal GM volume.{30} One study found an inverse relationship between executive function and orbital frontal volume.{32}

Findings regarding relationships between frontal brain measures and other cognitive domains were more mixed. Studies associating frontal measures with attention/working memory performance found positive (orbital frontal volume),{30} inverse (lateral frontal volume,{30} orbital PFC volume{32}), and null relationships (total PFC volume,{29} volume of all PFC regions other than orbital PFC{32}). Similarly, studies of learning and/or memory also yielded positive (frontal cortical GM,{31} lateral PFC{33}), inverse (middle frontal gyrus,{20} superior PFC{32}), and null associations (frontal lobe volume).{28} Only one study associated frontal measures with global cognition and found a positive relationship with PFC GM, longitudinally.{22}

Temporal Measures

Hippocampus and Related Structures: A positive relationship between hippocampal formation (HF) volume and global cognition was generally supported. Two cross-sectional studies{34,35} and three longitudinal studies{19,22,[36]} found a positive relationship, while two cross-sectional studies found no relationship.{18,[37]}

There is relatively strong evidence that larger HF structure predicts better memory performance, as evidenced by the findings of 11 cross-sectional{18,[24],[34],[35],[38]-[44]} and two longitudinal studies.{27,[36]} Nevertheless, this relationship was not universally observed. Four cross-sectional studies{33,[37],[45],46} and three longitudinal studies{19,47,[48]} found no

association between the structures of the HF and memory. An additional cross-sectional study found that greater hippocampal asymmetry (right > left), not total hippocampal volume, predicted better memory.{49} Futhermore, Van Petten et al.,{20} a cross-sectional study, found an inverse relationship between hippocampal volume and memory.

No significant relationships were observed between HF size and other specific cognitive domains.{20,[30],[33],[44],[47]}

Other Temporal Regions: Relationships between cognition and other temporal lobe measurements were explored much less frequently. The most consistent finding that emerged is that temporal measures, other than the HF, were unrelated to memory performance (total temporal volume,{46} superior temporal gyrus,{18,24,27,39} fusiform gyrus{39}). However, some studies of memory did find significant associations. For example, Lupien et al.{39} observed a positive relationship with volume of the middle inferior gyrus, while Van Petten et al.{20} observed an inverse relationship with total temporal neocortical volume, the inferior temporal gyrus, and the fusiform gyrus.

Parietal, Occipital, Subcortical, and Cerebellar Measures—Associations between parietal, occipital, subcortical, and cerebellar brain measures and cognition were rarely studied among older adults. The limited findings included a positive association between posterior parietal cortex and global cognition,{22} null relationships between occipital regions and memory or executive functions,{20} a positive relationship between amygdala volume and memory,{49} and null relationships between amygdala and putamen volumes and attention and executive function.{30} Woodruff-Pak et al.{50} hinted that larger cerebellar volume related to better associative learning abilities, but the relationship was not statistically tested, only graphed.

Summary of Structure-Cognition Findings among Older Adults—Thirty-five of the reviewed studies (n=27 cross-sectional, n=8 longitudinal) addressed potential structural correlates of cognition specific to older adulthood. (The remaining studies did not directly comment on structure-cognition relationships among older adults, often because age was treated as a covariate in samples including younger and older adults). Eighty-three percent of these studies (n=29; n=24 cross-sectional, n=5 longitudinal) found at least one positive association between brain structure size and cognitive performance; however, almost all also found at least one null relationship between a particular brain structure and cognitive domain. In contrast, only 9% of the studies (n=3) commenting on structure-cognition relationships in older adults provided evidence that smaller brain structure size was associated with better cognition.{20,30,32} These were all cross-sectional studies of GM, and most of these relationships concerned frontal regions.

Overall, significant structure-cognition relationships emerged more frequently with GM measures and CSF, than with WM measures. However, this may be because WM volume measures were studied infrequently among the reviewed studies. Among the specific brain regions studied, positive relationships between HF and cognition (memory and global cognition) and frontal structures and executive function were the most consistent structure-cognition findings. Other relationships that were studied produced inconsistent findings, and many brain structures were sparsely studied.

In order to explore whether the pattern of structure-cognition findings among older adults was related to characteristics of the studied samples, Table 3 lists the ratio of positive, negative, and null structure-cognition relationships by demographic and other sample differences. Studies with larger sample sizes, lower mean educations, and fewer female subjects appeared to find a higher proportion of positive structure-cognition relationships.

Differences in age between the samples and whether or not studies were cross-sectional or longitudinal in design did not appear to affect the ratio of positive, negative, and null structure-cognition findings.

Structure-Cognition Relationships across Adulthood

While the above findings are important for understanding structure-cognition relationships in older adulthood, they do not address whether these relationships are unique to older adulthood or equivalent to those in younger adulthood. Four cross-sectional studies commented on this issue. In some cases, positive structure-cognition relationships were found among older adults, while structure was unrelated to performance in younger adults.{23,[30],[33]} In other cases, the same positive{30,[50]} or negative{30} structure-cognition relationship held across adulthood. Only one longitudinal study{26} directly addressed this question and found that increases in lateral ventricle size were related to decreases in memory, a relationship that strengthened with age. Of note, there were no findings of stronger structure-cognition associations among younger individuals compared to older individuals.

Discussion

The vast majority (83%; n = 29 of 35) of studies addressing potential brain structural correlates of cognition in older adulthood suggested that bigger brain structures are associated with better cognitive performance among older adults, at least for some brain regions and some cognitive domains. This caveat is important, however, as most studies that found a significant structure-cognition relationship also found a lack of association for at least one other structure-cognition relationship that was tested. When significant relationships did exist, however, inverse relationships were rare. (The three studies supportive of this possibility were cross-sectional in design, and their findings concerned measures of regional GM, particularly in frontal cortex). When considered together, the above mixed findings imply that positive structure-cognition relationships exist, but inconsistently at best.

Despite inconsistencies within the findings, some structure-cognition relationships were relatively well-supported. Namely, positive associations were repeatedly observed between HF size and memory and global cognitive performance and between frontal brain measures and executive functions. However, inconsistent findings were evident even for these relationships (similar to those noted in a meta-analysis{51} of hippocampal–memory relationships among older adults). Such inconsistencies may be due to methodological differences between studies, such as variations in sample size, characteristics of the samples, and the particular measures of brain size that were used. Although the vast majority of studies measured brain volume, it is currently unclear whether volume, thickness, or surface area measures (or some combination of the above) are biologically most relevant for determining cognitive functioning. Stronger and/or more consistent structure-cognition relationships may be found when non-volumetric measures are more extensively examined. For example, it appears that cortical thickness and surface area may have very different genetic underpinnings,{52} and this may, in turn, cause these measures to relate differently to cognition and show distinct patterns of age-related changes. In addition, cognitive measures used to examine structure-cognition relationships may also contribute to inconsistent findings. Because most standardized neuropsychological measures were designed for use in clinical settings, they may not be sufficiently sensitive to detect subtle individual differences related to brain structure in non-clinical populations. Finally, the inconsistent findings may indicate heterogeneity within the older adult population.

