Effects of Age on Brain Activation During Auditory-Cued Thumb-to-Index Opposition
A Positron Emission Tomography Study

C. Calautti, MD; C. Serrati, MD; J-C. Baron, MD

Background and Purpose—Available data indicate a decline in fine finger movements with aging, suggesting changes in central motor processes. Thus far no functional neuroimaging study has assessed the effect of age on activation patterns during finger movement.

Methods—We used high-resolution perfusion positron emission tomography to study 2 groups of 7 healthy right-handed subjects each: a young group (mean age, 24 years) and an old group (mean age, 60 years). The task was a thumb-to-index tapping, auditory-cued at 1.26 Hz with a metronome, with either the right or the left hand. The control condition was a resting state with the metronome on.

Results—Significant differences between old and young subjects were found, suggesting significant overactivation in older subjects affecting the superior frontal cortex (premotor-prefrontal junction) ipsilateral to the moving fingers, as if the execution of this apparently simple motor task was judged more complex by the aged brain. Similar findings in previous perceptual and cognitive paradigms have been interpreted as a compensation process for the neurobiological changes of aging. Analysis of the control condition data in our sample showed, however, that this prefrontal overactivation in the old group was due at least in part to higher resting perfusion in anterior brain areas in the young subjects.

Conclusions—The changes in brain function observed in this study may underlie the subtle decline in fine motor functions known to occur with normal aging. Our findings emphasize the importance of using an age-matched control group in functional imaging studies of motor recovery after stroke. (Stroke. 2001;32:139-146.)

Key Words: aging ■ cerebral blood flow ■ motor activity ■ tomography, emission computed
Subjects and Methods

Fourteen healthy volunteers, 7 young (aged 24.4 ±5.1 years) and 7 old (aged 60.4 ±10.6 years) (mean ±SD), with 4 women and 3 men in each group, were enrolled in the study. They were recruited by advertisements in the local newspaper. All of them gave written informed consent before participation, and the research protocol was approved by the regional ethics committee. Written consent was obtained according to the Declaration of Helsinki. Enrollment was based on lack of clinical, biological, or neuroradiological abnormality, as follows: normal somatic examination (in particular, no orthopedic or rheumatologic problem affecting the arm, hand, or fingers); no vascular risk factors or smoking >10 cigarettes per day; no alcohol or coffee abuse; blood pressure within normal limits; no previous history or current evidence of neurological disease; no current use of medication (except birth control pill in young women and hormonal substitution therapy in postmenopausal women); lack of significant biological abnormality (including blood cell count, liver function tests, serum electrolytes, plasma glucose, and cholesterol and triglyceride levels); and lack of significant change at standard MRI (including T1- and T2-weighted scans) apart from: (1) rest with eyes closed, metronome on at the frequency of 1.26 Hz (rest); (2) right TIT, at same frequency; and (3) left TIT, at the same frequency. This frequency was chosen because it has been shown in previous PET studies to induce optimal activation responses32,33 and because it is considered physiological (ie, neither too rapid nor too slow). The task lasted a total of 1.75 minutes. All subjects were trained for the task before the experiment. Monitoring of the finger movements during scanning (by means of a video camera) showed that all subjects performed the task adequately in all runs.

Data Acquisition

Subjects were scanned while lying supine with their eyes closed in a darkened and quiet room. The head was gently immobilized in a dedicated head rest. Head position was aligned transaxially to the orbitomeatal line with a laser beam. Measurements of regional distribution of radioactivity were performed with an ECAT HR+ (Siemens) PET camera with full-volume acquisition, allowing the reconstruction of 63 planes (thickness, 2.4 mm; axial field of view, 158 mm; effective resolution was approximately 4.2 mm in all directions). Transmission scans were obtained with a 68Ge source before emission scans. The duration of each scan was 90 seconds. Approximately 7 mCi of H2 O15 was administered as a slow bolus in the left antecubital vein by means of an automated infusion pump. Each experimental condition was started approximately 15 seconds before data acquisition and continued until scan completion. This process was repeated for each of the 12 scans, for a total injected dose of approximately 80 mCi. The interval between injections was 7 minutes; the position of the head was controlled with the laser beams before each injection.

