
Effect of Age on Visuomotor Functional MR Imaging¹

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Rationale and Objectives. We sought to determine the effect of age on functional MR imaging experiments performed with visual and motor stimulation. We hypothesized that there would be a diminution in the amplitude of fMRI activation with increasing subjects' age.

Materials and Methods. We used fixed effects models to study the amplitude of activation during a block design visuomotor task in three different age groups: old (mean: 75 years; standard deviation: 6 years), middle-aged (mean: 52 years; standard deviation: 9 years) and young (mean: 29 years; standard deviation: 5 years). Each group included 7 subjects. Regions of interest (ROI) were left primary motor area (LM1), supplementary motor area (SMA), and right and left occipital (RO, LO) visual areas. Individual subjects and group statistical parametric maps (SPMs) were generated for each ROI, and then the mean amplitude of activation was compared using the group analysis and *t* test.

Results. The young age group showed higher amplitude of activation than middle and old age groups in all ROI ($P < 0.01$ uncorrected). Unpaired two tailed *t* test results between the groups showed significant differences between middle and young, and old and young age groups in all ROIs ($P \leq 0.05$), with the exception of old and young age groups in RO region ($P = 0.11$).

Conclusion. The group analysis, and unpaired *t* test results reveal higher amplitude of fMRI activation in the young versus the old and middle-aged groups.

Key Words. Amplitude; age; visuomotor task; functional MR imaging.

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The effect of age has not been adequately addressed with visuomotor functional MR imaging studies in previous studies (1–4). The impacts of age in performing a task could reflect vascular or neuronal activity changes as one ages (5). Age-related increases in the winding, coiling,

and number of “blind-ends” in the cerebral vascular micro-lattice may cause signal change in blood oxygenation level dependent (BOLD) functional MR imaging (fMRI) by affecting blood flow, blood volume, and oxygen consumption, all of which affect the oxygen concentration in the capillaries, venules, and arterioles (6,7). BOLD functional MR imaging is sensitive to these contributions from the vascular bed (4).

The effect of age using functional MR imaging (fMRI) has only been studied between widely disparate old and young age groups. We sought to determine the effect of age on fMRI experiments with visuomotor stimulation in old, middle-aged and young age groups. We debated whether the functional MR imaging correlate of aging would be a diminution in the amplitude of activation as

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subjects aged or a bell shaped curve with maximal amplitude in the middle-aged population.

MATERIALS AND METHODS

All subjects were recruited from an internal neuroradiology patient database or from the community by means of advertisements in the printed media and local flyers. Only subjects with no mass lesions or significant white matter changes (less than a grade of 4 on the Cardiovascular Health Study rating system) were included in the analysis. No subjects were taking medication that affected neurologic performance. Written informed consent from a protocol that was approved by the Johns Hopkins Institutional Review Board was obtained from all subjects.

Twenty-one healthy, right-handed subjects (12 females, and 9 males) were included in the study. There were 3 age groups, old (mean: 75, range: 69–85), middle (mean: 52, range: 42–61), and young (mean: 29, range: 26–33). Each group included 7 subjects; 4 females and 3 males.

Imaging was performed on a 1.5 T scanner (Gyrosan ACS-NT; Powertrak 6000, Philips Medical Systems, Best, The Netherlands) equipped with 2.3 G/cm gradients and echo-planar imaging. A standard head coil with foam padding to limit head motion was used. All patients underwent a screening T2-weighted scan (TR: 4000, TE: 102) to assess for masses as well as the presence and degree of white matter lesions. The functional MR imaging protocol employed a gradient echo blood oxygenation level dependent (BOLD) technique with a TR of 3000 ms, TE of 39 ms, 90 degree flip angle, 24 cm field of view, 60 time points in a 3 minute scan. Slices were acquired with a 5 mm thickness and an interslice spacing of 1 mm using a matrix of 128×128 .

At the TE of 39 ms there is not enough time to sample the 128×128 k-space data matrix fully, hence partial acquisition of the k-space data (60%) was performed. Nonetheless, the spatial resolution remains $1.875 \text{ mm} \times 1.875 \text{ mm}$ within the slice. Seventeen scan sections angled parallel to the intercommissural line and including both primary visual as well as sensorimotor cortices were obtained.