Relatively few of the reviewed studies addressed the question of whether structure-cognition relationships in older adulthood are different from those in younger adulthood. Those that did found either equivalent or stronger correlations of brain size with cognitive performance in older compared to younger individuals. As the number of these studies is quite limited, it is difficult to draw strong conclusions from them or to find patterns within them that explain why some showed equivalence and others showed stronger correlations among older participants. It is notable, however, that no studies found evidence for stronger relationships in younger individuals. This lack of findings argues against the idea that experience and/or cognitive strategies gained with age might attenuate the relationship between brain structure and cognitive performance.

Additional longitudinal research examining structure-cognition relationships across the adult lifespan is necessary in order to better understand the neural factors associated with successful cognitive aging. Given time and cost limitations of traditional longitudinal designs, an accelerated lifetime design, in which subgroups of individuals of overlapping age groups are followed, could best reveal the trajectory of change over a large age span. This research is needed as it is currently unclear whether individual variability in brain structure size merely persists into old age, leading those with larger structures to perform better cognitively, or whether there are neural changes that occur with age that promote successful cognitive aging. As previous findings suggest that experience can produce brain structural changes,{53,[54]} it is possible that interventions could be developed to facilitate successful cognitive aging through neural mechanisms.

Future research on successful cognitive aging would also benefit from standardization of the definition of “health” with careful consideration of screening for mild cognitive impairment (reported by only one study in the review). Additionally, since the brain regions examined in the reviewed studies were somewhat limited, future studies should expand consideration to other structures perhaps based on genetic or developmental evidence suggesting that they form larger, functionally-relevant structural units within the brain. Finally, a complete understanding of the neurobiological underpinnings of successful cognitive aging will likely require examination of both brain structural and functional measures and their interaction. {55}

There are several limitations to our review to consider when interpreting our findings. First, we may have failed to include some studies that met our inclusion criteria. Our review is also likely biased towards reporting significant structure-cognition relationships, as studies that do not find significant relationships are less likely to be published. Furthermore, our summaries of the reviewed studies are somewhat limited in regards to their level of detail due to the number, complexity, and diverse methodologies of the reviewed studies. In addition, while our review describes relationships between brain structure size and cognition, it does not indicate what these relationships might mean on a neurobiological level. We also did not include findings from DTI studies of white matter integrity (see Sullivan and Pfefferbaum{14} for thorough review of the age-related links between cognition and white matter integrity), and a recent paper not included in our review, Ziegler et al.,{56} suggests that associations between cognition and white matter integrity may be stronger than those with GM measures such as cortical thickness. Thus, stronger and more consistent relationships between brain structure and cognition may emerge among older adults when white matter integrity is considered. Finally, because successful aging is a broad concept without a consensus definition, our focus on cognitive performance means that the results of this review speak only to one aspect of successful aging. Indeed, results would likely differ if another aspect of successful aging (e.g. emotional well-being) was examined in relation to brain structure.

Research on the brain structure correlates of successful cognitive aging is a promising area of inquiry that has already received much attention in the literature. Research to date suggests positive structure-cognition relationships, particularly for the HF and frontal lobe; however findings are inconsistent at best. Further research is needed especially regarding whether the relationship between brain structure and cognition strengthens with age, thereby shedding light on how the processes of neural reserve and neural compensation might contribute to successful cognitive aging and perhaps suggesting when and how to intervene in order to enhance cognition in old age.

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References

1. Rowe JW, Kahn RL. Human aging: usual and successful. Science. 1987; 237(4811):143–149. [PubMed: 3299702]
2. Depp CA, Jeste DV. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. The American Journal of Geriatric Psychiatry. 2006; 14(1):6–20. [PubMed: 16407577]
3. Jeste DV, Depp CA, Vahia I. Successful cognitive and emotional aging. World Psychiatry. In Press.
4. Reichstadt J, Depp CA, Palinkas LA, et al. Building blocks of successful aging: a focus group study of older adults' perceived contributors to successful aging. The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry. 2007; 15(3):194–201. [PubMed: 17322132]
5. Wilson RS, Beckett LA, Barnes LL, et al. Individual differences in rates of change in cognitive abilities of older persons. Psychology and Aging. 2002; 17(2):179–193. [PubMed: 12061405]
6. McDaniel MA. Big-Brained People are Smarter: A Meta-Analysis of the Relationship between In Vivo Brain Volume and Intelligence. Intelligence. 2005; 33(4):337–346.
7. Flashman LA, Andreasen NC, Flaum M, et al. Intelligence and regional brain volumes in normal controls. Intelligence. 1997; 25(3):149–160.
8. Haier RJ, Jung RE, Yeo RA, et al. Structural brain variation and general intelligence. NeuroImage. 2004; 23(1):425–433. [PubMed: 15325390]
9. Posthuma D, De Geus EJC, Baaré WFC, et al. The association between brain volume and intelligence is of genetic origin. Nature Neuroscience. 2002; 5(2):83–84.
10. Atiya M, Hyman BT, Albert MS, et al. Structural magnetic resonance imaging in established and prodromal Alzheimer disease: a review. Alzheimer Disease and Associated Disorders. 2003; 17(3):177–195. [PubMed: 14512832]
11. Stern Y, Habeck C, Moeller J, et al. Brain networks associated with cognitive reserve in healthy young and old adults. Cerebral Cortex. 2005; 15(4):394–402. [PubMed: 15749983]
12. Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neuroscience and Biobehavioral Reviews. 2006; 30(6):730–748. [PubMed: 16919333]
13. Hedden T, Gabrieli JDE. Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci. 2004; 5(2):87–96. [PubMed: 14735112]
14. Sullivan EV, Pfefferbaum A. Diffusion tensor imaging and aging. Neuroscience & Biobehavioral Reviews. 2006; 30(6):749–761. [PubMed: 16887187]
15. Pfefferbaum A, Sullivan EV, Jernigan TL, et al. A quantitative analysis of CT and cognitive measures in normal aging and Alzheimer's disease. Psychiatry Research. 1990; 35(2):115–136. [PubMed: 2100804]

