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AJNR Am J Neuroradiol 2009, 30 (8) 1477-1481
doi: https://doi.org/10.3174/ajnr.A1634
http://www.ajnr.org/content/30/8/1477

ORIGINAL RESEARCH

Intelligence and Medial Temporal Lobe Function in Older Adults: A Functional MR Imaging–Based Investigation

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BACKGROUND AND PURPOSE: The influence of general intelligence and formal education on functional MR imaging (fMRI) activation has not been thoroughly studied in older adults. Although these factors could be controlled for through study design, this approach makes sample selection more difficult and reduces power. This study was undertaken to examine our hypothesis that intelligence and education would impact medial temporal lobe (MTL) fMRI responses to an episodic memory task in healthy elderly subjects.

MATERIALS AND METHODS: Thirty-six women and 38 men, 50–83 years of age (mean, 63.4 ± 7.9 years), completed an auditory paired-associates paradigm in a 1.5T magnet. The amplitude and volume of fMRI activation for both the right and left MTLs and MTL subregions were correlated with the intelligence quotients (IQs) and educational levels by using Pearson correlation coefficient tests and regression analyses.

RESULTS: The participants' mean estimated full scale IQ and verbal IQ scores were 110.4 ± 7.6 (range, 92–123) and 108.9 ± 8.7 (range, 88–123), respectively. The years of education showed a mean of 16.1 ± 3.2 years (range, 8–25 years). The paradigm produced significant activation in the MTL and subregions. However, the volume and amplitude of activation were unrelated to either IQ or years of schooling in men and/or women.

CONCLUSIONS: We found no evidence of an effect of IQ or education on either the volume or amplitude of fMRI activation, suggesting that these factors do not necessarily need to be incorporated into study design or considered when evaluating other group relationships with fMRI.

Most functional brain studies examining the effects of general intelligence demonstrate an inverse correlation between intelligence (Spearman *g*) and activation in frontal lobe circuitry, which is thought to reflect executive control of attention, working memory, and response selection.[1-4] A similar correlation with nonfrontal brain areas, including medial temporal lobe (MTL) structures, has also been reported.[5] Structural imaging studies have generally reported modest correlations between intelligence and total brain volume but have been less successful at correlating intelligence measures with regional brain volumes (eg, Flashman et al[6]). There is some evidence that both frontal and nonfrontal areas show such a correlation. For example, Haier et al[7] used optimized voxel-based morphometry to investigate structural correlates of intelligence on a voxel-by-voxel basis throughout the entire brain and found that intelligence quotient (IQ) positively correlated with gray matter volume in frontal, temporal, parietal, and occipital areas, suggesting that there is a nonspecific or distributed neural basis of intelligence that extends beyond frontal circuitry.

Received January 17, 2009; accepted after revision March 11.

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This work was supported by the National Institutes of Health, National Institute on Aging (AG016324-03, PI Susan S. Bassett, Ph.D.)

Indicates open access to non-subscribers at www.ajnr.org

DOI 10.3174/ajnr.A1634

Even though the MTL is not thought of as a locus of intelligence per se, this brain region is integral to declarative memory function, which requires the ability to learn and remember,[8] capacities fundamental to the manner in which intelligence is generally assessed. Studies of intelligence and memory performance uniformly report a direct relationship between the two.[9-11] In addition, years of formal education, which is often used as a proxy for intelligence, correlates with performance on cognitive screening instruments and test batteries,[12-15] though it appears that years of education may be less related to memory performance than general intellectual functioning.[10] Furthermore, the MTL is a common location of the brain investigated in patients with neurodegenerative disorders including Alzheimer disease. One recent functional MR imaging (fMRI) memory study reported an inverse relationship between years of education and temporal lobe activation among the elderly,[16] providing support for the cognitive reserve hypothesis that attempts to explain the seemingly protective effect of higher education against neurodegenerative disorders such as Alzheimer disease.[17]

