HHS Public Access

Author manuscript

Brain Imaging Behav. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Brain Imaging Behav. 2016 September ; 10(3): 652–659. doi:10.1007/s11682-015-9452-y.

Hippocampal volume and cingulum bundle fractional anisotropy are independently associated with verbal memory in older adults

Ali Ezzati[1,2], **Mindy J. Katz**[1], **Michael L. Lipton**[3,4], **Molly E. Zimmerman**[1,5], and **Richard B. Lipton**[1,6]

Ali Ezzati: aezzati@einstein.yu.edu

[1]Saul B. Korey Department of Neurology, Albert Einstein College of Medicine, Yeshiva University, 1165 Morris Park Avenue, Rousso Bldg. Rm. 330, Bronx, NY 10461, USA

[2]Department of Neurology, Montefiore Medical Center, Bronx, NY 10467, USA

[3]The Gruss Magnetic Resonance Research Center and Departments of Radiology, Psychiatry and Behavioral Sciences and the Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY 10461, USA

[4]The Department of Radiology, Montefiore Medical Center, Bronx, NY 10467, USA

[5]Department of Psychology, Fordham University, Bronx, NY, USA

[6]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY 10461, USA

Abstract

The objective of this study was to investigate the relationship of medial temporal lobe and posterior cingulate cortex (PCC) volumetrics as well as fractional anisotropy of the cingulum angular bundle (CAB) and the cingulum cingulate gyrus (CCG) bundle to performance on measures of verbal memory in non-demented older adults. The participants were 100 non-demented adults over the age of 70 years from the Einstein Aging Study. Volumetric data were estimated from T1-weighted images. The entire cingulum was reconstructed using diffusion tensor MRI and probabilistic tractography. Association between verbal episodic memory and MRI measures including volume of hippocampus (HIP), entorhinal cortex (ERC), PCC and fractional anisotropy of CAB and CCG bundle were modeled using linear regression. Relationships between atrophy of these structures and regional cingulum fractional anisotropy were also explored. Decreased HIP volume on the left and decreased fractional anisotropy of left CAB were associated with lower memory performance. Volume changes in ERC, PCC and CCG disruption were not associated with memory performance. In regression models, left HIP volume and left CAB-FA were each independently associated with episodic memory. The results suggest that microstructural changes in the left CAB and decreased left HIP volume independently influence

Correspondence to: Ali Ezzati, aezzati@einstein.yu.edu.

Electronic supplementary material The online version of this article (doi:10.1007/s11682-015-9452-y) contains supplementary material, which is available to authorized users.

Conflict of interest All authors declare that there are no financial, personal, or other potential conflicts of interest to report.

episodic memory performance in older adults without dementia. The importance of these findings in age and illness-related memory decline require additional exploration.

Keywords

Hippocampus; Cingulum; Verbalmemory; MRI volumetrics; Diffusion tensor imaging

Introduction

New diagnostic criteria have been proposed to include MRI biomarkers for the diagnosis of Alzheimer disease (AD) prior to the onset of clinical dementia (Dubois et al. 2007; Sperling et al. 2010). Since decline in episodic memory is an early neuropsychological correlate of AD (Backman et al. 2005; Sperling et al. 2010), changes in brain structure associated with different aspects of memory may facilitate the identification of MRI-based biomarkers (Wolk et al. 2011).

It is hypothesized that impairment in episodic memory results from the dysfunction of a complex brain network that includes the medial temporal lobe, mammillary bodies, posterior cingulate, and the connecting white matter tracts (Nestor et al. 2006). Prior volumetric and functional imaging studies have investigated early changes in brain structure or function associated with memory performance in normal aging, mild cognitive impairment (MCI) and Alzheimer's disease (AD). Reported early volumetric changes associated with memory performance include medial temporal lobe (MTL) structures, such as the hippocampus (HIP) and entorhinal cortex (ERC) (Braak and Braak 1991; Jack et al. 2004; Kramer et al. 2007). In addition, functional imaging studies suggest that hypometabolism or hypoperfusion in cingulate cortex, specifically its posterior segment, are implicated early in the course of cognitive impairment leading to MCI and AD (Chetelat et al. 2003; Nestor et al. 2003). Furthermore, prior diffusion tensor imaging (DTI) studies have reported micro-structural changes in cingulum bundle, which connects the MTL with the posterior cingulate cortex (PCC) (Catani and De Schotten 2008; Hua et al. 2008), early in the course of memory impairment (Lin et al. 2014; Nir et al. 2013). These changes have been reported mainly in MCI & AD populations using different imaging techniques, however fewer studies have investigated association of memory with different MRI measures using different modalities and in the same population. Furthermore the structural relationships between volumes of the ERC, hippocampus, and PCC have not been clarified in non-demented older adults.