Data Transformation

All calculations and image transformations were performed on UNIX SYSTEM workstations. First, the 12 scans of each subject were realigned with each other with the use of AIR 3.0 software.34 For subsequent data analysis, Statistical Parametric Mapping (SPM)
software (SPM96, Wellcome Department of Cognitive Neurology) implemented in the MATLAB environment was used. The images were nonlinearly transformed into standard space (MRI template) on the basis of the atlas of Talairach and Tournoux. The images were smoothed with a 12-mm gaussian filter.

**Data Analysis**

The images were scaled to an overall cerebral blood flow (CBF) grand mean of 50 mL/100 g per minute; we therefore refer to adjusted regional CBF (rCBF) in this analysis. We used a gray matter threshold of 80% of the whole brain mean; covariates were centered before inclusion in the design matrix. An ANCOVA, with global activity as a confounding covariate, was performed on a pixel-by-pixel basis. The results of \( t \) statistic [SPM \( (t) \)] were then transformed into a normal standard distribution [SPM \( (Z) \)], and they were set to \( Z > 3.09 \), with the results considered significant only if they passed the threshold of \( P < 0.05 \) corrected for multiple comparisons, using the theory of gaussian fields.

**Figure 1.** Right TIT vs rest (a) and left TIT vs rest (b) activation patterns in the young group \( (P < 0.05, \text{corrected}) \). Data were obtained with SPM96 software, shown here according to the classic Talairach’s “glass brain” display mode. The neurological convention was used. The activation pattern included, for both tasks, the contralateral primary sensorimotor cortex and inferior parietal lobule and the bilateral cerebellum and parietal operculum; additional activations included the contralateral Rolandic operculum, SMA proper, dorsal premotor cortex, and posterior cingulate cortex for right TIT and the ipsilateral Rolandic operculum and contralateral putamen and thalamus for left TIT.

<table>
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<td>40 −60, −24, 20</td>
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<td>24 −8, −10, 50</td>
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<td>14, −54, −14</td>
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<td>24 6, 2, 50</td>
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<td>6 −2, 0, 74</td>
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<td>−10, −54, −16</td>
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<td>26, −60, −24</td>
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<td>4 54, 2, 12</td>
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Clusters are listed in decreasing order of \( Z \) value; secondary peaks are shown in italic.
We first analyzed the activation patterns (ie, right TIT or left TIT versus rest) in the old and young subjects separately. We then looked for significant differences between the 2 groups in right or left TIT versus rest comparisons, ie, (TIT versus rest)old versus (TIT versus rest)young. The reverse comparisons, ie, rest versus right TIT and rest versus left TIT (so-called deactivations), as well as the comparison in rest condition–adjusted rCBF between the old and the young groups, were then assessed to refine the interpretation of the differences in activation patterns, if any. Anatomic/cytoarchitectonic localization of the significant activations was based on the SPM96 MRI template and Talairach’s coordinates (obtained from the coordinates supplied by the SPM96 software according to the equations computed by A. Meyer-Lederberg, personal communication; see spm@mailbox.ac.uk). All the coordinates listed in the sections below are SPM96 coordinates.

**Results**

**Activation Patterns**

The results for right TIT and left TIT in the young and old groups are shown in Tables 1 and 2 and Figures 1 and 2, respectively. In the young group, the activation pattern included (1) for both tasks, the contralateral primary sensorimotor cortex and inferior parietal lobule as well as the bilateral cerebellum and parietal operculum; additionally, (2) the contralateral rolandic operculum, supplementary motor area proper (SMA proper), dorsal premotor cortex, and posterior cingulate cortex, for right TIT; and (3) the ipsilateral rolandic operculum and contralateral putamen and thalamus, for left TIT. In the old group, the activation pattern included (1) for both tasks, the contralateral primary sensorimotor cortex, parietal operculum, and anterior cingulate cortex, as well as ipsilateral cerebellum; and additionally, (2) the ipsilateral SMA proper, bilateral putamen, and contralateral cerebellum, for left TIT.

**Intergroup Comparisons**

Regarding the old versus young comparisons, for right TIT there was a significant cluster of overactivation in the anterior part of the right superior frontal sulcus, at the junction between the superior and middle frontal gyri (Brodmann’s area [BA] 6/8, peak coordinates x=28, y=24, z=54; cluster size=279; Z score=4.35) (Figure 3; see Figure 4 for the data plot for this peak), whereas for left TIT this comparison did not reveal any significant cluster at P<0.05, corrected for multiple comparisons. The reverse comparisons (ie, young versus old) likewise did not disclose significant differences for either right or left TIT.