It is important to understand whether functional changes observed in response to memory activation paradigms are a reflection of individual characteristics, in this case the intellect or education of the participant. As is already appreciated, there are a number of factors that influence the signal intensity observed during the performance of fMRI paradigms designed to explore cognitive function. Some of these factors are task-specific and integral to the experimental design, reflecting both the intensity and complexity of the activation paradigm. However, others, such as age, sex, and handedness, are subject-specific and, therefore, are potential sources of bias, which can affect both the validity and interpretation of the blood

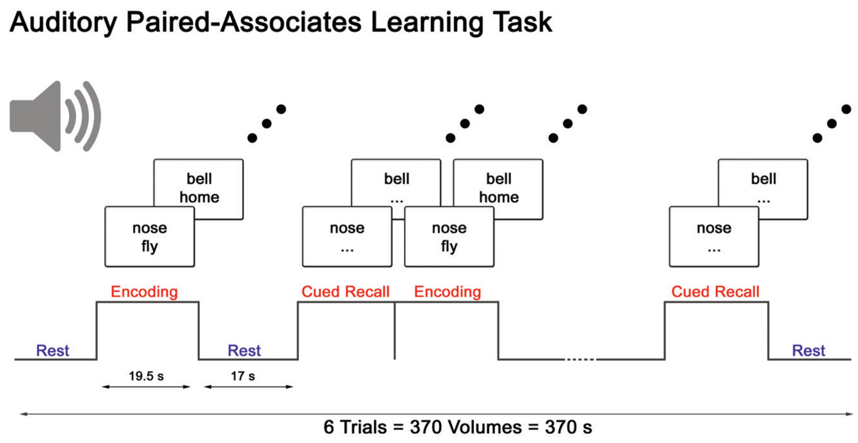

Fig 1. fMRI paradigm. s indicates seconds.

oxygen level–dependent (BOLD) signal-intensity change. Studies have demonstrated, for example, the influence of age and sex on fMRI activation patterns during a variety of cognitive activation tasks[18-23] and have noted structural neuroanatomic differences as well.[17,24,25] These subject-specific factors are generally controlled by matching samples or statistically adjusting for differences in subsequent analyses, practices that can pose problems for sample recruitment and can reduce statistical power if done unnecessarily.

This analysis was, therefore, undertaken to examine directly the impact of general cognitive function as measured by IQ and educational achievement on MTL activation patterns in response to an episodic memory task in a sample of healthy controls older than 50 years of age. We sought to determine whether IQs and levels of education are correlated with activation in MTL structures during memory encoding and retrieval. According to the neural efficiency hypothesis, in which less activation signifies a more efficient brain operation, we hypothesized that as IQ and number of years of schooling increase, MTL activation would decrease[3]—that is, individuals with greater cognitive ability would recruit fewer neural resources to complete the task successfully than those for whom the task may be more of a cognitive strain. This study was undertaken to examine our hypothesis that intelligence and education would impact MTL fMRI responses to an episodic memory task in healthy older adults.

Materials and Methods

Participants. The 74 right-handed individuals included in this analysis currently serve as healthy controls for an ongoing study of brain function and cognition.[26] They range from 50 to 83 years of age (mean, 63.4 ± 7.9 years) and include 36 women and 38 men. As part of an extensive evaluation, the years of education and the performance on the North American Adult Reading Test (NAART) were recorded. The NAART scores were converted to both verbal and full-scale IQs. The IQs, years of education, and ages of the subjects were used as variables for subsequent statistical analysis. The study was approved by the institutional review board, and all participants provided informed consent.

