Relationship between age, episodic memory performance, fMRI correlates of encoding and retrieval, and estimates of regional brain structures

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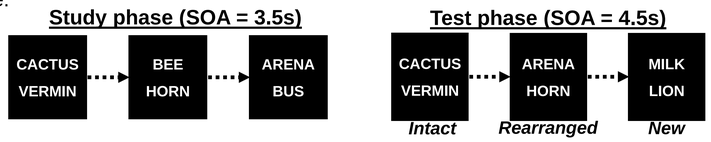
Introduction

Episodic memory performance declines with age[1], as do estimates of regional brain thickness and volume[2]. Previous studies[3,4] have reported that encoding-related functional activity in the inferior frontal gyrus (IFG) and hippocampus, and retrieval-related activity in the hippocampus, predict associative memory performance in older adults.

Here, we use hierarchical regression models to examine whether structural estimates of the same brain regions can explain any additional variation in associative memory performance, over and above that explained by functional measures.

Methods

Participants: 36 young (mean age: 22; age range: 18-29), 36 middle-aged (mean age: 49; age range: 43-55), and 64 older (mean age: 68; age range: 63-76) adults. Data from 62 older adults who had complete functional and structural measures were employed here.



MRI methods: T2*-weighted EPI (33 axial images/volume, 3mm thick, 1mm interslice gap, 3x3 mm in-plane, 80x80 matrix, TR=2s, TE=30 ms) images were obtained for the functional data. For the structural data, a T1-weighted (MP-RAGE) anatomical image was obtained after the Test phase (FOV=256×224, voxel size 1×1×1 mm3, 160 slices, sagittal acquisition).

Behavioral measures: Associative recognition accuracy (pR) was the measure of memory performance, as indexed by the difference between the proportion of associative hits, i.e. intact study pairs judged as intact during test, and the proportion of associative false alarms, i.e. rearranged test pairs incorrectly judged as intact.

Functional measures: Encoding-related functional activity (subsequent memory effects or SMEs) was identified as BOLD activity elicited for studied pairs later correctly judged intact (associative hits) > that for studied pairs later incorrectly judged rearranged (associative misses). Similarly, recollection-related functional activity was identified as BOLD activity elicited at test for the contrast associative hits > associative misses.

Whole brain fMRI contrasts conducted across the three age groups were thresholded at p < 0.001 with 21 contiguous voxels for the SMEs, and at p < 0.05 (FWE) for the recollection effects. Parameter estimates were extracted for the BOLD responses elicited by studied items that went on to become associative hits and misses across all voxels within a 5 mm radius of the LIFG (and homotopic RIFG) peak, and within a 3 mm radius of each hippocampal peak.

Structural measures: Estimates of IFG thickness were obtained using FreeSurfer (V5.3.0) through the standard analysis pipeline. Hippocampal volume was estimated by manual tracings[5,6], on individual T1-weighted anatomical images using 3D-Slicer (V4.4). Volume estimates were residualized against intra-cranial volume (ICV).

The IFG region corresponding to the functional ROIs, according to the FreeSurfer aparc2009 atlas, was the Pars Orbitalis.

Manual edits were made when necessary. Cortical thickness was measured as the distance from the gray/white matter boundary and pial surface on a vertex-by-vertex basis across the entire cortical mantle. Left and right Pars Orbitalis thickness was employed in the present analyses.

References

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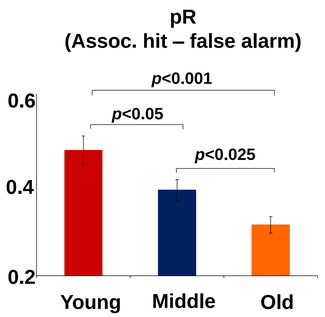
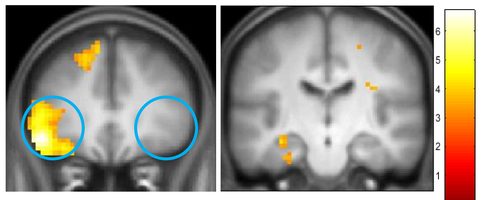
Behavioral Results



Functional data were collapsed across homotopic left and right IFG on the basis of our prior analyses demonstrating almost identical patterns of correlation with memory performance for the two hemispheres[3]. For the same reason, retrieval-related hippocampal activity was also collapsed across the hemispheres[4]. None of these functional measures declined with age.

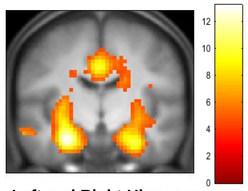
Subsequent Memory Effects



LIFG and Homotopic RIFG y=32

Left Hippocampus y=-19

Retrieval Effects



Left and Right Hippocampus y=-13

Regression Models

A regression was performed predicting pR from ventral IFG SMEs, mean hippocampal SMEs, and mean hippocampal Retrieval Effects, as shown below.