16. Rodrigue KM, Raz N. Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2004; 24(4):956–963. [PubMed: 14749440]
17. MacLullich AMJ, Ferguson KJ, Deary IJ, et al. Intracranial capacity and brain volumes are associated with cognition in healthy elderly men. Neurology. 2002; 59(2):169–174. [PubMed: 12136052]
18. Convit A, Wolf OT, Tarshish C, et al. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. Proceedings of the National Academy of Sciences of the United States of America. 2003; 100(4):2019–2022. [PubMed: 12571363]
19. Marquis S, Moore MM, Howieson DB, et al. Independent predictors of cognitive decline in healthy elderly persons. Archives of Neurology. 2002; 59(4):601–606. [PubMed: 11939895]
20. Van Petten C, Plante E, Davidson PSR, et al. Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. Neuropsychologia. 2004; 42(10):1313–1335. [PubMed: 15193940]
21. Staff RT, Murray AD, Deary IJ, et al. Generality and specificity in cognitive aging: a volumetric brain analysis. NeuroImage. 2006; 30(4):1433–1440. [PubMed: 16410052]
22. Tisserand DJ, van Boxtel MPJ, Pruessner JC, et al. A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. Cerebral Cortex. 2004; 14(9):966–973. [PubMed: 15115735]
23. Fjell AM, Walhovd KB, Reinvang I, et al. Selective increase of cortical thickness in high-performing elderly--structural indices of optimal cognitive aging. NeuroImage. 2006; 29(3):984–994. [PubMed: 16176876]
24. Golomb J, Kluger A, de Leon MJ, et al. Hippocampal formation size in normal human aging: a correlate of delayed secondary memory performance. Learning & Memory. 1994; 1(1):45–54. [PubMed: 10467585]
25. Earnest MP, Heaton RK, Wilkinson WE, et al. Cortical atrophy, ventricular enlargement and intellectual impairment in the aged. Neurology. 1979; 29(8):1138–1143. [PubMed: 313534]
26. McArdle JJ, Hamgami F, Jones K, et al. Structural modeling of dynamic changes in memory and brain structure using longitudinal data from the normative aging study. The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences. 2004; 59(6):294–304.
27. Golomb J, Kluger A, de Leon MJ, et al. Hippocampal formation size predicts declining memory performance in normal aging. Neurology. 1996; 47(3):810–813. [PubMed: 8797485]
28. Hänninen T, Hallikainen M, Koivisto K, et al. Decline of frontal lobe functions in subjects with age-associated memory impairment. Neurology. 1997; 48(1):148–153. [PubMed: 9008510]
29. Gunning-Dixon FM, Gur RC, Perkins AC, et al. Age-related differences in brain activation during emotional face processing. Neurobiology of Aging. 2003; 24(2):285–295. [PubMed: 12498962]
30. Zimmerman ME, Brickman AM, Paul RH, et al. The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. The American Journal of Geriatric Psychiatry. 2006; 14(10):823–833. [PubMed: 17001022]
31. Tullberg M, Fletcher E, DeCarli C, et al. White matter lesions impair frontal lobe function regardless of their location. Neurology. 2004; 63(2):246–253. [PubMed: 15277616]
32. Salat DH, Kaye JA, Janowsky JS. Greater orbital prefrontal volume selectively predicts worse working memory performance in older adults. Cerebral Cortex. 2002; 12(5):494–505. [PubMed: 11950767]
33. Kennedy KM, Raz N. Age, sex and regional brain volumes predict perceptual-motor skill acquisition. Cortex. 2005; 41(4):560–569. [PubMed: 16042032]
34. Hackert VH, den Heijer T, Oudkerk M, et al. Hippocampal head size associated with verbal memory performance in nondemented elderly. NeuroImage. 2002; 17(3):1365–1372. [PubMed: 12414276]
35. O'Brien JT, Desmond P, Ames D. Magnetic resonance imaging correlates of memory impairment in the healthy elderly: Association with medial temporal lobe atrophy but not white matter lesions. International Journal of Geriatric Psychiatry. 1997; 12(3):369–374. [PubMed: 9152723]

36. Visser PJ, Scheltens P, Verhey FR, et al. Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. Journal of Neurology. 1999; 246(6):477–485. [PubMed: 10431775]
37. Laakso MP, Hallikainen M, Hänninen T, et al. Diagnosis of Alzheimer's disease: MRI of the hippocampus vs delayed recall. Neuropsychologia. 2000; 38(5):579–584. [PubMed: 10689035]
38. Golomb J, de Leon MJ, Kluger A, et al. Hippocampal atrophy in normal aging. An association with recent memory impairment. Archives of Neurology. 1993; 50(9):967–973. [PubMed: 8363451]
39. Lupien SJ, de Leon M, de Santi S, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nature Neuroscience. 1998; 1(1):69–73.
40. Lye TC, Piguet O, Grayson DA, et al. Hippocampal size and memory function in the ninth and tenth decades of life: the Sydney Older Persons Study. Journal of Neurology, Neurosurgery, and Psychiatry. 2004; 75(4):548–554.
41. Reiman EM, Uecker A, Caselli RJ, et al. Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Annals of Neurology. 1998; 44(2):288–291. [PubMed: 9708558]
42. Rosen AC, Prull MW, Gabrieli JDE, et al. Differential associations between entorhinal and hippocampal volumes and memory performance in older adults. Behavioral Neuroscience. 2003; 117(6):1150–1160. [PubMed: 14674836]
43. Raz N, Gunning-Dixon FM, Head D, et al. Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. Neuropsychology. 1998; 12(1):95–114. [PubMed: 9460738]
44. Zimmerman ME, Pan JW, Hetherington HP, et al. Hippocampal neurochemistry, neuromorphometry, and verbal memory in nondemented older adults. Neurology. 2008; 70(18): 1594–1600. [PubMed: 18367703]
45. Dickerson BC, Feczko E, Augustinack JC, et al. Differential effects of aging and Alzheimer's disease on medial temporal lobe cortical thickness and surface area. Neurobiology of Aging. 2009; 30(3):432–440. [PubMed: 17869384]
46. de Toledo-Morrell L, Dickerson B, Sullivan MP, et al. Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. Hippocampus. 2000; 10(2):136–142. [PubMed: 10791835]
47. Cohen RM, Small C, Lalonde F, et al. Effect of apolipoprotein E genotype on hippocampal volume loss in aging healthy women. Neurology. 2001; 57(12):2223–2228. [PubMed: 11756601]
48. Du AT, Schuff N, Zhu XP, et al. Atrophy rates of entorhinal cortex in AD and normal aging. Neurology. 2003; 60(3):481–486. [PubMed: 12578931]
49. Soininen HS, Partanen K, Pitkänen A, et al. Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: correlation to visual and verbal memory. Neurology. 1994; 44(9):1660–1668. [PubMed: 7936293]
50. Woodruff-Pak DS, Vogel RW, Ewers M, et al. MRI-assessed volume of cerebellum correlates with associative learning. Neurobiology of Learning and Memory. 2001; 76(3):342–357. [PubMed: 11726241]
51. Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia. 2004; 42(10):1394–1413. [PubMed: 15193947]
52. Panizzon MS, Fennema-Notestine C, Eyler LT, et al. Distinct Genetic Influences on Cortical Surface Area and Cortical Thickness. Cerebral Cortex. 2009; 19(11):2728–2735. [PubMed: 19299253]
53. Draganski B, Gaser C, Busch V, et al. Neuroplasticity: changes in grey matter induced by training. Nature. 2004; 427(6972):311–312. [PubMed: 14737157]
54. Maguire EA, Woollett K, Spiers HJ. London taxi drivers and bus drivers: A structural MRI and neuropsychological analysis. Hippocampus. 2006; 16(12):1091–1101. [PubMed: 17024677]
55. Greenwood PM. Functional Plasticity in Cognitive Aging: Review and Hypothesis. Neuropsychology. 2007; 21(6):657–673. [PubMed: 17983277]