MR Imaging Evaluations. Each individual underwent an MR imaging evaluation, which included coronal magnetization-prepared rapid acquisition of gradient echo (MPRAGE) T1-weighted scanning for total brain and temporal lobe volumetry, a screening T2-weighted scanning to assess any mass lesions or extensive brain injury (TR, 4000 ms; TE, 120 ms; 5 mm with 1-mm intersection gap; 23-cm FOV, and 256 × 512 matrix), and a T1-weighted scanning in the coronal plane corresponding to the sections for which the subsequent fMRI paradigm was performed (TR, 600 ms; TE, 7 ms; 23-cm FOV; and 256 × 256 matrix with a 4.5-mm thickness and 0.5-mm intersection gap). Incidental findings that were noted for the subjects on the screening portion of the MR imaging study included minimal (n = 25) and moderate (n = 5) small vessel ischemic changes (graded by Cardiovascular Health Study criteria), lacunar infarctions of the basal ganglia (n = 7), sinusitis (n = 15), and mastoiditis (n = 2). One patient each had a noncompressive subdural hygroma, posterior fossa arachnoid cyst, and asymptomatic focal occipital lobe infarction.

fMRI Paradigm. Participants were presented with an auditory word-pair-associates learning task, which consisted of two 6-minute 10-second sessions, each with 6 trials. Each trial included an encoding phase, in which 7 unrelated word-pairs (eg, "food" and "book") were presented through MR imaging−compatible headphones, and a cued recall phase, in which the first word from the pair was presented and the participant was instructed to recall silently the second word of the pair. Both encoding and recall were preceded by rest (baseline) periods (see Fig 1 for paradigm diagram). At the end of each session, participants were asked to recall the word pairs.[26]

fMRI Scanning, Data Processing, and Analysis. Functional scans were acquired on a 1.5T Intera NT scanner (Philips Medical Systems, Best, the Netherlands) at the F.M. Kirby Functional Imaging Research Center (Kennedy Krieger Institute, Baltimore, Md). The system is equipped with galaxy gradients (66 mT/m at 110 mT/m/s). A standard head coil was used to limit head motion. A sagittal localizer scan was obtained to pinpoint the exact location of the brain. Two functional scans were acquired using echo-planar imaging (EPI) and a BOLD technique with TR = 1000 ms, TE = 39 ms, flip angle (FA) = 90°, FOV = 230 mm in the xy plane, and matrix size = 64 × 64. Eighteen coronal sections were acquired with a 4.5-mm thickness and an intersection gap of 0.5 mm, oriented perpendicular to the anteroposterior commissure line. Sections were acquired sequentially along the z-axis, yielding a total coverage of 90 mm centered on the temporal lobe. Functional scanning was performed in 2 sessions, each with 370 time points. Total functional acquisition time was 12 minutes 20 seconds. A high-resolution whole-brain scan was obtained by using a T1-weighted 3D MPRAGE sequence with the following parameters: TR = 8.6 ms, TE = 3.9 ms, FOV = 240 mm, FA = 80°, matrix size = 256 × 256, section thickness = 1.5 mm, 124 sections.

Functional data preprocessing was conducted on Windows XP workstations, by using Statistical Parametric Mapping (SPM99; Wellcome Department of Imaging Neuroscience, University College, London, UK) running under the Matlab 6.1 (MathWorks, Sherborn, Mass) programming and runtime environment. Rigid-body registration (motion correction) was performed by realigning all the scans from both sessions to the mean image of all the functionals in both sessions. This was conducted by using a 6-parameter affine transformation (3 translations and 3 rotations in x-, x-, and z-axes), followed by reslicing using a "windowed" sinc interpolation. Twelve-parameter affine transformation and nonlinear normalization using $7 \times 8 \times 7$ basis functions were used to warp each individual's data into standard stereotaxic space (standard atlas). Template space was defined by the EPI template of the Montreal Neurologic Institute (MNI; McGill University, Montreal, Ontario, Canada) included with SPM. The template was manually cut to fit each individual scan to improve the quality of normalization. Normalized scans were resliced to isotropic voxels (2 mm^3), using trilinear interpolation, and spatially smoothed with a full width at half maximum gaussian kernel of 5 mm^3.

Individual time series analysis was conducted using the general linear model within the framework of SPM99. Data were modeled as epochs (blocks) and convolved with the canonical hemodynamic response function of SPM to account for the lag between stimulation and the BOLD signal intensity. The model was estimated by using the implementation of ordinary least squares of SPM. The contrasts of interest subtracted activation during the "rest" condition from the "encoding" and "recall" conditions.

