Size does matter in the long run

Hippocampal and cortical volume predict recall across weeks

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Abstract—*Objective:* To study the morphometric determinants of recall of verbal material for an extended period in an adult lifespan sample. *Methods:* Healthy adults of varying ages were studied using automated segmentation of MRI scans with volumes of hippocampus, cortex, and white matter, and verbal memory tests assessing recall after 5 minutes, 30 minutes, and a mean period of 11 weeks. Stepwise regression analyses were performed with 5 minutes, 30 minutes, and 11-week recall as the dependent variables. Hippocampal, cortical, and white matter volumes were included in the initial set of predictor variables in each case, and the analyses were repeated with age as an additional predictor variable. *Results:* When age was not included, cortical volume was the only variable predicting recall after 5 and 30 minutes, whereas hippocampal and cortical volumes predicted recall after 11 weeks. When age was included in the model, this was the only variable predicting recall after 5 and 30 minutes, whereas age and hippocampus gave contributions in prediction of recall after several weeks. *Conclusion:* This study supports a critical role of cortical and hippocampal size in recall. Hippocampal size seems more important in recall after 11 weeks than after a shorter time interval.

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The size of various brain structures may partly determine human abilities,[1,2] and the role of hippocampal volume in memory has evoked much interest. The importance of hippocampus for memory function is well documented, but other structures also are necessarily involved, depending somewhat on the length of retention interval. Theoretical and empirical accounts imply that memories are maintained or strengthened across an extended period by hippocampal-cortical interactions.[3,4] However, the role of volume of cortex and other gross structures in memory has scarcely been examined, and extended retention intervals have not been used in morphometric studies. The present study investigates the role of hippocampal, white matter, and cortical volume across recall intervals of 5 and 30 minutes and several weeks.

Hippocampal reductions have been documented in amnesic and demented patients.[5-8] Some have also found normal individual differences in hippocampal size to be related to recall,[9-11] but others have not observed any such association independently of age.[1,7,12,13] Thus, some have concluded that hippocampal size before onset of atrophy does not predict memory ability.[1,13] However, only retention intervals of ≤1 hour have been used. Consolidation takes place over several days[14] or years,[15] and hippocampus may be involved for a prolonged interval.[3,4,16] Even though hippocampus also is important in initial encoding and retrieval,[8,17-19] the use of short retention intervals may preclude observation of an association. A relationship between hippocampal size and retention may manifest itself more strongly across weeks. The same may apply to cortex, which can be increasingly important in storage of memories with time.[3,4] This is investigated in an adult lifespan sample, and because age affects recall[20] and brain structures,[21-27] analyses were performed without and with age included among the predictors.

Methods. *Sample.* Volunteers were recruited by advertisements placed on campus and in local newspapers. Participants were required to be right-handed, feel well and healthy, and not have diseases or conditions known to affect CNS functioning (e.g., hypothyroidism, multiple sclerosis, Parkinson disease, stroke, and head injury). Those satisfying these criteria were further screened for health problems and cognitive problems by a structured interview, Beck Depression Inventory (BDI),[28] the Mini-Mental State Examination (MMSE),[29] the Wechsler Abbreviated Intelligence Scale (WASI),[30] and the California Verbal Learning Test (CVLT).[20] Participants scoring >14 on the BDI, <26 on the MMSE, or ≥2 SDs below the population mean on the IQ test or on any of free recall measures of the CVLT at initial testing[20,31] used in the

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Table 1 *Characteristics of the total sample (n = 54)*

	Mean	SD	Range
Age, y	51.0	21.6	20–88
IQ	113.4	10.5	85–134
MMSE	28.8	1.0	26–30
BDI	4.1	3.6	0–14
Education	15.3	2.8	7–20
5-minute recall	12.1	2.9	4–16
5-minute intrusions	0.3	0.6	0–3
30-minute recall	12.4	2.9	3–16
30-minute intrusions	0.5	0.7	0–3
Multiweek recall	4.1	3.7	0–14
Multiweek intrusions	1.5	1.4	0–6

Recall values represent number of correctly recalled items. Intrusion values represent number of incorrectly remembered items. Beck Depression Inventory (BDI) was only included in the study at a later point; therefore, data on this inventory are presented for only 46 of the 54 participants.