In the current study, we investigated the relationship between memory performance and volumetric changes in HIP, ERC, PCC, and integrity of the cingulum fibers. Subsequently, we explored the association between volumetric changes and integrity of the cingulum bundle in the same models.

Methods

Participants

The participants were 100 non-demented adults over the age of 70 years drawn from the Einstein Aging Study (EAS). The study design and methods of the EAS have been described

in detail previously (Katz et al. 2012). Briefly, potential participants were recruited through systematic sampling from Medicare and voter registration lists for Bronx County, New York. Eligible participants were at least 70 years old, Bronx residents, non-institutionalized, and English-speaking. Exclusion criteria included visual or auditory impairments that preclude neuropsychological testing, active psychiatric symptomatology that interfered with the ability to complete assessments, and non-ambulatory status. Participants receive annual in-person assessments which include medical history, neuropsychological testing and general medical and neurologic examinations.

Participants were ineligible for the study if they had dementia or if they were unable to undergo MRI (e.g., metallic implants, claustrophobic). Dementia diagnosis was based on standardized clinical criteria from the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV. 2000) and required impairment in memory plus at least one additional cognitive domain [for more details see (Katz et al. 2012)]. Diagnoses were assigned at consensus case conferences, which included a comprehensive review of cognitive test results, relevant neurological signs and symptoms, and functional status.

This study was approved by institutional review board of Albert Einstein College of Medicine.

Neuropsychological assessment

To reduce the number of comparisons (Type I error) and to increase reliability, many groups including our own group combine individual neurocognitive tests to generate summary measures of cognitive domains (Wilson et al. 2005; Zammit et al. 2014). For the purpose of this study, based on a within sample principal component analysis (PCA), we calculated a verbal episodic memory domain score. Details of this PCA analysis has been described previously (Zammit et al. 2014). Verbal episodic memory domain comprised the free recall scores and total recall scores from the Free and Cued Selective Reminding Test (FCSRT) (Buschke 1984; Grober et al. 2000), and the total score from a test of category fluency, also known as semantic fluency (Monsch et al. 1992). Tests were administered using standard procedures (Lezak 2012; Mitrushina 2005; Strauss et al. 2006). Verbal episodic memory domain scores were calculated as the average of the Z-scores of each of the tests in the domain, using means and standard deviations from a robust normative sample derived from the EAS. In addition, participants were categorized into two groups of normal cognition and amnestic mild cognitive impaired (aMCI) on the basis of the criteria described in detail previously (Katz et al. 2012).

MRI acquisition

Imaging was performed using a 3.0 T MRI scanner (Achieva Quasar TX; Philips Medical Systems, Best, the Netherlands) and 32-channel head coil (Sense Head Coil; Philips Medical Systems, Best, the Netherlands). T1-weighted whole-head structural imaging was performed using sagittal three-dimensional magnetization-prepared rapid acquisition gradient echo (TFE- turbo field echo) with TR/TE 9.9/4.6 ms; 240 mm^2 FOV; 240×240 matrix; partition thickness, 1 mm; and parallel acceleration factor 2.0. In addition, a 3D T2-weighted fluid-

attenuated inversion recovery (T2W-FLAIR) acquisition was obtained with the following pulse sequence parameters: TR/TE/TI 11000/120/2800 ms; 240×240 mm FOV; 240×240 matrix; 1 mm partition thickness and parallel acceleration factor 2.0. Diffusion tensor MRI employed a single shot spin-echo echoplanar acquisition with TR/TE 3000/65 ms; 256×240 mm FOV; 128×117 matrix; mm slice thickness with no gap; parallel acceleration factor 2.8, b value=800 and 32 diffusion sensitizing directions.

Image processing

MRI data was automatically processed using the FreeSurfer software package (version 5.2, available at http://surfer.nmr.mgh.harvard.edu/). Briefly, the processing stream starts with a hybrid watershed algorithm, which removes non-brain tissue, automated transformation to the Talairach reference space and segmentation of the subcortical white matter and deep gray matter. T2W-FLAIR images were used for pial surface refinement. All structures were segmented using FreeSurfer's standard segmentation procedure using a probabilistic brain atlas (Fischl et al. 2002). The regions of interests (ROI) selected for the purpose of this study were right and left HIP, PCC, and ERC grey matter (GM) volumes. Additionally, for each subject the estimated total intracranial volume (TICV) was calculated based on the procedure described by Buckner et al. (2004). Segmentation results were visually inspected for errors in all datasets, but no manual edits were needed.