The block design was written in E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA). The block design paradigm consisted of a round, multicolored visual cue appearing on the screen for 0.5 sec in a 30 second “off”, and 30 second “on” paradigm. During the

30 seconds of “on” condition there were repetitive presentations of the visual cue presented to the subject at 3-second intervals, however random “blank screen” in which a cue was omitted were placed to prevent anticipatory responses. The “on” condition alternated with the “off” condition in which 30 seconds of a blank screen except for a fixation point was presented. The total scan time was 3 minutes with 3 off-on repetitions of the task. The subjects were asked to tap a finger press button with the index finger of their right hand as soon as they saw the visual cue. The functional data processing for each subject was performed on SUN Ultra workstations using SPM99 (Wellcome Dept. of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherbon, MA, USA) (8). Realignment for motion correction was performed, followed by spatial normalization using the standard brain template from the Montreal Neurological Institute (MNI) and then converted to the standard stereotaxic atlas of Talairach space (9) using an algorithm developed by Matthew Brett (<http://www.mrc-cbu.cam.ac.uk/Imaging/>). Images were then smoothed at 5 mm full width half maximum Gaussian kernel. The model was created using a standard linear approach, in which the epochs are convolved with the hemodynamic function. All sixty time-points in the scan are used. This model was fit to the data and the percent signal change was computed for each voxel. Individual subject model estimation and thresholding using thresholds of $P < .01$ (uncorrected) were then performed. The subset of voxels within the region of interest (ROI) was defined for the individual statistical map, ie, voxels which were significant at the individual level and were within the ROI were used. Thus the number of voxels included for each subject was fixed. We computed the individual maps to be more sensitive to differences in activated voxels within the ROIs. In the same manner, the subset of voxels within the ROI was defined for the individual statistical map for each group for group comparisons. Then group analysis was done in each age group separately (old, middle, and young) utilizing the amplitude estimates (% signal change) of the 7 subjects in each group with a threshold of $P < .01$ (uncorrected).

Using an in-house developed “measure” program (10) and a canonical MNI normalized single-subject template, the masks for the 4 ROIs were drawn. Experts (NMB and MAM) determined ROI masks for the left primary sensorimotor area (LM1), right and left combined supplementary motor area (SMA), and left occipital (LO) and right occipital (RO) visual cortices