MODEL	B	SEb	β	Adj. R^2	p
				.337	<.001
(constant)	.227	.022			<.001
Mean Ventral IFG SME	.026	.037	.087		=.485
Mean Hippocampal SME	.131	.048	.337		=.008
Mean Hippocampal Retrieval Effect	.098	.023	.449		<.001

While the overall model was significant, the inclusion of the hippocampal effects resulted in a model where the IFG SME contribution was not significant. Hence, for the subsequent analysis, the IFG SME effect was not included.

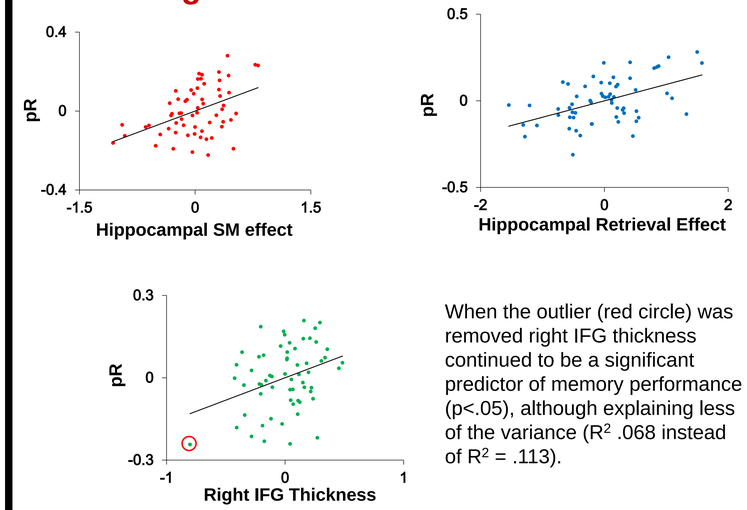
Hierarchical regression was performed with the mean hippocampal SME, mean hippocampal retrieval effect and, in separate models, hippocampal or IFG structural measures along with intra-cranial volume (ICV). In the case of left and right hippocampal volume, and left IFG thickness, the overall model was significant but the contributions of the structural estimates to the model were not significant.

Including right IFG thickness estimate in the model produced a different result (below). Not only was the model significant [F(3,58) = 15.00, p <0.001], but so was the contribution of the IFG thickness estimate.

Regression model predicting pR from Hippocampal SMEs, Hippocampal Retrieval Effects and Right IFG Thickness and ICV

MODEL	B	SEb	β	Adj. R^2	p
Model 1				.343	<.001
Mean Hippocampal SME	.149	.040	.383		<.001
Mean Hippocampal Retrieval Effect	.100	.023	.456		<.001
Model 2				.408	<.001
Mean Hippocampal SME	.145	.038	.374		<.001
Mean Hippocampal Retrieval Effect	.095	.022	.434		<.001
Right IFG Thickness	.161	.060	.267		=.009
ICV	-1.19×10^{-7}	-.97	-.981		=.331

Partial Regression Plots for the Final Model

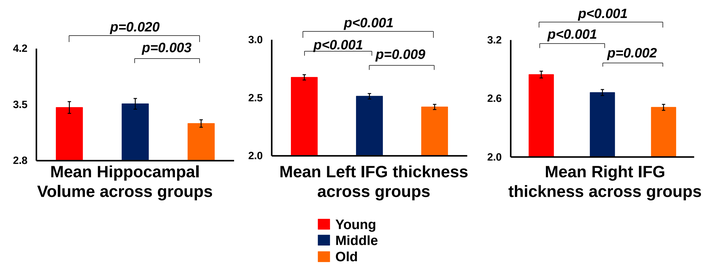


When the outlier (red circle) was removed right IFG thickness continued to be a significant predictor of memory performance (p<.05), although explaining less of the variance (R^2 .068 instead of R^2 = .113).

Age-sensitivity of Structural Measures

The relationship between right IFG thickness and memory performance was observed only in the older group.

However, controlling for pR and ICV, ANCOVAs revealed that hippocampal volume and left and right IFG thickness each differed significantly according to age group. Whereas hippocampal volume did not differ between middle-aged and young age groups, IFG thickness demonstrated a graded age effect.



Summary and Conclusions

fMRI subsequent memory effects in bilateral IFG and hippocampus, together with the fMRI recollection effects in bilateral hippocampus, accounted for approximately 34% of the variance in associative memory performance (pR) across our older participants. Including the structural measures of hippocampal volume and left IFG thickness to the regression model did not improve its fit. In contrast, including right IFG thickness did improve the fit of the model, with the structural measure accounting for additional variance in older participants' pR estimates. We speculate that right IFG thickness reflects the capacity of this region to compensate in older individuals for age-related degradation of other brain regions.

Consistent with prior findings, the structural measures all demonstrated age-related declines, in contrast to the functional data obtained from the same regions.

These findings indicate that functional and structural measures can dissociate with respect to their sensitivity to individual differences in memory performance and chronological age.

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