Tractography

For each subject, eddy current distortions and head motion were corrected by aligning diffusion-weighted images to the b=0 image (DTI volume with no diffusion sensitization) using FMRIB software library's Diffusion Toolbox (www.fmrib.ox.ac.uk/fsl). We used a recently developed global tractography method included in FreeSurfer, TRActs Constrained by UnderLying Anatomy (TRACULA; (Yendiki et al. 2011)), to reconstruct the cingulum bundle. Global tractography parameterizes a connection between 2 regions at a global level, instead of tracking through a local orientation field. This global top-down approach has several advantages over local tractography in that it eschews local uncertainty issues due to noise or partial volume effects, and it can increase the sensitivity and robustness of the tractography solutions by informing tractography process of a known connection between 2 regions (Jbabdi et al. 2007). TRACULA uses a Bayesian framework for global tractography with anatomical priors (Yendiki et al. 2011) and minimizes the bias due to the need of manual intervention.

As described by Wakana et al. (Wakana et al. 2007), the cingulum is defined as two separate segments; the upper segment along the cingulate gyrus (CCG: cingulum cingulate gyrus – supracallosal- bundle) and lower segment along the ventral aspect of the hippocampus (CAB: cingulum angular –infracallosal- bundle; please see Fig. 1 and supplementary material movie-1 for the illustration of pathways in one of the subject). For the purpose of this study, we used the estimated average Fractional anisotropy (FA) and mean diffusivity (MD) over the entire support of the path distribution of each tract.

Statistical analyses

All statistical analyses were conducted using SPSS, version 20 (Chicago, IL: SPSS Inc.). We examined the bivariate associations of Volumetric and DTI measures with demographic variables (age, education, gender) and TICV using Spearman rank correlation coefficients. Two individuals with verbal memory score that exceeded ±2.5 standard deviations from the sample mean, were excluded from the study as outliers.

A series of linear regression analyses were performed to examine MR-derived predictors of verbal memory. We used separate regression models with verbal memory as the outcome and ERC, PCC and HIP volumes as independent predictors. Each model was adjusted for age, gender, education, and TICV. We ran similar models with outcome of verbal memory and DTI measures as predictors, while controlling for total white matter (WM) volume -as surrogate for partial white matter volume loss- in addition to demographic covariates (age, gender, and education). In addition, to test the hypothesis that HIP volume mediates the effects of disruption in integrity of cingulum bundle on verbal memory, we included HIP volume and cingulum-FA and all other covariates in a single model predicting verbal memory as the outcome.

Results

Demographic and sample characteristics

The sample had a mean age of 79.2 years (SD=5.0; range: 70– 91) and was 63 % women, 56 % white, 31 % black, and 13 % other races. Sample characteristics are summarized in Table 1. There was a significant correlation between educational level and verbal memory (r_s=0.36, p<0.001), but the correlation between age and verbal memory was not significant (r_s=−0.10, p=0.31). Older age was associated with smaller HIP volume bilaterally (Left HIP: r_s=−0.36, p=0.001; R HIP: rs=−0.56, p<0.001) and smaller right PCC (r_s=−0.22, p=0.04). There was no significant correlation between volumetric measures and education level or handedness. Men had higher FA values than women in left CCG (t=2.5, p=0.014), right CCG (t=2.5, p=0.013) and right CAB (t=2.8, p=0.006). Finally, there was no significant correlation between FA value and age, education, or handedness.

Correlations between volumetric and DTI measures

We used regression models to assess association between HIP, ERC, and PCC volumes with FA and MD of CAB and CCG controlling for age, gender, education and TICV. In the left hemisphere, higher CCG-MD was associated with smaller PCC (β=−0.20, p=0.044) and ERC (β= −0.32, p=0.003); CCG-FA was also associated with bigger HIP (β=0.19, p=0.04); there was no association between HIP volume and CAB-FA (β=0.04, p=0.71). In the right hemisphere, higher CAB-MD was associated with smaller HIP (β= −0.18, p=0.03). Other volumetric and DTI measures were did not show significant correlations with each other.

Correlations between memory and MRI measures

Table 2 shows the results of separate multiple regression models with ERC, PCC and HIP volumes as independent predictors and verbal memory as the outcome. Each model was adjusted for age, gender, education, and TICV. Left HIP volume significantly predicted

verbal memory left (β=0.23, p=0.04). ERC and PCC volumes were not associated with verbal memory (see Table 2).