56. Ziegler DA, Piguet O, Salat DH, et al. Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. Neurobiology of Aging. In Press, Corrected Proof http://www.sciencedirect.com/science/article/B6T09-4V57XTK-1/2/7efb23342acdd2779b964184d7f2b6ba.
57. Brickman AM, Zimmerman ME, Paul RH, et al. Regional white matter and neuropsychological functioning across the adult lifespan. Biological Psychiatry. 2006; 60(5):444–453. [PubMed: 16616725]
58. Driscoll I, Hamilton DA, Petropoulos H, et al. The aging hippocampus: cognitive, biochemical and structural findings. Cerebral Cortex. 2003; 13(12):1344–1351. [PubMed: 14615299]
59. Head D, Raz N, Gunning-Dixon F, et al. Age-related differences in the course of cognitive skill acquisition: the role of regional cortical shrinkage and cognitive resources. Psychology and Aging. 2002; 17(1):72–84. [PubMed: 11931289]
60. Paul R, Grieve SM, Chaudary B, et al. Relative contributions of the cerebellar vermis and prefrontal lobe volumes on cognitive function across the adult lifespan. Neurobiology of Aging. 2009; 30(3):457–465. [PubMed: 17869383]
61. Raz N, Torres IJ, Spencer WD, et al. Neuroanatomical correlates of age-sensitive and age-invariant cognitive abilities: An in vivo MRI investigation. Intelligence. 1993; 17(3):407–422.
62. Raz N, Briggs SD, Marks W, et al. Age-related deficits in generation and manipulation of mental images: II. The role of dorsolateral prefrontal cortex. Psychology and Aging. 1999; 14(3):436–444. [PubMed: 10509698]
63. Raz N, Williamson A, Gunning-Dixon F, et al. Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. Microscopy Research and Technique. 2000; 51(1):85–93. [PubMed: 11002356]
64. Schretlen D, Pearlson GD, Anthony JC, et al. Elucidating the contributions of processing speed, executive ability, and frontal lobe volume to normal age-related differences in fluid intelligence. Journal of the International Neuropsychological Society. 2000; 6(1):52–61. [PubMed: 10761367]
65. Seidman LJ, Faraone SV, Goldstein JM, et al. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. Archives of General Psychiatry. 2002; 59(9):839–849. [PubMed: 12215084]
66. Sullivan EV, Marsh L, Mathalon DH, et al. Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. Neurobiology of Aging. 1995; 16(4):591–606. [PubMed: 8544910]
67. Tisserand DJ, Visser PJ, van Boxtel MP, et al. The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. Neurobiology of Aging. 2000; 21(4):569–576. [PubMed: 10924774]
68. Cook IA, Leuchter AF, Morgan ML, et al. Longitudinal progression of subclinical structural brain disease in normal aging. The American Journal of Geriatric Psychiatry. 2004; 12(2):190–200. [PubMed: 15010348]
69. Raz N, Lindenberger U, Rodrigue KM, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cerebral Cortex. 2005; 15(11):1676–1689. [PubMed: 15703252]
70. Walhovd KB, Fjell AM, Reinvang I, et al. Size does matter in the long run: hippocampal and cortical volume predict recall across weeks. Neurology. 2004; 63(7):1193–1197. [PubMed: 15477537]