**Deactivations (Rest Versus TIT)**

The results for the young group are illustrated in Figure 5. At the chosen statistical cutoff, deactivations concerned mainly anterior–superior brain areas, with a roughly similar pattern for both tasks. Regarding the old group, no significant
deactivation was found for right TIT, while for left TIT, deactivations concerned anterior-inferior brain regions only (Figure 6).

**Rest Condition Comparison**

The results are shown in Table 3 and Figure 7. This comparison revealed highly significant lower adjusted rCBF in the old group compared with the young group, affecting exclusively the anterior brain bilaterally, as well as the lateral cerebellum bilaterally.

**Discussion**

In this study we explored in young and old healthy subjects the functional neuroanatomy of an auditory-cued thumb-to-index opposition task, well suited to investigate patients still recovering from stroke. In both the young and old groups, the network of cortical and cerebellar areas engaged by our task is largely consistent with earlier studies of noncomplex and cued motor tasks using rates of approximately 1 Hz, although no previous study used a design identical to ours. Even though our task did not explicitly involve learning, there was an activation of subcortical structures during left TIT in both groups (namely, the bilateral putamen in the old group and the contralateral putamen and thalamus in the young group), which may reflect the engagement of the brain “timing network” by our task when the nondominant hand is used. In this study no quantitative assessment of rCBF was obtained, which may have prevented us from a complete

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**Figure 4.** Comparison of activations (right TIT vs rest) between young and old groups for the superior frontal cortex (BA 6/8), showing a higher adjusted CBF during rest in the young group compared with the old group, with deactivation during TIT in the young group but with activation in the old group (right BA 6/8; coordinates x=28, y=24, z=54). A indicates activation; R, rest; Y, young; and O, old. See also Figures 5 to 7.

**Figure 5.** Rest vs right TIT (a) and rest vs left TIT (b) deactivation patterns in the young group (P<0.05, corrected). See Figure 1 for details. These glass brain representations illustrate significant deactivations in the anterior-superior brain regions for both tasks.

**Figure 6.** Deactivation patterns in the old group for rest vs left TIT (P<0.05, corrected). See Figure 1 for details. Significant deactivation in the anterior-inferior brain regions is illustrated (there was no significant deactivation for right TIT).
Superior frontal gyrus, left 10
Middle frontal gyrus, left 9
Anterior cingulate cortex, right 24
Medial frontal gyrus, right 8
Pre-SMA, right 6
Anterior cingulate cortex, left 32
Ventral premotor cortex, left 6
Anterior putamen, left
Interior frontal gyrus, left 47
Middle frontal gyrus, right 10
Middle frontal gyrus, right 8
Middle frontal gyrus, right 45
Interior frontal gyrus, right 47
Superior temporal gyrus, right 22
Posterior putamen, right
Anterior putamen, right 32
Medial frontal gyrus, left 10
Orbitofrontal gyrus, right 11
 Inferior frontal gyrus, right 47
Cerebellum, left
Cerebellum, right 52
Middle frontal gyrus, right 8

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<td>30, 22, 54</td>
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<td>4.75</td>
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Secondary peaks are shown in italics.

This robust result of significantly greater activation in the ipsilateral superior frontal cortex (BA 6/8) during right TIT in the old subjects has never been reported before. Although during left TIT there was no significant overactivation in the old subjects, a cluster was found in almost exactly the same (ipsilateral) area, but it did not pass the stringent correction for multiple tests (Z=4.37; cluster size, 128; x = -28, y = 36, z=48). At an even lower threshold, there was also an overactivation of the right anterior cingulate gyrus during left TIT (Z=4.29). Thus, performing this apparently simple motor task requires the aged brain to recruit additional dorsal frontal areas (perhaps as well as the anterior cingulate gyrus). The exact extent and functions of BA 8 are still a matter of debate, especially regarding its boundaries with BA 6 of Vogt and Vogt.47 the overactivated area found here would fall very near or at area 6a, which is considered a premotor area. Activation of the premotor cortex in healthy subjects takes place during implicit procedural learning as well as with complex tasks or tasks involving visual cues.5 Likewise, area 8 is activated with finger sequence tasks that are either complex,41 very slow,32 new,48,49 or free-choiced,50 but also when information has to be maintained within working memory.51 Thus, the aged brain may need to engage any or all of these cognitive processes to perform this apparently simple motor task. Previous findings concerning visual and memory tasks also suggested anterior frontal overactivation in aged subjects (see Introduction).16–24 Excessive premotor and prefrontal as well as anterior cingulate activations have also been reported in recovered stroke patients performing motor tasks.2,5,38 Although simple visual inspection in our subjects showed that they all performed the task as instructed, it would be interesting to obtain objective measures of movement characteristics to correlate with the activation patterns according to age.