Table 3 shows the results of separate regression models investigating the association between DTI measures (Right and left CAB and right and left CCG) and verbal memory, while adjusting for age, gender and education as covariates. Higher FA values in the left CAB were associated with better verbal memory performance (β=0.20, p=0.043) (Fig. 2).

Since the initial regression analyses showed that both left HIP volume and left CAB-FA were significant predictors of verbal memory after controlling for covariates, we next examined whether HIP volume mediated the effects left CAB-FA on verbal memory. Table 4 shows the results of the mediation analysis. In the final model, education, left HIP volume, and left CAB-FAwere independently associated with verbal memory.

Finally, since we found a unilateral effect in our results, we repeated all previous models adding handedness to the models as a covariate. Addition of handedness resulted in very similar findings.

Discussion

In this study, we examined the association between verbal memory to measures of regional volume and white matter integrity in a series of candidate structures selected based on prior research. We showed that in non-demented older adults, smaller left HIP volume and lower FA in the cingulum angular (parahippocampal) bundle on the left side were associated with reduced performance on verbal memory. Volume of the PCC and ERC and FA of the cingulum cingulate bundle were not associated with verbal memory. Our study sample of non-demented elderly provides a good opportunity to investigate the MRI correlates of mild memory loss. Our results suggest that lower HIP volume may be an earlier marker of memory performance than PCC or ERC volumes. Similarly, these results suggest that the CAB-FA may be an earlier or more robust correlate of verbal memory performance than CCG-FA. Longitudinal data are required to assess the relationship of MRI and DTI based measures and memory decline.

Many previous studies have contrasted imaging findings among clinical defined groups such as normal aging, aMCI and AD. Volume loss in ERC, PCC and HIP occur in normal aging (Sasson et al. 2013), MCI (Choo et al. 2010; Jones et al. 2006), and AD (Choo et al. 2010; Pennanen et al. 2004) population. Changes in volumetric measures in healthy older adults have been associated with cross-sectional performance and rates of decline on tests of episodic memory (Kramer et al. 2007). Previous studies (Van Petten 2004) also indicate a strong correlation between HIP volume and memory performance. Neuropathological abnormalities in the ERC and HIP are among the earliest detectable changes reported in memory disorders (Braak and Braak 1991). Decreased performance in delayed verbal recall test is associated with anisotropy in posterior cingulum fibers (Fellgiebel et al. 2005). Another study reported that HIP volume, parahippocampal cingulum FA, and HIP glucose metabolism are all associated with episodic memory in each of normal, MCI and AD samples. (Choo et al. 2010) Although correlational studies in healthy older adults have

limitations, a meta-analysis of case–control studies of diffusion tensor imaging (DTI) in patients with MCI and AD showed that FA was decreased in AD in all cingulum bundle regions including anterior, middle, posterior and parahippocampal regions (Sexton et al. 2011). This difference in the literature and in comparison to our findings might be due to difference in degree of memory impairment and also to differences in methods used to identify regions of interest.

In the current study, only FA in the left CAB was associated with verbal memory. Previous studies have reported unilateral left-greater-than-right asymmetry in different segments of cingulum (Gong et al. 2005) and unilateral association of cingulum bundle FA with executive function and memory (Lin et al. 2014; Sasson et al. 2013). In a recent study (Nir et al. 2013), FA and diffusivity of the left HIP component of the cingulum distinguished normal, MCI, and AD groups, and was correlated with cognitive scores. Functional neuroimaging studies have also demonstrated that left cingulate gyrus activation is more involved with language-based tasks (Zago et al. 2008). Since our memory tasks were all verbal memory paradigms, the laterality seen in our results may be explained by preponderance of left hemisphere and specifically MTL structures in language-based tasks.

Previous pathology and MRI studies have reported that the earliest changes related to memory impairment appear in the HIP and ERC (Braak and Braak 1991; Jack et al. 2004; Kramer et al. 2007). Other studies, using PET, SPECT, and DTI, also suggest that changes in the PCC and white matter tracts, specifically the cingulum bundle, might precede volumetric changes (Chetelat et al. 2003; Choo et al. 2010; Nestor et al. 2003). Our results imply that HIP atrophy and decreased FA in the CAB, are independently associated with verbal memory performance. While volumetric and functional imaging studies are primarily reflective of presence and activity of cells in a target brain regions, DTI or regional cerebral blood flow studies, might reflect decreased axonal integrity and synaptic density of axons projecting from other brain regions. These differences might be an explanation for the observed differences in prior studies. Overall, our results suggest that DTI measures might be as valuable as measures of GM volume in detecting the earliest structural brain alterations associated with cognitive impairment.