MMSE = Mini-Mental State Examination.

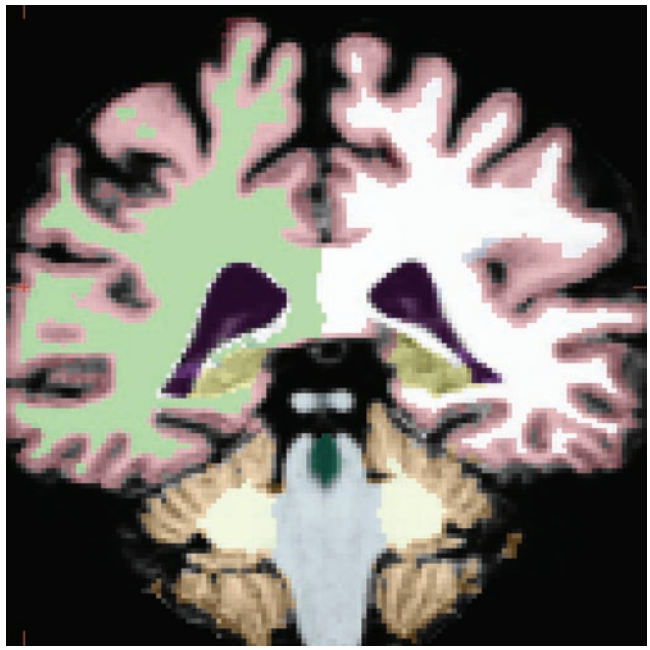

Figure. A sample of automated labeling of hippocampus (yellow areas), white matter (green areas of the right hemisphere and white areas of the left hemisphere), and cerebral cortex (violet areas) in the coronal view of the brain of a young female participant.

present analyses were excluded from the study. This led to the exclusion of three participants. The remaining sample consisted of 54 persons (29 women) aged 20 to 88 years. Sample characteristics are shown in table 1. IQ did not correlate with age ($r = -0.01$; $p = 0.939$).

MRI scanning. A Siemens Symphony Quantum 1.5-T MR scanner (Munich, Germany) with a conventional head coil was used. The pulse sequences used for morphometric analysis were two three-dimensional magnetization-prepared gradient echo (MP-RAGE) T1-weighted sequences in succession (repetition time [TR]/ echo time [TE]/T1/FA = 2,730 ms/4 ms/1000 ms/7°; matrix, 192 × 256; field of view [FOV], 256 mm), with a scan time of 8.5 minutes per volume. Each volume consisted of 128 sagittal slices with slice thickness of 1.33 mm and in-plane pixel size of 1 mm × 1 mm. The image files in Digital Imaging and Communications in Medicine format were transferred to a Linux workstation (Red Hat, Research Triangle Park, NC) for morphometric analysis.

MRI volumetric analyses. The automated procedures for volumetric measures of the different brain structures are described by Fischl et al.[32] This procedure automatically assigns a neuroanatomic label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set. Briefly, the segmentation is carried out as follows. First, an optimal linear transform is computed that maximizes the likelihood of the input image, given an atlas constructed from manually labeled images. Next, a nonlinear transform is initialized with the linear one, and the image is allowed to further deform to better match the atlas. Finally, a Bayesian segmentation procedure is carried out, and the maximum a posteriori (MAP) estimate of the labeling is computed. The segmentation uses three pieces of information to disambiguate labels: 1) the previous probability of a given tissue class occurring at a specific atlas location; 2) the likelihood of the image given that tissue class; and 3) the probability of the local spatial configuration of labels given the tissue class. This latter term represents a large number of constraints on the space of allowable segmentations and prohibits label configurations that never occur in the training set (e.g., hippocampus is never anterior to amygdala). The technique has previously been shown to be comparable in accuracy with manual labeling. The segmentations were visually inspected for accuracy. None were discarded. In the present article, measures of white matter and cortical and hippocampal volume (summed for left and right hemisphere) were chosen for analyses. Intracranial volume (ICV) was calculated based on low-flip angle, fast-low angle shot (FLASH) scans obtained during the same session as the scans used for automated labeling. The MRI measures were regressed on ICV, and the standardized residuals were used for the analyses reported here (figure).