Table 1

Cross-Sectional Studies

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Education *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correction to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
Samples of Older Adults	Convit et al., 2003{18}	30	68.6	53-89	56.7%	16.2	Physical, Cognitive, Psychological	MRI	Manual	Volume of hippocampus, parahippocampal gyrus, superior temporal gyrus, global atrophy [L+R]	Volume of cerebral vault	Global, Verbal Memory	↑ Global atrophy. ↓ Hippocampus (trend).	↑ Hippocampus & memory†	---
	Dickerson et al., 2009{45}	47	76.2	66-90	63.8%	---	Physical, Cognitive, Psychological	MRI	Mixed	Mean thickness, surface area, and volume of L&R entorhinal, perirhinal, posterior parahippocampal cortices	ICV	Verbal Memory	**O** < **Y** in L&R entorhinal cortex volume, surface area (trend for thickness). **O** < **Y** in L&R posterior parahippocampal cortex volume, surface area.	↑ Entorhinal cortex thickness & memory (trend).	---
	Earnest et al., 1979{25}	59	78	60-99	81.4%	13.2	Physical, Cognitive, Substance Abuse	CT	Manual	Widths of 4 largest sulci, size of lateral ventricles	None	Attention/ Working Memory, Executive Function, Processing Speed, Visual Memory, Visuospatial Processing	↑ Size of largest sulci and ventricle size. **80-99 year-olds** > **60-79 year-olds** in widths of largest sulci and ventricle size.	↓ Ventricles & processing speed†	---
	Golomb et al., 1993{38}	145	70	55-88	52.6%	---	Physical, Cognitive, Psychological, Substance Abuse	MRI or CT	Manual	Hippocampal atrophy [L+R]	None	Attention/ Working Memory, Verbal & Visual Memory	**Hippocampal atrophy group** > **no hippocampal atrophy group** in age	**No hippocampal atrophy group** > **hippocampal atrophy group** in verbal memory†. **No hippocampal atrophy group** > **hippocampal atrophy group** in non-verbal memory (trend)†.	---
	Golomb et al., 1994{24}	54	69	55-87	57.4%	15.0	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Volume of HF, superior temporal gyrus, CSF [L+R]	Head Size	Attention/ Working Memory, Verbal & Visual Memory	↓ Hippocampus, superior temporal gyrus. ↑ CSF.	↑ Hippocampus & memory†, ↓ CSF & memory†	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Edu-cation *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correct-ion to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
	Gunning-Dixon and Raz, 2003{29}	139	63.7	50-81	59.7%	---	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Volume of PFC, fusiform gyrus [L+R]	Height	Attention/ Working Memory, Executive Function	↓ PFC and fusiform gyrus.	↑ PFC & executive function†	---
	Hackert et al., 2002{34}	511	73	60-90	48.9%	"primary": 31%, "inter-mediate/ higher": 60%, "college": 9%	Cognitive	MRI	Manual	Volume of hippocampus [L&R]	ICV	Global, Verbal Memory	↓ Hippocampal head, body, and tail [L&R]	↑ Hippocampus (L&R total, L & R head) & memory†. ↑ Hippocampus (L&R head) & global cognitive performance†.	---
	Hanninen et al., 1997{28}	90	70.5	50+	61.3	9.1	Cognitive, Psychological	MRI	Manual	Volume of frontal lobe [L&R]	---	Executive Function, Verbal & Visual Memory	---	**Controls**: ↑ Frontal lobe [L&R] & executive function†. **Age-Associated Memory Impairment group**: ↑R frontal lobe & executive function†.	---
	Laasko et al., 2000{37}	34	72	64-79	58.8%	---	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Volume of hippocampus [L&R]	ICV	Global, Visual Memory	---	Hippocampal volume unassociated with cognition.	---
	Lupien et al., 1998{39}	9	73.9	---	---	11.2	Physical, Cognitive	MRI	Mixed	Volume of hippocampus, parahippocam-pal gyrus, fusiform gyrus, middle -inferior temporal gyrus, superior tempo-ral gyrus [L+R]	Head Size	Visual Memory	No relationship between age and volumes.	↑ Hippocampus & memory. ↑ Middle inferior gyrus & memory.	---
	Lye et al., 2004{40}	57	85.1	80+	50.9%	10.4	Cognitive	MRI	Mixed	Volume of hippocampus [L&R]	Total volume	Verbal & Visual Memory	---	↑ L hippocampus & memory (depending on memory measure)†.	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Education *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correction to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
	MacLullich et al., 2002{17}	97	67.8	65-70	0.0%	---	Physical	MRI	Mixed	Volume of hippocampus, temporal lobes, frontal lobes [L&R]; Intracranial area.	Intracranial area	Abstract Reasoning, Executive Function, Premorbid Function, Processing Speed, Verbal & Visual Memory	---	↑ General brain size factor & general cognitive factor.	---
	O'Brien, 1997{35}	40	71.6	55-96	50%	11.9	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Hippocampal/ amygdala atrophy [L+R]	---	Global, Abstract Reasoning, Executive Function, Language, Motor Skills, Verbal & Visual Memory	↑ Hippocampal/ amygdala atrophy	**No hippocampal/ amygdala atrophy group > hippocampal/ amygdala atrophy group** in memory, global cognition†	---
	Reiman, et al. 1998{41}	33	56	50-62	72.7%	15.9	Physical, Cognitive, Psychological	MRI	Manual	Volume of hippocampus [L&R]	ICV	Verbal Memory	No relationship between age and hippocampal volume.	↑ Hippocampus [L&R] & memory	---
	Rosen et al., 2003{42}	14	70.0	---	85.7%	16.1	Physical, Cognitive, Psychological	MRI	Manual	Volumes of entorhinal cortex, hippocampus [L&R]	ICV	Verbal Memory	---	**High Memory group > Low Memory group in** entorhinal cortex, hippocampus [L&R]. ↑ L entorhinal cortex & memory (immediate and delayed). ↑ L hippocampus & delayed memory.	---
	Salat et al., 2002{32}	31	84	72-94	51.6%	14.9	Physical, Cognitive, Psychological	MRI	Manual	Total PFC volume, PFC WM volume, and PFC GM volume; Superior, middle, inferior, orbital, anterior cingulate PFC ROIs [L+R]	ICV	Attention/ Working Memory, Executive Function, Other ("Conditional Association Learning")	↑ Orbital PFC.	↓ Superior PFC & learning. ↓ Orbital PFC (relative to other ROIs) & working memory, executive function.	---
	Soininen, 1994{49}	32	69.0	---	---	10.2	Physical, Cognitive	MRI	Manual	Volume of hippocampus, amygdala [L&R]	Total volume	Verbal & Visual Memory	No relationship between age and volumes.	**Controls = Age-Associated Memory Impairment group** in hippocampal, amygdala	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Education *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correct-ion to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
														volumes. **Controls** > **Age-Associated Memory Impairment group** in hippocampal asymmetry (R > L). **Groups combined**: ↑ **R** hippocampus & visual memory, ↑ hippocampal asymmetry & visual memory, ↑ amygdala [L&R] & verbal memory.	
	Staff et al., 2006{21}	98	---	79-80	---	---	Physical, Cognitive	MRI	Automated	VBM; Total GM and WM	ICV	Abstract Reasoning, Premorbid Function, Processing Speed, Verbal Memory	---	↑ WM & processing speed, abstract reasoning. ↑ GM & processing speed, abstract reasoning, general intelligence.	---
	de Toledo et al., 2000{46}	30	72.4	64-84	---	---	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Volume of hippocampus, parahippocam-pal gyrus, temporal lobe [L&R]	ICV	Verbal & Visual Memory	---	Volumes unassociated with memory†	---
	Tullberg et al., 2004{31}	78	77.5	---	---	---	Physical, Cognitive	MRI	Mixed	Frontal and posterior cortical GM volumes [L+R]	ICV	Attention/ Working Memory, Executive Function, Verbal Memory (Executive Function and Memory composites)	---	↑ Frontal cortical GM & memory.	---
	Van Petten et al., 2004{20}	48	73.2	65.5-85.8	68.8%	15.0	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Total cerebral volume; GM volume of frontal (superior, middle, inferior gyri), temporal (HF; superior, middle, inferior, fusiform, and parahippocam-	Both raw and ICV-corrected measures reported	Attention/ Working Memory, Executive Function, Verbal & Visual Memory (Memory and "Frontal factor" composites)	↓ Total cerebral volume, GM in temporal lobe (superior and middle temporal gyri, L temporal neocortex), and frontal lobe (inferior frontal gryus, sum of frontal ROIs).	↓ GM in middle frontal gyrus and most temporal ROIs including hippo-campus & memory. ↑ Cranial vault & "frontal factor".	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Edu-cation *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correct-ion to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
										pal gyri), occipital regions [L&R]					
	Zimmerman et al., 2008{44}	48	81.8	>70	47.9%	13.1	Physical, Cognitive	MRI	Manual	Volume of hippocampus [L&R]	ICV (midsag-ittal area)	Executive Function, Processing Speed, Verbal Memory	↓ Hippocampus [L+R]	↑ Hippocampus [L+R] & memory (for 1 out of 2 measures)†. When analyzed by group, relationship held in **Normal Memory group** but not **Mild Memory Impairment group**†	---
Samples of Younger and Older Adults	Brickman et al., 2006{57}	Y: 77, M: 82, O: 40	Y: 25.2; M: 43.7; O: 63.2	Y: 21-30; M: 31-54; O: 55-79	Y: 62%; M: 46%; O: 42%	Y: 14.7; M: 14.1; O:12.2	Physical, Psychological, Substance Abuse	MRI	Automated	VBM; WM volume in frontal, temporal, parietal, occipital lobes [L&R]	Total WM volume	Attention/ Working Memory, Executive Function, Verbal Memory	**O** < **Y** & **M** in global WM (**Y** = **M**). **O** < **Y** in frontal and temporal WM (**M** < **Y** but not **O**). Quadratic relationship in L&R frontal, L&R temporal, L&R parietal, and R occipital WM.	↑ R frontal WM & cognition (especially executive function, memory). ↑ R temporal WM & cognition (especially executive function, memory). ↑ L frontal WM & executive function, memory. ↑ L temporal WM & executive function, memory.	Age-memory relationship partially mediated by L&R frontal WM. Age-executive function relationship partially mediated by L frontal WM. Age x structure interaction not directly tested.
	Driscoll et al., 2003{58}	Y: 16; O: 16	Y: 26.1; O: 77.6	Y: 20-39; O: 60-85	Y: 50%; O: 50%	---	Physical, Cognitive, Psychological	MRI	Automated	Volume of hippocampus [L&R]	ICV	Visual Memory, Visuospatial Processing	**O** < **Y** in hippocampus [L&R]	↑ Hippocampal volume [L+R] & visuospatial performance	---
	Fjell et al., 2006{23}	Y: 35, O: 39	Y: 35.5; O: 70.7	20-88	55.4%	Y: 15.8; O: 14.6	Physical, Cognitive	MRI	Automated	Cortical thickness at each vertex of cortical mantle	---	Abstract Reasoning, Attention/ Working Memory, Executive Function,, Visuospatial Processing (combined into "Fluid" Function and Executive Function domains)	**O with High Fluid Function** vs. **Y**: Thinner cortex in most regions, but thicker cortex in R posterior cingulate gyrus and L subcallosal gyrus. **O with Average Fluid Function** vs. **Y**: Thinner cortex in	---	**O with High** vs. **O with Average Fluid Function:** Thicker cortex especially in R posterior cingulate gyrus, frontal and prefrontal regions, medial structure, gyrus of cingulate isthmus. **Y with High** vs. **Y with Average Fluid Function:** No differences in R posterior cingulate or L subcallosal region. **O with High** vs. **O with Average Executive Function**: Thicker cortex in R