The aforementioned interpretation needs to be qualified, however, in light of the adjusted rCBF data concerning the right frontal area. As shown in Figure 4, the data plots indicate that in this area the adjusted rCBF was high in the young subjects during rest and decreased during the execution of the movement, whereas in the old subjects it was low at rest but increased during the execution of the task. This pattern is fully supported by the findings of the deactivation and rest condition analyses. First, the deactivation analysis revealed significant deactivations in the anterior regions of the brain, including the frontal cortex, in the young group...
during either right or left TIT (Figure 5), while in the old group the deactivated areas were mostly located in inferior brain regions and only concerned left TIT (Figure 6). Second, the rest condition analysis revealed that the adjusted rCBF was significantly higher in the young than in the old subjects in large areas of the anterior brain, including the superior dorsal frontal and anterior cingulate cortices (Table 3 and Figure 7). In particular, there was a significantly lower adjusted rCBF at rest in the right BA 6/8, with almost the same coordinates as the area overactivated in the group comparison (see Results and Table 3). Third, as already mentioned, there existed a marginally significant activation of right BA 6/8 in the old subjects during right TIT.

Altogether, therefore, the data indicate that the frontal overactivation observed in the aged subjects reflects in part a difference already present in the rCBF rest pattern and further exaggerated by inverse trends during finger movement. However, the question of whether an overactivation of this area truly occurred in the aged group can be raised since Figure 4 suggests that the adjusted rCBF in this area was similar during right TIT in the 2 groups, and a post hoc SPM analysis directly comparing the PET scans during right TIT did not reveal any significant difference in this frontal area (data not shown). Although this would suggest that the differences found in the right TIT versus rest group comparison are due entirely to differences in the rest condition, we noted that, relative to the reference condition, this frontal area was differentially activated in the 2 groups according to the widely accepted definition of activation.

Surprisingly, none of the previous studies that reported excessive activation in the aged brain during perceptual or cognitive tasks\textsuperscript{16–24} took into account the differences in the resting state when interpreting their activation data. The lower resting adjusted rCBF in anterior brain regions in aged subjects found here is remarkably similar to all previous voxel-based studies of aging, whether concerning perfusion or glucose consumption.\textsuperscript{26–30} Although these differences may represent tissue atrophy and synapse loss, which tend to predominate in the association cortex and particularly in the prefrontal and medial-frontal regions with normal aging,\textsuperscript{26} this interpretation would not readily account for the apparent deactivations in these regions during finger motion. Thus, the alternative hypothesis is that in the young subjects these anterior brain areas were more neurally active during rest than during the motor task. A kind of anticipation of the motor task may have occurred, resulting in an anterior brain activation that relaxed during the actual task, but this would hardly explain the similar age-related differences found in resting glucose consumption studies independent of any motor task.\textsuperscript{24–30} One could also speculate that the condition of immobility during scanning requires some inhibition of motor action in the young, which tends to disappear with age. Indeed, it is increasingly recognized that the resting pattern of rCBF contains behavioral information.\textsuperscript{52}

This study is the first to document significant differences in brain activity patterns according to age during a motor task. These changes mainly consisted of significant superior frontal overactivation in older subjects, suggesting the recruitment of additional areas during the execution of an apparently simple motor task as a compensation process for the age-related neurobiological changes. These changes may underlie the subtle decline in fine motor functions that are known to occur with normal aging. However, the findings were at least in part explained by age-related differences in the control (rest) condition, an issue that has been neglected thus far in similar studies. This study shows the importance of using an age-matched control group in functional imaging studies involving aged subjects, such as those investigating recovery after stroke.

Acknowledgments

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References


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