Memory assessment. For assessment of verbal memory, CVLT was administered in a standardized way. A list of 16 items was read five times consecutively, and each time the participants were immediately instructed to list all items he or she could recall. After these five trials, another 16-item list was read, with instructions of immediate recall of as many items as possible, whereupon the participants were asked to recall the first list, the one that had been read five times (5-minute recall). After a 30-minute delay, the participants were asked, without having been forewarned, to recall this list again. In the present study, CVLT was modified so that an additional free recall test was administered by telephone after a mean of 79 days (range, 42 to 241; SD, 42). The large range of intervals was caused by difficulties reaching the participants. To avoid rehearsal effects, they were not forewarned that they would be asked to recall the material again; therefore, appointments for retesting could not be made. However, retention intervals were random and did not correlate with age ($r = -0.19$; $p = 0.172$), number of correctly remembered items ($r = -0.01$; $p = 0.951$), or number of correctly remembered items minus number of intrusions/incorrectly remembered items ($r = -0.17$; $p = 0.234$). However, retention intervals did correlate with number of intrusions ($r = 0.39$; $p = 0.003$). Thus, although intrusions do affect memory performance and will be dealt with in a separate subanalysis, the possible interpretation of this is limited. The main analyses were performed on recall scores that were calculated as number of correctly remembered items only. This approach was chosen in consideration of the aforementioned relationship between retention interval and intrusions, and theoretical and empirical accounts viewing intrusions to be determined by partly other factors than those determining correct recall.[20] Descriptive data for number of hits and intrusions at the different retention intervals are shown in table 1.

Statistics. Correlation analyses were performed with all the studied variables to assess their covariance. Three stepwise regression analyses were performed with the three types of verbal memory scores (5 minutes, 30 minutes, and several weeks) as dependent variables and the three neuroanatomic volumes entered simultaneously as predictor variables. The same analyses were repeated with age as an additional predictor variable. These analyses were done to assess the relative power of the different

Table 2 *Correlations between age, number of correctly remembered items at three different retention intervals, and each anatomic measure*

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
(1) Age	1.00	−0.63	−0.64	−0.57	−0.50	−0.52	−0.85
(2) 5-minute recall		1.00	0.94	0.61	0.47	0.34	0.54
(3) 30-minute recall			1.00	0.60	0.44	0.34	0.54
(4) Multiweek recall				1.00	0.57	0.37	0.55
(5) Hippocampus					1.00	0.55	0.55
(6) White matter						1.00	0.62
(7) Cortical volume							1.00

All relationships shown are significant ($p < 0.01$).

neuroanatomic volumes to predict memory at the three retention intervals. Analyses were also performed with number of intrusions as the dependent variable.

Results. In cubic millimeters, the mean automatically labeled volume of hippocampus was 7,152 (SD, 787); mean cortical volume was 454,364 (SD, 60,802); and mean white matter volume was 384,444 (SD, 59,275). Correlations between age, memory measures, and anatomic measures are shown in table 2. There were significant intercorrelations between all variables. All brain volumes showed robust correlations with age. Cortical size was clearly the most strongly related to age, and hippocampal and white matter volume showed more moderate age correlations of approximately equal size. Of the anatomic volumes, cortical volume generally covaried the most with all memory measures and approximately equally strongly at all retention intervals. Hippocampal volume correlated the most highly with multiweek recall and somewhat less with the shorter-interval recall scores. The correlations between white matter volume and recall scores were lower than for the other volumes and were approximately equal across retention intervals.

The results of the stepwise regression analyses with 5 minutes, 30 minutes, and multiweek recall as the dependent variables and hippocampal, cortical, and white matter volume as multiple regressors are presented in table 3. Only cortical volume gave a unique contribution in the prediction of 5-minute and 30-minute recall. For multiweek recall, only hippocampal volume was included in the first model, and hippocampal and cortical volumes were included in the second, yielding an increase in the explained variance from 32 to 40%. The results of the same stepwise regression analyses with age included among the predictors are presented in table 4. Only age gave a unique contribution in the prediction of 5-minute and 30-minute recall. For multiweek recall, age was included in the first model, and age and hippocampal volume were included in the second, increasing the amount of explained variance from 33 to 43%.