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	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Education *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correction to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
										[L&R]			all regions.		middle frontal gyrus.
	Head et al., 2002{59}	68	48.9	22-80	61.8%	---	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Volume of lateral PFC, HF, caudate nucleus, putamen, visual cortex, cerebellar hemispheres [L+R]	Height	Attention/ Working Memory, Executive Function, Visuospatial Processing	↓ Lateral PFC, putamen, cerebellar hemispheres	↑ Lateral PFC & working memory in early-stage skill acquisition (only when including individuals with hypertension)†.	---
	Kennedy and Raz, 2005{33}	Y: 30, M: 29, O: 26	47.4	Y: 20-39; M: 40-60; O: 60-80	56.5%	16.0	Physical, Psychological	MRI	Manual	Volume of lateral PFC, hippocampus, caudate, cerebellar hemispheres [L+R]	Height	Motor Skills, Visuospatial Processing ("Perceptual-Motor Skill Acquisition")	---	Brain not associated with cognitive performance across all ages.	**O**: ↑ Lateral PFC volume & skill acquisition (strengthened with practice). **Y**: No similar "practice effect."
	Paul et al., 2009{60}	Y: 158; M: 67; O: 26	Y: 26.5; M: 49.8; O: 66.2	Y:18-39; M: 40-59; O: 60-79	Y: 55.1%; M: 67.2%; O: 53.8%	Y: 14.5; M: 14.5; O: 13.3	Physical, Cognitive, Psychological, Substance Abuse	MRI	Automated	Volume of PFC, cerebellar GM, cerbellar vermis [L+R]	PFC volume or cerebellar GM volume	Attention/ Working Memory, Executive Function, Motor Skills, Visuospatial Processing, Other (Time Estimation)	**O** < **Y** and **M** in total cerebellar GM. **O** < **Y** in posterior superior vermian GM. **O** < **Y** and **M** in prefrontal volume.	Mixed results for relationship between PFC and executive function. ↑ PFC & processing speed. ↑ PFC & visuospatial processing.	---
	Pfefferbaum et al., 1990{15}	105	62.2	20-82	60.0%	16	Physical	CT	Mixed	CSF in lateral ventricles, vertex sulci, frontal sulci, Sylvian fissures, parieto-occipital sulci, third ventricle	---	Abstract Reasoning, Attention/ Working Memory, Executive Function, Language, Processing Speed, Verbal & Visual Memory, Visuospatial Processing, Vocabulary	↑ CSF in all ROIs	↓ CSF in vertex sulci and Sylvian fissure & performance IQ measures. ↓ CSF in Sylvian fissure & language. Brain measures no longer associated with cognition†.	---
	Raz et al., 1993{61}	29	43.8	18-78	41.40%	15	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Volume of cerebrum, inferior parietal lobule, HF. Cross-sectional	Head Size	Global, Vocabulary	↓ Cerebral volume, dorso-lateral PFC area, prefrontal WM area.	↑ Cerebrum & "fluid" intelligence. ↑ Cerebral asymmetry (L>R) & "fluid" intelligence, vocabulary. ↑ Dorso-	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Edu-cation *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correct-ion to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
										area of dorso-lateral PFC, postcentral gyrus, prefrontal WM [L+R, asymmetry]				lateral PFC & "fluid" intelligence. ↑ Prefrontal WM asymmetry (L>R) & fluid" intelligence. ↑ Cerebral asymmetry (L>R)& fluid intelligence, vocabulary†. All other relationships became non-significant†.	
	Raz et al., 1998{43}	95	44	18-77	56.8%	16.1	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Volume of dorsolateral PFC, orbito-frontal cortex, visual cortex, fusiform gyrus, inferior parietal lobe, parahip-pocampal gyrus, HF. [L+R]	Height	Attention/ Working Memory, Executive Function, Verbal & Visual Memory, Visuospatial Processing	↓ PFC, fusiform gyrus, hippo-campus, visual cortex.	↑ PFC volume & executive function†. ↑ Visual cortex & working memory†.	**60-77 year-olds with poorest memory scores**: ↑ hippocampus & memory. Relationship not found in whole sample.
	Raz et al., 1999{62}	60	47.5	19-77	58.3%	16.3	Physical, Psychological, Substance Abuse	MRI	Manual	Volume of dorsolateral PFC, inferior temporal gyrus, fusiform gyrus, occipital cortex [L+R]	Height	Attention/ Working Memory, Visuospatial Processing	↓ Dorsolateral PFC, fusiform gyrus	↑ Dorsolateral PFC & visuospatial processing†.	---
	Raz et al., 2000{63}	68	45.5	22-80	55.9%	---	Physical, Cognitive, Psychological, Substance Abuse	MRI	Manual	Volume of dorsolateral PFC, hippo-campus, caudate, putamen, cerebellum [L+R]	Height	Attention/ Working Memory, Visuospatial Processing, Motor Skills	↓ Dorsolateral PFC, hippo-campus, putamen, cerebellum.	↑ Cerebellum & motor skills†. ↑ Putamen & motor skills†. ↑ Cerebellum & working memory†.	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Edu-cation *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correct-ion to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
	Schretlen et al., 2000{64}	112	54	---	57.1%	13.5	Physical, Cognitive, Psychological, Substance Abuse	MRI	Mixed	Frontal and nonfrontal volume [L+R]	Non-frontal volume	Abstract Reasoning, Attention/ Working Memory, Executive Function, Premorbid Function, Processing Speed, Verbal & Visual Memory, Visuospatial Processing, Vocabulary	↓ Frontal volume.	↑ Frontal volume = & executive function. ↑ Frontal volume & fluid-spatial ability†.	---
	Seidman et al., 2002{65}	47	40.1	20-68	43.7%	15.1	Physical, Psychological, Substance Abuse	MRI	Mixed	Volume of hippocampus [L&R]	Total cerebral volume	Premorbid Function, Verbal Memory, Visuospatial Processing, Vocabulary	---	↑ Hippocampus [L&R] & memory.	---
	Sullivan et al., 1995{66}	64	43.9	21-70	0%	16.3	Cognitive, Psychological, Substance Abuse	MRI	Mixed	Volume of hippocampus, temporal lobe GM and WM, CSF [L&R]	Head size	Attention/ Working Memory, Premorbid Function, Verbal & Visual Memory, Vocabulary	↓ L&R temporal GM. ↑ CSF.	↑ Hippocampus [L&R] & verbal memory. ↓ Hippocampus [L&R] & visual memory. ↓ L hippocampus & attention/working memory. ↑ R temporal GM & visual memory, attention/working memory. ↓ CSF & memory, attention/ working memory. ↑ Cortical GM & attention/working memory.	---
	Tisserand et al., 2000{67}	61	55.7	21- 81	57.4%	2.6 ("1 = primary school, 5 = university degree")	Physical, Cognitive, Psychological	MRI	Mixed	Volume of hippocampus, parahippocam-pal gyri [L&R]; mammillary bodies, CSF in third ventricle	ICV	Attention/ Working Memory, Executive Function, Verbal Memory	↓ Total volume. ↓ Hippocampus [L&R]. ↓ Para-hippocampal gyri [L&R]. ↑ CSF.	↑ Hippocampus [L+R] & memory, executive function. ↑ Parahippo-campal gyrus [L+R] & memory, executive function. ↑ Total volume & memory, executive function. ↓ CSF & memory, executive	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Edu-cation *(Years)*	Criteria for "Health"	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correct-ion to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
														function. Brain measures no longer associated with cognition†.	
	Woodruff-Pak et al., 2001{50}	Y: 8; O: 8	Y: 27.3; O: 82.5	Y: 21-35; O: 77-95	Y: 62.5%; O: 50%	---	Cognitive	MRI	Manual	Volume of cerebellum [L+R]	ICV	Other (Acquisition of conditioned response)	**O** < **Y** in cerebellar volume	**Y** and **O** combined: ↑ cerebellum & acquisition of conditioned response.	**Y**: ↑ Cerebellum & acquisition of conditioned response (trend). *O*: Scatter plot suggests same relationship holds.
	Zimmerman et al., 2006{30}	148	40.1	21-76	49.0%	14.6	Physical, Psychological , Substance Abuse	MRI	Automated	GM volume in hippocampus, amygdala, putamen, lateral frontal lobe, medial frontal lobe, orbital frontal lobe [L+R]	---	Attention/ Working Memory, Executive Function	↓ Hippocampus, amygdala, putamen, lateral frontal, medial frontal, and orbital frontal. Quadratic relationship in caudate and thalamus (↓ until age 50, then ↑).	---	From graph, <**40 years old:** lateral frontal volume not associated with executive function; >**40 years old:** ↑ Lateral frontal volume & executive function. ↓ Lateral frontal volume & attention regardless of age. ↑ Orbital frontal volume & attention regardless of age.