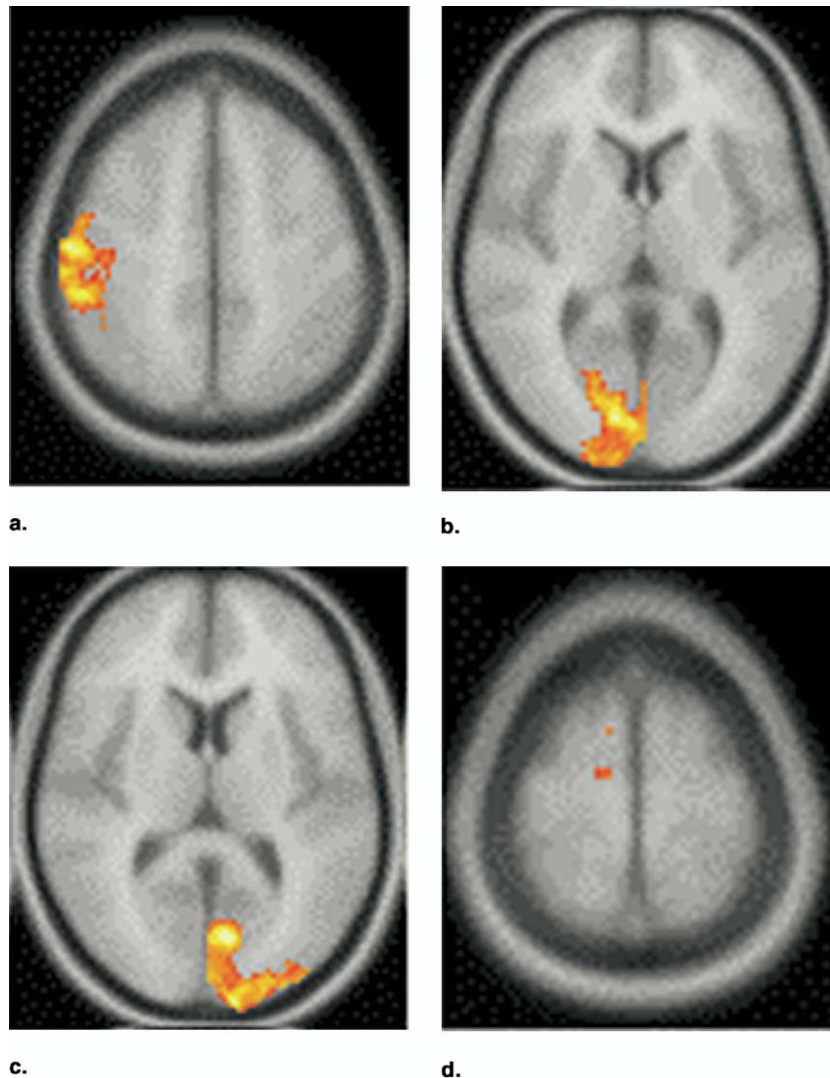


Figure 1. ROIs drawn in measure. LM1: left motor area; SMA: supplementary motor area; RO: right occipital; LO: left occipital.

(Fig. 1). The coordinates for each area were defined using the Talairach and Tournoux atlas and converted from millimeters into voxels according to the origin of our template.

The height threshold for mean amplitude calculation for subjects was fixed for all subjects at $t = 2.49$ ($P < .01$). Results for the mean amplitude were calculated for each subject and each group, in the four ROI. For individual subjects' analysis we used the threshold at $t = 2.35$ ($P < .01$), and this was constant for each subject. For the fixed effects group analysis the threshold was $t = 2.49$ ($P < .01$), and again constant for each group. A simple regression analysis between the age and mean amplitude in each ROI was performed

across all 21 subjects. Then an analysis of variance (ANOVA) between each age group in the 4 ROI, and unpaired t test analysis between young, and middle and old age group collapsed were performed.

RESULTS

Mean amplitude results were obtained for each subject in LM1, SMA, LO, and RO regions using SPM99 (Fig. 2). With the exceptions of subject 6 in RO and subject 21 in SMA, all subjects in the 3 age groups showed supra-threshold activation in all ROIs on individual maps when the uncorrected P value was set at $< .01$. Regression

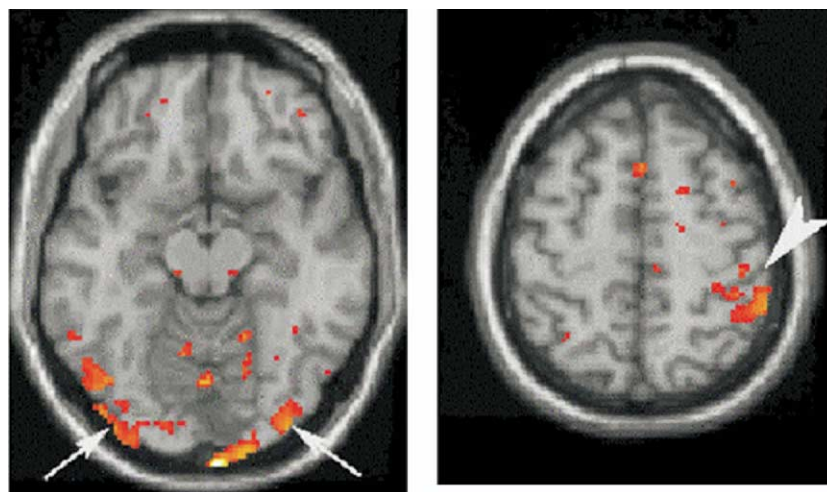


Figure 2. 70-year-old male with activation map using block design paradigm ($P < .001$ uncorrected for multiple comparisons) (images presented in radiologic convention, where right side of image is left side of brain). **(a)** Transverse motor activation map showing activation in visual cortices (arrows). **(b)** Transverse motor activation map showing activation in left motor area (arrowhead)

Table 1
Regression Analysis Between the Age and the Mean Amplitudes of the 4 ROI in 21 Subjects:

	R	P
LM1	-0.49	0.012
SMA	-0.57	0.005
RO	-0.62	0.002
LO	-0.53	0.007

LM1: Left sensorimotor area, SMA: Supplementary motor area
LO: Left occipital visual cortex, RO: Right occipital visual cortex

analysis showed a statistically significant ($P < .01$) negative correlation between the age and the mean amplitude in each ROI (Table 1).