The stepwise regression analyses with intrusions as the criteria variables showed no significant relationship between neuroanatomic volumes, age, and intrusions at either 30-minute or multiweek recall. However, white matter volume predicted intrusions at 5-minute recall (standardized beta = 0.385; $R^2 = 0.149$; F = 9.073; $p = 0.004$). This was also the only significant relationship when age was included among the regressors initially entered.

Discussion. The present results support a critical role of cortical and hippocampal size in verbal recall across different retention intervals. Cortical volume predicted recall after 5 minutes, 30 minutes, and several weeks. No difference in the role of cortical volume in memory prediction across these different intervals was observed. For hippocampal volume, the results differed in that weaker relationships were observed across shorter retention intervals; therefore, a unique contribution was only seen for multiweek recall. White matter volume did not give any unique contribution at any retention interval. These relationships may be influenced by the neuroanatomic volumes' differential sensitivity to age. In the present study, cortical volume was tightly related to age, whereas more moderate relationships were observed for hippocampal and white matter volumes. Because different analyses have been used, a direct comparison of effect sizes cannot be done; however, the present results seem to correspond to previous findings indicating that gray matter is more influenced by age than is white matter.[33] Age is a powerful predictor of recall scores,[20] and when age was

Table 3 *Stepwise regression analyses with 5-minute, 30-minute, and multiweek recall as the dependent variables and hippocampal, cortical, and white matter volume as multiple regressors*

	Beta	R^2	F
5-minute recall, model I			
Cortical volume	0.54*	0.29	21.647*
30-minute recall, model I			
Cortical volume	0.54*	0.29	20.867*
Multiweek recall, model I			
Hippocampal volume	0.57*	0.32	24.529*
Multiweek recall, model II			
Hippocampal volume	0.38†		
Cortical volume	0.34†	0.40	17.165*

* $p < 0.001$.
† $p < 0.05$.

Beta values are standardized.

Table 4 *Stepwise regression analyses with 5-minute, 30-minute, and multiweek recall as the dependent variables and age, hippocampal, cortical, and white matter volume as multiple regressors*

	Beta	R^2	F
5-minute recall, model I			
Age	−0.63*	0.40	34.134*
30-minute recall, model I			
Age	−0.64*	0.41	36.619*
Multiweek recall, model I			
Age	−0.57*	0.33	25.374*
Multiweek recall, model II			
Age	−0.39†		
Hippocampal volume	0.37†	0.43	19.342*

* $p < 0.001$.
† $p < 0.05$.

Beta values are standardized.

included among the regressors, this was the only variable uniquely predicting 5-minute and 30-minute recall. For multiweek recall, age was also the only variable included in the first model. However, age and hippocampal volume were included in the second model, showing that hippocampal size explained an additional 10% of the variance. These data support a critical role of hippocampal volume in recall after several weeks, more than after shorter intervals, and indicate that hippocampal volume is a unique predictor of verbal memory because its influence was upheld even when the contribution of age was accounted for.

Why does size matter? Although intuitively appealing, a direct and positive brain-behavior correspondence should not necessarily be expected. There is evidence that size does not always correlate positively with performance. For structures such as the orbital prefrontal cortex, larger size has been associated with lower performance on neuropsychological measures of frontal function in elderly persons.[34] This may be the result of processes such as gliosis. Conversely, there is evidence that larger brains have more neurons.[35] Size may signify the number of neurons or functional connections with associated cortical and subcortical structures important in memory processes. A larger number of neurons or functional connections may positively affect recall after several weeks by improving the hippocampal-neocortical dialogue that maintains or strengthens the memory traces over time.[3,4] Thus, although hippocampal size to some degree seems important for initial retrieval, the present data show that the benefit of larger hippocampal volume may increase with long retention intervals. In the present study, no age-independent relationship between hippocampal size and memory across a shorter interval was found. As mentioned previously, this has sometimes been found and sometimes not. Often, studies finding such a relationship have used older samples[9-11] rather than adult lifespan samples. We believe that this may facilitate identification of the relationship, perhaps because of a naturally broader range of individual differences that come with age.[36] For example, it may be that hippocampal size matters only if it is above or below a certain limit and that the variance of interest is not always found in younger samples. However, beyond such methodological differences, it is probable that a relationship between hippocampal size and recall generally exists but only in a weaker form at initial stages of memory processing. Evidence for this is also found in the present study: there is a relationship between hippocampal size and recall after 5 and 30 minutes (22 and 19% explained variance). The relationship is strengthened across weeks (32% explained variance) and is then age independent. Based on the present data, it seems that individual differences in hippocampal size become a more valuable predictor at a longer retention interval. This is likely related to a temporally graded consolidation process depending partly on hippocampal size and its correlates, as discussed previously.