Hand-drawn segmentations of right and left medial temporal subregions (hippocampus, parahippocampal cortex, entorhinal cortex, and amygdala) by an expert rater on the single-subject T1-weighted MNI template were used as region-of-interest masks in this analysis. All of these subregions of the MTL were hand-drawn by an experienced neuroanatomist who has been encircling these subregions for over 10 years. For data on the reliability and validity of the manual segmentation method see Honeycutt et al.[27] We calculated the amplitude and volume of activation for both the right and left MTLs and subregions for each subject's statistical image. These region-specific summaries were correlated with verbal and full-scale IQs and education values by using Pearson correlation coefficient tests. We also performed multiple regression analyses, adjusting for the age and sex of the subjects.

Results

The mean estimated full-scale IQ score was 110.4 ± 7.6 (range, 92–123), and the estimated verbal IQ scores averaged 108.9 ± 8.7 (range, 88–123). The mean years of education corresponded to a college graduate (mean and median, 16.1 ± 3.2 years; range, 8–25 years). Total word-pair recall following the 2 scanning sessions averaged 5.86 ± 3.8 word pairs of 7 possible word pairs.

Group maps of activation for memory encoding and recall minus baseline demonstrated MTL activation for the 74 subjects (Fig 2). Areas of significant activation included the left parahippocampal gyrus and the hippocampus bilaterally ($P <$ .05, corrected for total MTL volume).

Spearman correlations between the left and right medial temporal lobes, subject-level regional summaries, full-scale IQ, verbal IQ, and education level, respectively, were calculated and are presented in Table 1. Results are given for both the encode and recall portions of the paradigm task compared with baseline. Volume of activation represented the extent of voxels within the region of interest with a *t*-contrast value above a 3.1 statistical threshold (the volume that surpassed the statistical threshold of $P < .05$ corrected).

The "mean" was the mean of the subject-specific contrast estimates within the region of interest, whereas the upper quartile was the 75th percentile of the subject-specific contrast estimates. No significant correlations were found between any of our MR imaging measures (volumes and amplitudes of activity) and full-scale or verbal IQ or educational levels in any of

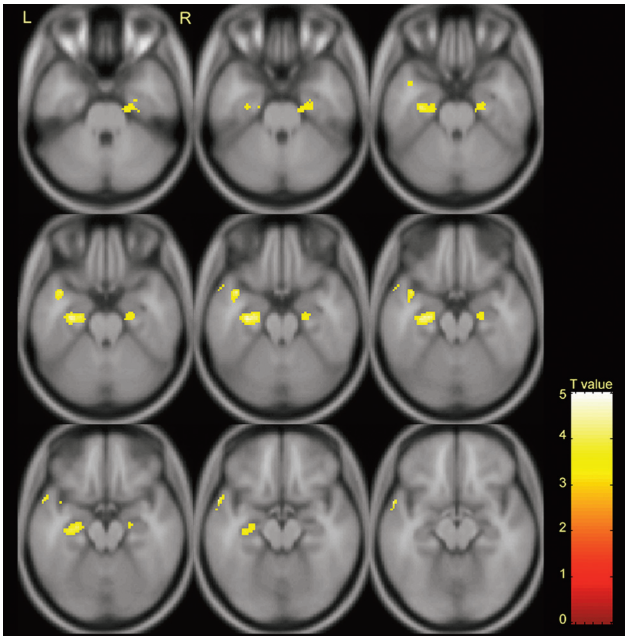

Fig 2. fMRI activation map collapsed over encoding and recall shows activated left and right MTL subregions ($P < .05$, corrected for total MTL volume). Results are overlaid on an averaged T1-weighted template (MNI).