In the fixed effect group analysis ($P < .01$), the young group showed higher mean amplitude than old and middle groups in all ROIs. In SMA and LO regions the middle-aged group showed slightly higher amplitude than the older group (Table 2).

To further analyze the significance of the difference between age groups, we performed ANOVA analyses between each group for the 4 ROI (Table 3). The results showed significant differences in all ROI between middle and young, and old and young age groups ($P < .001$). There was no statistically significant difference between old and middle age groups. To check the strength of difference between the young group and the others, we col-

Table 2
Mean Amplitudes in Each Age Group Using SPM99 $p .01$

	LM1	SMA	RO	LO
Old	3.13	3.43	3.15	2.80
Middle	2.91	3.75	2.94	2.95
Young	8.35	5.83	8.22	6.42

amplitude: % signal change
LM1: Left sensorimotor area, SMA: Supplementary motor area
LO: Left occipital visual cortex, RO: Right occipital visual cortex

lapsed the middle and old age groups into one single sample and performed unpaired *t* test analyses. These analyses revealed statistically a significant difference in all ROIs between the young and collapsed middle and old groups ($P < .05$) (Table 4).

DISCUSSION

The main regions of interest (ROIs) along the visuo-motor pathway are the right and left visual occipital cortices, which are responsible for the perception of the visual stimulus, as well as the supplemental motor areas (SMA) and the sensorimotor cortex, which are responsible for the motor movement function. Recently Mohamed et al have shown that activation begins in the visual cortices followed by the supplemental motor area and lastly the pri-

Table 3
ANOVA Analysis Between 3 Age Groups in All ROI

	LM1	SMA	RO	LO
Old-young	0.02*	0.0001*	0.03*	0.01*
Middle-young	0.04*	<0.0001*	0.01*	0.01*
Middle-old	0.82	0.97	0.29	0.79

overall analysis reveal $P < 0.001$

LM1: Left sensorimotor area, SMA: Supplementary motor area

LO: Left occipital visual cortex, RO: Right occipital visual cortex

*: statistically significant value

Table 4
Unpaired Both Tailed t Test Results Between Young and Collapsed Old and Middle

	mean diff	DF	t value	pvalue
LM1	-5.87	19	-3.07	0.01*
SMA	-10.63	19	-4.47	0.003*
RO	-6.12	19	-2.44	0.02*
LO	-7.13	19	-3.82	0.001*

mean diff: mean difference

DF: Degrees of freedom

*: statistically significant values

mary sensorimotor regions, using a latency-resolved event-related fMRI study (11).

The visuomotor system has been previously studied for the effect of aging (1–3), effect of gender (12), and correlation of fMRI data with simple reaction time task (13, 14). Ross et al (1) used photic stimulation and investigated activation in visual cortices, D'Esposito et al (2) used a visual cue and investigated activation in primary sensorimotor cortex, and Hesselmann et al (3) used auditory stimulus and investigated activation in left motor cortex. We know of no literature to use visual stimulation and investigate motor, sensorimotor, and visual cortices all together in one experiment to compare the amplitude of activation in brain in three different age groups as old, middle, and young.

Mattay et al studied the effect of aging in the physiology of brain systems subserving simple motor behavior (15). They found that elderly subjects demonstrated greater activation both in amplitude and volume of activation, and elderly subjects recruited additional cortical and subcortical areas (contralateral sensorimotor cortex, lateral premotor area, supplementary motor area, and ipsilateral cerebellum) even for the performance of a simple motor task (button-press with the dominant right hand). Our study differs in the paradigm design and adds the addi-

tional middle-aged subject group. Their study revealed an increase in reaction time in the elderly compared to young subjects. Taoka et al found prolonged time lag with increasing age, and T-inc (the time for the signal changing ratio to reach half of the maximum ratio during the task) showed positive age correlation (16).