Cortical volume was also related to recall. This is not surprising given the many and diverse functions of cortex and fits with theoretical frameworks emphasizing a hippocampal-neocortical dialogue in the maintenance and strengthening of memories.[3,4] Given these theoretical accounts, one may speculate that cortical size could take on an increasingly important role at longer retention intervals, when memories are thought to be more cortically distributed. However, unlike for hippocampus, no differential role at different retention intervals was observed. This may be because total cortical volume was measured. The hippocampus is, as reviewed previously, theoretically and empirically specifically involved in memory processes. Although cortex certainly also is involved in memory,[3,4] it is functionally more parsed; therefore, large parts are devoted to other processes (e.g., sensory and motor control). If more specific parts had been targeted, the relationships with the various recall intervals might have changed. Conversely, one may argue that cortex is fundamental to all higher-order cognitive processes, and thus, a relationship at all retention intervals is not surprising. The fact that cortical volume explained little beyond what was explained by age, whereas hippocampal volume added 10% to the amount of explained variance, might have to do with the differential age sensitivity of these neuroanatomic volumes. Because cortical volume and verbal recall are closely related to age, a unique relationship between them is difficult to identify in a lifespan sample. An age-homogenous sample would be ideal for testing this.

A relationship was found between white matter volume and number of intrusions at 5-minute recall: larger white matter volume was positively associated with number of intrusions. Little is known about the role of white matter volume in normal abilities. White matter abnormalities have been extensively

studied, and it is known that white matter hyperintensities are related to neuropathologic conditions and memory capability in normal cognitive aging.[37] Although this indicates that white matter integrity is important, studies have not systematically related white matter volume to normal memory ability. The relationship observed here may represent an artifact, but further research is needed before any firm conclusions can be made. White matter volume did not contribute in the prediction of number of hits at any recall interval beyond what was explained by hippocampal and cortical volumes. As seen from table 2, the relationships between white matter volume and recall scores are weaker than those observed for the other neuroanatomic volumes but are approximately equal across different retention intervals.

Again, looking at table 2, it is noteworthy that all neuroanatomic volumes show relationships with recall scores after several weeks that are at least equal to or stronger than those observed for short intervals (5 and 30 minutes). This may be of clinical utility. In everyday life, our ability to retain information for a considerable time interval—weeks, months, and years—obviously is important. In clinical neuropsychology, verbal long-term memory capability is typically tested with list learning, followed by an immediate test and a test after a 20- to 30-minute retention interval. This is sensitive to individual differences in memory capability, both within the normal range and between healthy persons and patients with dementing illness.[20] Clinical observations still indicate that even persons who perform rather well on such tests may complain about their long-term memory. It is beyond the scope of clinical examinations to test memory for days, weeks, or months. However, knowledge of the neuroanatomic determinants of individual retention for prolonged intervals may be relevant for clinical predictions of everyday function. The present findings fit with and further refine previous empirical and theoretical reports, indicating that hippocampal and cortical size normally does matter in memory, and this is true also for recall of remote memories. Based on the present data, hippocampal size appears to matter more in the long run than at shorter retention intervals. Further, the role of hippocampal size in explaining long-term verbal memory seems unique because it accounts for variance that cannot be explained by age and total cortical or white matter volume.

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