While our findings are promising, a few limitations should be noted. First, neuropsychological performance is dependent on complex neural networks rather than individual brain regions. However, the involvement of other potential cortical and white matter tracts is not clear and exploration of these networks is an important next step. In addition, although our findings suggest that HIP atrophy and CAB disruption are correlated to poorer performance on tests of verbal memory among older adults, the cross-sectional design does not permit definitive causal inferences. In addition, this study was merely focused on association of structural changes in brain with memory; further studies are required to assess the effect of genetic and environmental factors on brain structure and function, and their mediation role on cognitive performance. Finally, the sample size of our study was relatively small, and comparison of different sub-populations (e.g., high functioning, normal cognition, aMCI, or naMCI) was not possible and further larger imaging studies are required to confirm and expand our findings.

In summary, we showed that bilateral HIP atrophy and decreased integrity of the left CAB, are independently associated with episodic memory performance in nondemented older adults. These white matter microstructural changes are associated with memory performance and may precede ERC and PCC atrophy as well as microstructural changes in other parts of the cingulum bundle.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This research was supported by National Institute on Aging Grant AG03949 and AG026728.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders : DSM-IV-TR. 4th. Washington, DC: American Psychiatric Association; 2000. American Psychiatric Association. Task Force on DSM-IV.

Backman L, Jones S, Berger AK, Laukka EJ, Small BJ. Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. Neuropsychology. 2005; 19(4):520–31. DOI: 10.1037/0894-4105.19.4.520 [PubMed: 16060827]

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica. 1991; 82(4):239–59. [PubMed: 1759558]

Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, Snyder AZ. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. NeuroImage. 2004; 23(2):724–38. DOI: 10.1016/j.neuroimage.2004.06.018 [PubMed: 15488422]

Buschke H. Cued recall in amnesia. Journal of Clinical Neuropsychology. 1984; 6(4):433–40. [PubMed: 6501581]

Catani M, De Schotten MT. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex. 2008; 44(8):1105–32. [PubMed: 18619589]

Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology. 2003; 60(8): 1374–7. [PubMed: 12707450]

Choo IH, Lee DY, Oh JS, Lee JS, Lee DS, Song IC, Youn JC, Kim SG, Kim KW, Jhoo JH, Woo JI. Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. Neurobiology of Aging. 2010; 31(5):772–9. DOI: 10.1016/j.neurobiolaging.2008.06.015 [PubMed: 18687503]

Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurology. 2007; 6(8):734–46. DOI: 10.1016/S1474-4422(07)70178-3 [PubMed: 17616482]

Fellgiebel A, Muller MJ, Wille P, Dellani PR, Scheurich A, Schmidt LG, Stoeter P. Color-coded diffusion-tensor-imaging of posterior cingulate fiber tracts in mild cognitive impairment. Neurobiology of Aging. 2005; 26(8):1193–8. DOI: 10.1016/j.neurobiolaging.2004.11.006 [PubMed: 15917103]

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002; 33(3):341–55. [PubMed: 11832223]

Gong G, Jiang T, Zhu C, Zang Y, Wang F, Xie S, Xiao J, Guo X. Asymmetry analysis of cingulum based on scale-invariant parameterization by diffusion tensor imaging. Human Brain Mapping. 2005; 24(2):92–8. DOI: 10.1002/hbm.20072 [PubMed: 15455461]

Grober E, Lipton RB, Hall C, Crystal H. Memory impairment on free and cued selective reminding predicts dementia. Neurology. 2000; 54(4):827–32. [PubMed: 10690971]

Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, Calabresi PA, Pekar JJ, van Zijl PC, Mori S. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. NeuroImage. 2008; 39(1):336–47. [PubMed: 17931890]

Jack CR Jr, Shiung MM, Gunter JL, O'Brien PC, Weigand SD, Knopman DS, Boeve BF, Ivnik RJ, Smith GE, Cha RH, Tangalos EG, Petersen RC. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology. 2004; 62(4):591–600. [PubMed: 14981176]

Jbabdi S, Woolrich MW, Andersson JL, Behrens TE. A Bayesian framework for global tractography. NeuroImage. 2007; 37(1):116–29. DOI: 10.1016/j.neuroimage.2007.04.039 [PubMed: 17543543]

Jones BF, Barnes J, Uylings HB, Fox NC, Frost C, Witter MP, Scheltens P. Differential regional atrophy of the cingulate gyrus in Alzheimer disease: a volumetric MRI study. Cerebral Cortex. 2006; 16(12):1701–8. DOI: 10.1093/cercor/bhj105 [PubMed: 16400164]