Key: Y = younger adults; M = middle-aged adults; O = older adults; GM = gray matter; WM = white matter; CSF = cerebrospinal fluid; PFC = prefrontal cortex; HF = hippocampal formation; ROI = region of interest; VBM = voxel-based morphometry; ↑ = positive association; ↓ = negative association; † = controlling for age; [L+R] = bilateral regions combined in analyses; [L&R] = both hemispheres analyzed separately.

Note: Only statistically significant results are reported, except when otherwise noted.

Table 2

Longitudinal Studies

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Education *(Years)*	Criteria for "Health"	Factors Measured Longitudinally	Study Interval: Mean *(SD)*; Range	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correction to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
Samples of Older Adults	Cohen et al., 2001{47}	25	57.1	50+	100%	16.7	Physical, Cognitive	Brain and Cognition	~2 years	MRI	Mixed	Volume of hippocampus [L+R]	---	Attention/ Working Memory, Executive Function, Verbal & Visual Memory, Visuospatial Processing	↓ Hippo-campus	Volume changes unassociated with cognitive changes. Baseline hippo-campal volume* unassociated with baseline cognition*.	---
	Cook et al., 2004{68}	29	74.8	60-89	58.6%	15.5	Physical, Psychological. Substance Abuse	Brain and Cognition	3.6 years *(0.8)*; 2-6 years	MRI	Mixed	Volume of sulcal and ventricular CSF	ICV	Abstract Reasoning, Executive Function, Language, Processing Speed	↑ Sulcal & ventricular CSF	Minimal change in cognition, thus unable to examine longitudinal effects. Cognition at follow-up* unrelated to CSF at follow-up*.	---
	Du et al., 2003{48}	23	76.5	---	30.4%	---	Physical, Cognitive, Psychological, Substance Abuse	Brain	1.8 years	MRI	Manual	Volume of entorhinal cortex [L&R]	ICV	Verbal Memory	↓ Entorhinal cortex [L&R]	Volume change not associated with memory*.	---
	Golomb et al., 1996{27}	44	68.5	55+	59.1%	15.1	Physical, Cognitive, Psychological, Substance Abuse	Cognition	3.8 years *(1.0)*; 2-6 years	MRI	Manual	Volume of HF, superior temporal gyrus, CSF [L+R]	ICV	Global, Verbal Memory	---	Smaller hippocampus (baseline)* = ↓ memory†.	---
	Marquis et al., 2002{19}	108	83.2	65+	63.0%	14.1	Physical, Cognitive, Substance Abuse	Cognition	6 years *(2.6)*	MRI	Manual	Volume of hippocampus, total volume [L+R]	---	Global, Verbal Memory	↓ Hippo-campus	Smaller hippo-campus [L+R], total volume (baseline)* = ↓ global cognition†. No relationships with memory.	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Education *(Years)*	Criteria for "Health"	Factors Measured Longitudinally	Study Interval: Mean *(SD)*; Range	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correction to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
	Tisserand et al., 2004{22}	75	72.2	52-84	50.7%	"lower vocational education / intermediate secondary education"	Physical, Cognitive, Substance Abuse	Cognition	~3 years	MRI	Automated	Total GM, WM, and CSF volume. VBM of GM. ROIs: PFC and medial temporal lobe (all measured at "follow-up")	---	Global, Attention/ Working Memory, Executive Function, Processing Speed, Verbal Memory ("non-decliners" vs. "decliners")	Overall: ↓ GM*, ↑ CSF*. **Non-decliners**: ↓ GM* (especially PFC [L&R], medial temporal lobe [L&R], striate cortex).	**Non-decliners** > **Decliners** in GM* (especially in PFC, R temporal lobe, and R posterior parietal cortex). **Non-decliners** < **Decliners** in CSF*.	---
	Visser et al., 1999{36}	18	76.8	65-85	56%	8.2	Cognitive, Psychological	Cognition	~3 years	MRI	Mixed	Volume of hippocampus, parahippo-campal gyrus, medial temporal lobe [L+R]	ICV	Global, Verbal & Visual Memory	---	No relationship between volumes* and cognition* at baseline. Larger parahippocampal gyrus* = ↑ memory, global cognition	---
Samples of Younger and Older Adults	McArdle et al., 2004{26}	225	---	30-80	51.6%	14.4	Physical, Psychological	Brain and Cognition	~ 7 years	CT	---	Lateral ventricle size [L+R]	Head size	Attention/ Working Memory, Verbal & Visual Memory	↑ Lateral ventricle size	↑ Lateral ventricle size = ↓ memory	Relationship between lateral ventricle size and memory strengthens with age
	Raz et al., 2005{69}	72	52.6	20-77	58.3%	15.9	Physical, Cognitive, Psychological	Brain and Cognition	5.3 years *(0.3)*; 4.8-6.1 years	MRI	Manual	Volume of lateral PFC, orbital frontal cortex, prefrontal WM, inferior parietal lob-ule, inferior parietal WM, inferior temp-oral cortex, fusiform cortex, percalcarine cortex, hippocampus,	ICV	Global	Mean ↓ all ROIs except visual cortex. Individual ↓ for all ROIs except inferior parietal lobule. **O** < **Y** in rate of ↓ in prefrontal WM, inferior temporal cortex, hippocampus, entorhinal	Minimal change in cognition. No relationship with structural changes.	---