Table 1: Spearman correlations between left and right MTL; left and right subject-level regional summaries; and full-scale IQ, verbal IQ, and education level, respectively*

	FS IQ		Verbal IQ		Education	
Measure	Cor	*P* Value	Cor	*P* Value	Cor	*P* Value
MTL left						
Encode						
Volume	.062	.602	.059	.619	.115	.333
UQ	−.149	.211	−.143	.232	−.050	.674
Mean	−.133	.265	−.127	.288	−.056	.637
Recall						
Volume	.096	.424	.092	.440	.005	.965
UQ	−.147	.217	−.146	.221	−.080	.502
Mean	−.124	.299	−.123	.302	−.061	.607
MTL right						
Encode						
Volume	−.093	.436	−.098	.412	−.051	.669
UQ	−.053	.660	−.056	.639	−.072	.542
Mean	−.058	.627	−.063	.599	−.083	.486
Recall						
Volume	.032	.792	.030	.800	−.007	.955
UQ	−.077	.520	−.076	.527	.034	.774
Mean	−.053	.627	−.063	.599	−.083	.486

Note:—FS IQ indicates full-scale IQ; Cor, correlation coefficient; UQ, upper quartile; MTL, medial temporal lobe; IQ, intelligence quotient.
* Results are given for the encoding and recall tasks, both compared with baseline.

Table 2: Spearman correlations of volume of activation in the MTL of men versus IQ and education for memory encoding and recall show no significant associations

	FS IQ		Verbal IQ		Education	
Measure	Cor	*P* Value	Cor	*P* Value	Cor	*P* Value
MTL left						
Encode						
Volume	.148	.374	.150	.368	.005	.978
UQ	.029	.862	.034	.841	−.121	.468
Mean	.025	.883	.029	.863	−.113	.498
Recall						
Volume	.337	.039	.340	.037	−.225	.175
UQ	−.019	.909	−.014	.932	−.249	.131
Mean	−.021	.901	−.017	.921	−.239	.148
MTL right						
Encode						
Volume	−.050	.766	−.053	.750	−.135	.418
UQ	−.029	.861	−.027	.873	−.146	.382
Mean	−.005	.974	−.004	.981	−.173	.298
Recall						
Volume	.132	.427	.128	.440	−.188	.257
UQ	.006	.971	.009	.957	−.001	.996
Mean	−.005	.974	−.004	.981	−.173	.298

Table 3: Spearman correlations of volume of activation in the MTL of women versus IQ and education for memory encoding and recall show no significant associations

	FS IQ		Verbal IQ		Education	
Measure	Cor	*P* Value	Cor	*P* Value	Cor	*P* Value
MTL left						
Encode						
Volume	.177	.308	.174	.315	.285	.097
UQ	−.266	.123	−.247	.152	.072	.681
Mean	−.230	.183	−.212	.220	.048	.785
Recall						
Volume	−.130	.455	−.141	.417	.205	.237
UQ	−.285	.097	−.281	.102	.103	.552
Mean	−.236	.173	−.231	.181	.112	.522
MTL right						
Encode						
Volume	−.007	.967	−.013	.940	.011	.951
UQ	.019	.915	.013	.943	.004	.982
Mean	−.024	.892	−.032	.853	.008	.963
Recall						
Volume	−.017	.924	−.016	.927	.153	.379
UQ	−.218	.208	−.218	.207	.049	.779
Mean	−.024	.892	−.032	.853	.008	.963

the MTL regions and certainly none when accounting for multiplicity. These same results (absence of correlation) were replicated for the parahippocampal gyrus, entorhinal cortex, hippocampus, and amygdala when these subregions were separately analyzed. When the amplitudes of activation were considered as well, there also were no correlations seen.

The same analysis was repeated after stratifying by subject sex (Tables 2 and 3). Once again for the overall MTLs and for the subregions of the right and left temporal lobes, there were no statistically significant correlations found between volumes and amplitudes of activation and IQ or education for men or women. Adjusting for age did not influence these findings either. Further analyses stratifying education into a dichotomy of college-educated or non-college-educated subjects and directly comparing genders also showed no relationship to the degree of fMRI activation in any region. Lack of a significant correlation was observed during both encoding and recall components of the task and on a combined contrast adding both components.