Grady et al have shown that older subjects show less activation than younger subjects in the extrastriate cortex, but greater activation than younger subjects in the prefrontal and parietal cortices during visual processing of faces and location (17).

Ross et al found that the amplitude of the response in elderly subjects in the visual cortex was significantly reduced relative to younger individuals (1). They also noted that atrophy in the aged does not necessarily correspond to depression of the amplitude of functional MR imaging activation (1). In the PET literature there are suggestions that global cerebral glucose utilization may be independent of brain size and age as well (18).

In a study of activation volume, D'Esposito et al found that the number of suprathreshold voxels in older subjects was four times less than that in younger subjects (2). These results were in accordance with the study done by Yousem et al studying the olfactory system. They demonstrated that a decrease in performance in odor identification and detection corresponds with decreases in the activation volume of olfactory eloquent areas (19).

Hesselmann et al have shown an age-related decline ($P < .05$) in absolute and relative signal amplitude, and number of suprathreshold voxels during blood oxygen level-dependent functional MR imaging motor tasks (3). There were 86 subjects in the study and the age ranges were 24–83 years in men, and 20–83 years in women.

Positron emission tomography (PET) literature reveals controversial results on the effect of aging in brain activation. Initial PET studies included a limited age range (20–23). With an age range of 19–38 years there was no age difference in regional and global glucose metabolic rates among the subjects (23,24). However age-related reductions for glucose rates in the resting state in women less than 40 years old and over 64 years old were significant in frontal and parietal regions (25).

In order to understand the effect of aging in the brain we set up an analysis of 3 different age groups as old (mean: 75, range: 69–85), middle (mean: 52, range: 42–61), and young (mean: 29, range: 26–33) and we correlated the age with the mean BOLD hemodynamic amplitude values using a block design fMRI imaging. In each group we had 4 females and 3 males to control the effects

of gender. Mikhelashvili-Browner et al (12) have shown a lack of gender effects on brain activity during a visuomotor task functional MR imaging, but previous results were controversial (26,27). Yousem et al have shown that women have larger volume of activation (28) using odor-stimulated fMRI, and Mohamed et al found that the BOLD signal response was 38% lower in women during photic stimulation paradigms (29).

Our results are consistent with Ross et al and Hesselmann et al's studies showing that older age groups show less amplitude of activation than young ones (1,3). Unlike our results D'esposito et al did not find any significant change in the amplitude of activation; however they found marked disparity in the volume of activation, elder subjects showing one quarter of activated brain volume of the younger ones (2). Buckner et al found marked reduction in the amplitude of activation in older subjects in visual cortex but amplitude of activation did not differ across age groups in the motor cortex (30). This is in contrast with our findings that age groups did not differ in the amplitude of activation across ROIs. ANOVA analyses between each group for the 4 ROIs (Table 3) showed significant differences in all ROIs between middle and young, and old and young age groups ($P < .001$) with decreasing amplitude of activation as one ages (similar to Buckner's findings in the occipital lobes). There was no statistically significant difference between old and middle age groups. When we combined old and middle age groups, unpaired two-tailed t test results were statistically significant ($P < .05$) in all ROIs.

Age-related decrease in the BOLD fMRI response may represent reduced neuronal activation, reduced vascular response to normal activation, structural change, or a difference in the coupling of blood oxygenation changes in response to focal activation in the elderly (31–33) either of which cannot be separated from the other using current technology. The influence of small vessel atherosclerosis, which probably decreases the elasticity and compliance of affected vessels (34) in the elderly, on their ability to mount a vascular response to neuronal stimulation may account for some of the differences between the young and the old subjects.

CONCLUSION

Our results show a negative association between age and BOLD fMRI amplitude in LMI, SMA, RO, and LO regions. We suggest that diminution in amplitude of activation

by aging should be taken into account when performing clinical fMRI applications. In our study, there is a significant decline in the amplitude of activation between young subjects and the old and middle-aged subjects, but there was no statistically significant difference between the middle and old age groups. This may reveal that detectable amplitude changes in aging by fMRI occurs around the sixth decade and does not show significant changes in the amplitude of activation in age groups beyond the 6th decade. Extra caution should be taken when subjects of middle and old age are analyzed for clinical applications, since detectable amplitude of activation is already low in this group.

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