Katz MJ, Lipton RB, Hall CB, Zimmerman ME, Sanders AE, Verghese J, Dickson DW, Derby CA. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. Alzheimer Disease and Associated Disorders. 2012; 26(4):335–43. DOI: 10.1097/WAD.0b013e31823dbcfc [PubMed: 22156756]

Kramer JH, Mungas D, Reed BR, Wetzel ME, Burnett MM, Miller BL, Weiner MW, Chui HC. Longitudinal MRI and cognitive change in healthy elderly. Neuropsychology. 2007; 21(4):412–8. DOI: 10.1037/0894-4105.21.4.412 [PubMed: 17605574]

Lezak, MD. Neuropsychological assessment. 5th. Oxford: Oxford University Press; 2012.

Lin YC, Shih YC, Tseng WY, Chu YH, Wu MT, Chen TF, Tang PF, Chiu MJ. Cingulum correlates of cognitive functions in patients with mild cognitive impairment and early Alzheimer's disease: a diffusion spectrum imaging study. Brain Topography. 2014; 27(3):393–402. DOI: 10.1007/s10548-013-0346-2 [PubMed: 24414091]

Mitrushina, MN. Handbook of normative data for neuropsychological assessment. 2nd. New York: Oxford University Press; 2005.

Monsch AU, Bondi MW, Butters N, Salmon DP, Katzman R, Thal LJ. Comparisons of verbal fluency tasks in the detection of dementia of the Alzheimer type. Archives of Neurology. 1992; 49(12):1253–8. [PubMed: 1449404]

Nestor PJ, Fryer TD, Smielewski P, Hodges JR. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. Annals of Neurology. 2003; 54(3):343–51. DOI: 10.1002/ana.10669 [PubMed: 12953266]

Nestor PJ, Fryer TD, Hodges JR. Declarative memory impairments in Alzheimer's disease and semantic dementia. NeuroImage. 2006; 30(3):1010–20. [PubMed: 16300967]

Nir TM, Jahanshad N, Villalon-Reina JE, Toga AW, Jack CR, Weiner MW, Thompson PM. Alzheimer's Disease Neuroimaging, I. Effectiveness of regional DTI measures in distinguishing Alzheimer's disease, MCI, and normal aging. NeuroImage Clinical. 2013; 3:180–95. DOI: 10.1016/j.nicl.2013.07.006 [PubMed: 24179862]

Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hanninen T, Laakso MP, Hallikainen M, Vanhanen M, Nissinen A, Helkala EL, Vainio P, Vanninen R, Partanen K, Soininen H. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiology of Aging. 2004; 25(3):303–10. DOI: 10.1016/S0197-4580(03)00084-8 [PubMed: 15123335]

Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. Frontiers in Neuroscience. 2013; 7:32.doi: 10.3389/fnins.2013.00032 [PubMed: 23493587]

Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP. A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neurobiology of Aging. 2011; 32(12):2322 e5–18. DOI: 10.1016/j.neurobiolaging.2010.05.019 [PubMed: 20619504]

Sperling RA, Dickerson BC, Pihlajamaki M, Vannini P, LaViolette PS, Vitolo OV, Hedden T, Becker JA, Rentz DM, Selkoe DJ, Johnson KA. Functional alterations in memory networks in early Alzheimer's disease. Neuromolecular Medicine. 2010; 12(1):27–43. DOI: 10.1007/s12017-009-8109-7 [PubMed: 20069392]

Strauss, E.; Sherman, EMS.; Spreen, O.; Spreen, O. A compendium of neuropsychological tests: administration, norms, and commentary. 3rd. Oxford: Oxford University Press; 2006.

Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia. 2004; 42(10):1394–413. DOI: 10.1016/j.neuropsychologia.2004.04.006 [PubMed: 15193947]

Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl P, Mori S. Reproducibility of quantitative tractography methods applied to cerebral white matter. NeuroImage. 2007; 36(3):630–44. DOI: 10.1016/j.neuroimage.2007.02.049 [PubMed: 17481925]

Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. Journal of the International Neuropsychological Society: JINS. 2005; 11(4):400–7. [PubMed: 16209420]

Wolk DA, Dickerson BC. Alzheimer's Disease Neuroimaging, I. Fractionating verbal episodic memory in Alzheimer's disease. NeuroImage. 2011; 54(2):1530–9. DOI: 10.1016/j.neuroimage.2010.09.005 [PubMed: 20832485]

Yendiki A, Panneck P, Srinivasan P, Stevens A, Zollei L, Augustinack J, Wang R, Salat D, Ehrlich S, Behrens T, Jbabdi S, Gollub R, Fischl B. Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. Frontiers in Neuroinformatics. 2011; 5:23.doi: 10.3389/fninf.2011.00023 [PubMed: 22016733]