Discussion

This large fMRI study demonstrates that the intelligence and education levels of these older healthy research study participants do not influence the volume or amplitude of MTL activation seen in an auditory episodic memory experiment. The paradigm produced significant increases in activation in the MTL, including the left parahippocampal gyrus and bilateral hippocampus. However, these increases were unrelated to either IQ or years of schooling. This lack of association is apparent for both periods of memory encoding and periods of memory recall.

Studies have reported associations between levels of education and intelligence and brain atrophy, as well as performance on neuropsychological testing,[17,28,29] which may be expected to reflect underlying neural functioning. However, this relationship is not as apparent in the context of functional hemodynamic blood flow, with a number of studies reporting functional alteration without structural change, possibly indicating that functional changes precede neuronal loss. One such study[26] found functional differences between individuals at familial risk for Alzheimer disease and matched controls in the absence of any memory performance differences or structural differences in MTL regions.

There is evidence for functional differences related to IQ and education in regions other than the MTL on some imaging studies. Scarmeas et al[30] found, for example, that a composite factor incorporating both education and IQ was associated with greater positron-emission tomography (PET) activity in the left cuneus for older subjects and in the right inferior temporal gyrus, right postcentral gyrus, and cingulate in younger subjects during a visual memory task. Springer et al[16] recently noted a contrast between the young and the old with respect to the relationship of activation maps and level of education. Using an fMRI memory task, they found that among elderly participants, higher education was associated with increased frontal activity, whereas lower education was associated with increased MTL activity. The authors suggest that education may play a role in an underlying ability to shift neural resources. Finally, a recent PET study investigating the impact of cognitive reserve in healthy elderly subjects, as quantified by a combination of education and IQ, found that subjects with higher cognitive reserves demonstrated a dynamic shift in frontal and medial temporal networks in response to a spatial recognition memory task as task difficulty increased.[31] This suggests that intelligence and education may have an indirect effect on MTL function, in the context of increasing task demand.

Although this study of relatively intelligent and well-educated older individuals provided robust results, it is possible that these findings will not generalize to younger or less-well-educated samples. On average, the participants had completed college and registered an IQ (mean, 108.9–110.4) at the higher end of the normal range of intelligence, and all were at least middle-aged. In addition, the results generated by this specific paired-associates memory task may not generalize to findings from other fMRI memory paradigms. On the other hand, the strength of this study lies in the large sample size tested. Although the average intelligence and educational level in this sample may be high, the data may be apropos to the subject population typically enrolled in most fMRI research labs recruiting from their local university populations.

This study does not support the cognitive reserve hypothesis, which would have predicted that there would be an inverse correlation of IQ and education with functional activation such that increased intelligence and years of schooling would result in lower levels of BOLD activation in the MTL in response to this task. However, it is possible that the paradigm used here was not sufficiently challenging to elicit differential performance, though analysis of the free-recall data following scanning produced only about 83.7% memory retention rate, suggesting that the subjects were being "challenged" by the paradigm. There is evidence from functional studies of motor output, attention, and spatial-recognition memory that increased task difficulty results in altered neural activation.[31-33] There are, however, inherent problems in modulating task difficulty. For example, in initial pilot work for this task, increasing the unfamiliarity and length of the words used for the word pairs or increasing the speed of delivery resulted in less activation because individuals reported they were frustrated because they could not accomplish the task and essentially stopped trying.

Conclusions

Our results suggest that the level of education and verbal and full-scale IQs have little influence on encoding and recall MTL activation in response to an auditory episodic memory task in healthy older adults. This conclusion impacts the potential need to control for these demographic and neuropsychological variables for the analysis of the described memory-based fMRI task. This finding is somewhat at odds with conventional wisdom that considers education and IQ as primary confounders between cognitive or health predictors and fMRI activation. Our results suggest that this conventional wisdom should be tempered in some settings, especially because unnecessary control for potential confounders can inflate variances and lead to type II errors.

Whether these findings can be generalized to a wider population and to other stimulus paradigms needs to be examined. For example, other study populations may have a wider range of education levels and intelligence quotients. Further study needs to be undertaken because these questions have important ramifications for subject inclusion criteria, statistical power calculations, and analysis of fMRI research studies.

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