	Study	N	Mean Age	Age Range	Gender *(% Female)*	Mean Education *(Years)*	Criteria for "Health"	Factors Measured Longitudinally	Study Interval: Mean *(SD)*; Range	Imaging Modality	Image Analysis Method	Brain Measure(s)	Correction to Brain Measures	Cognitive Domains Measured	Age Effect on Brain Structure	Relationship between Brain Structure and Cognition	Comparison of Structure-Cognition Relationships in Older Adults vs. Younger Adults
												entorhinal cortex, caudate, cerebellum [L+R]			cortex, cerebellar hemispheres.		
	Rodrigue and Raz, 2004{16}	48	57.6	26-82	60.4%	16	Physical, Cognitive, Psychological, Substance Abuse	Brain	5.2 years *(0.2)*; 5.0-5.9 years	MRI	Manual	Volume of entorhinal cortex, hippocampus, lateral PFC [L&R]	ICV	Verbal Memory	↓ PFC, hippocampus, and entorhinal cortex. Rate of ↓ increased with age in PFC and hippocampus, but not entorhinal cortex. [L+R]	↓ Entorhinal cortex = worse memory*†.	---
	Walhovd et al., 2004{70}	54	51	20-88	53.7%	15.3	Physical, Cognitive	Cognition	79 days *(42)*; 42-241 days	MRI	Automated	Volume of WM, cortex, hippocampus [L+R]	ICV	Verbal Memory	↓ WM*, cortical*, hippocampal volumes*	Bigger cortical* and hippocampal volume* = better memory*. Bigger hippocampal volume* = better memory*†.	---

Key: Y = younger adults; O = older adults; GM = gray matter; WM = white matter; CSF = cerebrospinal fluid; PFC = prefrontal cortex; HF = hippocampal formation; VBM = voxel-based morphometry; ↑ = increase / positive association; ↓ = decrease / negative association; * = variable NOT measured longitudinally; † = controlling for age; [L+R] = bilateral regions combined in analyses; [L&R] = both hemispheres analyzed separately.

Note: Only statistically significant results are reported, except when otherwise noted.

Table 3

Summary of Sample Characteristics and Related Structure-Cognition Findings in Older Adults

	All Reviewed Studies (N=50)		**Studies with Findings Specific to Older Adults (N=35)**		**Structure – Cognition Relationships in Older Adults (# of Positive/Negative/Null Findings)** *	
Sample Size	*Median*	*Range*	*Median*	*Range*	*Small Sample Size*	*Large Sample Size* †
	58.5	9 – 511	48	9 – 511	15/6/27	29/1/23
Design	*Cross-Sectional*	*Longitudinal*	*Cross-Sectional*	*Longitudinal*	*Cross-Sectional*	*Longitudinal*
	39	11	27	8	34/7/39	10/0/11
Age	*Median of Means*	*Overall Age Range*	*Median of Means*	*Overall Age Range*	*Lower Mean Age*	*Higher Mean Age* †
	62.5	18 – 99	72.0	18 – 99	21/1/24	18/6/21
Education *Years*	*Median of Means*	*Range of Means*	*Median of Means*	*Range of Means*	*Lower Mean Education*	*Higher Mean Education* †
	15.1	8.2 – 16.7	14.6	8.2 – 16.7	23/1/15	10/6/21
Gender *% female*	*Median*	*Range*	*Median*	*Range*	*Lower % Female*	*Higher % Female* †
	56.5	0 – 100	56.6	0 – 100	24/4/15	11/3/24

*Findings of the association between CSF and cognition not included

†Divisions based on median split

Table 4

Structure-Cognition Relationships in Older Adults: # of Studies Finding Positive, Negative, and Null Relationships

	Cognitive Domain														
Brain Structure	**Global**			**Attention / Working Memory**			**Learning/ Memory**			**Executive Function**			**Other**		
Whole Brain Measures	+	−	ø	+	−	ø	+	−	ø	+	−	ø	+	−	ø
Global Volume	2	--	1	--	--	--	--	--	3	1	--	--	--	--	--
Global GM	3	--	--	--	--	--	--	--	1	1	--	--	1	--	1
Global WM	--	--	2	--	--	--	--	--	1	1	--	--	1	--	1
Regional Brain Measures	+	−	ø	+	−	ø	+	−	ø	+	−	ø	+	−	ø
Frontal GM	1	--	--	1	2	2	2	2	1	5	1	3	--	--	--
Hippocampal Formation	5	--	2	--	--	2	13	1	8	--	--	4	--	--	2
Other Temporal GM	1	--	2	--	--	--	1	1	6	--	--	1	--	--	--
Parietal GM	1	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Occipital GM	--	--	--	--	--	--	--	--	2	--	--	1	--	--	--
Subcortical	1	--	--	--	--	1	2	--	1	--	--	1	--	--	--
Cerebellum	--	--	--	--	--	--	1	--	--	--	--	1	--	--	--
Ventricles/CSF	--	1	--	--	--	1	--	2	2	--	--	2	--	1	3

Key: GM = gray matter; WM = white matter; CSF = cerebrospinal fluid; + = positive relationship; − = negative relationship; ø = null relationship.