Zago L, Petit L, Turbelin MR, Andersson F, Vigneau M, Tzourio-Mazoyer N. How verbal and spatial manipulation networks contribute to calculation: an fMRI study. Neuropsychologia. 2008; 46(9):2403–14. [PubMed: 18406434]

Zammit AR, Katz MJ, Lai JY, Zimmerman ME, Bitzer M, Lipton RB. Association between renal function and cognitive ability domains in the Einstein aging study: a cross-sectional analysis. The Journals of Gerontology Series A, Biological Sciences and Medical Sciences. 2014; doi: 10.1093/gerona/glu185

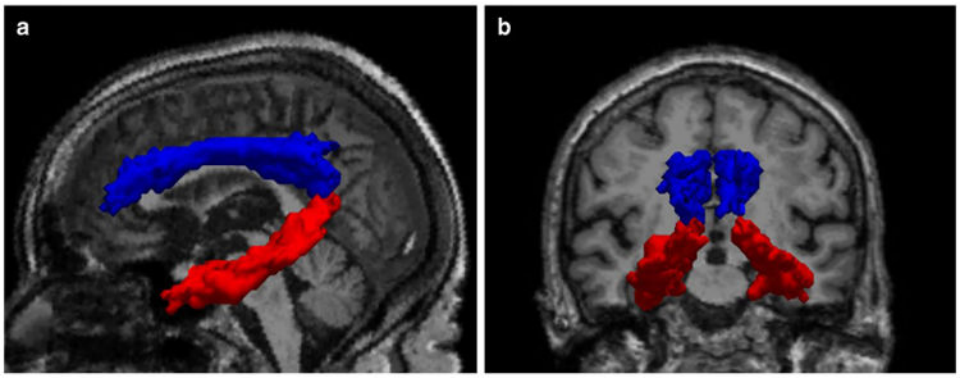

Fig. 1.

Pathways reconstructed automatically with TRACULA in one of the subjects. Lateral (**a**) and anterior (**b**) views of 3D reconstructions of the CCG (*blue*), and CAB (*red*). Cross-sectional T1W sagittal (**a**) and coronal (**b**) images of the same subject are shown for reference. *CCG* cingulum cingulate gyrus bundle, *CAB* cingulum angular bundle

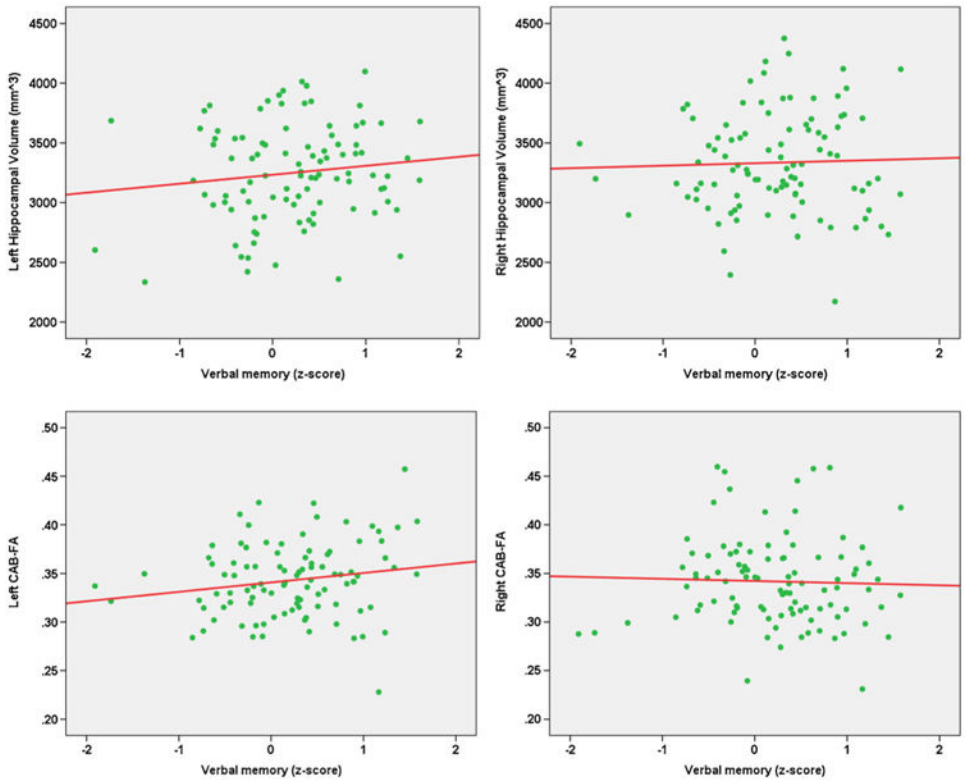

Fig. 2.

Scatterplots showing the correlations between volume of the hippocampus Vs memory performance (*top row*) and CAB-FA Vs memory performance (*bottom row*) in both hemispheres

Table 1

Sample demographics

	total sample (*N*=98)
Men/Women	62/36
% White	55
Right/left handed	88/10
Age, years	79.2(5.0)
Education, years	14.3(3.6)
Verbal Memory (z-score)	0.21(0.68)
BIMC	2.23(2.36)
aMCI/Normal	9/89
Left HIP volume[a]	3.25(0.41)
Right HIP volume	3.33(0.42)
Left ERC volume	1.63(0.38)
Right ERC volume	1.62(0.39)
Left PCC volume	3.18(0.49)
Right PCC volume	3.22(0.53)
Left CAB-FA	0.34(0.04)
Right CAB-FA	0.34(0.05)
Left CCG-FA	0.53(0.04)
Right CCG-FA	0.51(0.04)
TICV	1347(200)

Values are expressed as means (S.D.) unless otherwise specified

BIMC Blessed Information-Memory-Concentration Score, *MCI* Mild cognitive impairment, *TICV* total intracranial volume, *HIP* hippocampus, *ERC* entorhinal cortex, *PCC* posterior cingulate cortex, *CCG* cingulum cingulate gyrus bundle, *CAB* cingulum angular bundle, *FA* fractional anisotropy, *MD* mean diffusivity

[a]MRI volumetric data are all given in cubic centimeters

Table 2

Regression models separately examining the effects of entorhinal cortex, posterior cingulate cortex, and hippocampal volume on verbal memory

ROI	Models based on ROI for episodic memory*		
	β	t	ρ
HIP Volume			
Left	**0.23**	**2.08**	**0.040**
Right	0.04	0.31	0.751
PCC Volume			
Left	−0.09	−0.83	0.405
Right	0.17	1.20	0.232
ERC Volume			
Left	−0.03	−0.28	0.780
Right	0.01	0.13	0.895

ROI Region of interest, *HIP* Hippocampus, *PCC* Posterior-isthmus Cingulate Cortex, *ERC* Entorhinal cortex

* Each model includes age, gender, education, and total intracranial volume as covariates. Model results for covariates are left out of this table for simplicity. Significant results are bolded in the table

Table 3

Regression models for the effect of fractional anisotropy and mean diffusivity of cingulum bundle on episodic memory

Region of interest	Models for episodic memory *			
	β	t	ρ	
LEFT CAB	FA	**0.22**	**2.38**	**0.019**
	MD	−0.08	−0.83	0.405
Right CAB	FA	0.02	0.21	0.828
	MD	−0.03	−0.38	0.701
LEFT CCG	FA	−0.13	−1.37	0.173
	MD	0.14	1.41	0.160
Right CCG	FA	−0.08	−0.78	0.434
	MD	0.11	1.08	0.283

CCG cingulum cingulate gyrus bundle, *CAB* cingulum angular bundle, *FA* Fractional Anisotropy, *MD* Mean Diffusivity

* Models include age, gender, education, and total white matter volume as covariates. Significant results are bolded in the table

Table 4

Summary of the left HIP and left CAB mediation regression models of episodic memory

	Model for HIP volume			Model for CAB-FA			Mediation model		
	β	t	ρ	β	t	ρ	β	t	ρ
Age	−0.06	−0.60	0.550	−0.14	−1.53	0.128	−0.07	−0.73	0.466
Gender(male)	−0.18	−1.56	0.121	−0.18	−1.55	0.124	−0.21	−1.87	0.064
Education	**0.36**	**3.74**	**<0.001**	**0.35**	**3.79**	**<0.001**	**0.38**	**4.10**	**<0.001**
TICV	−0.05	−0.44	0.660	0.02	0.15	0.881	−0.02	−0.21	0.830
Left HIP Volume	**0.23**	**2.08**	**0.040**				**0.21**	**2.04**	**0.044**
Left CAB-FA				**0.24**	**2.56**	**0.012**	**0.23**	**2.52**	**0.013**

TICV total intracranial volume, *HIP* Hippocampus, *PCC* Posterior-isthmus Cingulate Cortex, *CAB* cingulum angular bundle, *FA* fractional anisotropy. Significant results are bolded in the table