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

Recently, functional neuroimaging has provided us with fundamental new insight into the reorganization of cortical maps and the redistribution of functional networks underlying hand movement recovery after stroke.1-6 However, most studies published thus far neither controlled for age among the patients nor used an age-matched control group. Contrary to the long-held assumption that age does not affect hand movement patterns, 3 studies from the early 1980s reported a correlated decrease with age in both hand strength and dexterity, suggesting changes in the central motor processes.7-9 Notably, older people require progressively longer reaction time as movement complexity increases, suggesting slower and less efficient brain processes, especially when the response cannot be anticipated.10-12 Importantly, slower reaction times and increased error rates with aging are not specific to the motor domain.13-15

Whether these age-related differences in motor function would translate into changes in brain network activation during task execution is unknown, however. Previous studies concerning the perceptual (visual) and cognitive (mnemonic) domains16-24 have frequently observed an increase in the number of activated regions in aged compared with young subjects, even though performance was not necessarily impaired or only so in the form of longer reaction times. One favored interpretation for these findings is that a recruitment of new brain areas becomes necessary to perform the task as a compensatory process for the age-related cell changes. Interestingly, these increased activations have most frequently been found to concern the prefrontal cortex, suggesting the need for increased control during task performance with aging, consistent with hypotheses from experimental psychology.25 Interestingly, declines in resting-state brain perfusion and glucose consumption with normal aging have also been found to involve the prefrontal cortex.26-30

Because of the importance of the issue in relation to studies of motor recovery after stroke, we have investigated with positron emission tomography (PET) 2 groups of right-handed subjects of different age performing a controlled motor task consisting of auditory-cued thumb-to-index tapping (TIT) with either the dominant or the nondominant hand, ie, a task that can be considered simple. This fixed design should allow a direct comparison of activation patterns between the 2 age groups.
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); 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 what would be considered part of normal aging. In the group of aged people, the Mini-Mental State Examination score was 29.8 ± 0.4 (mean ± SD; maximum score is 30), indicating no incipient dementia. The Edinburgh Inventory Test\(^1\) showed right-handedness in all subjects (LQ, 99.4 ± 2.2; mean ± SD). All the recruited people had at least 8 years of schooling and were able to perform the motor task without any difficulty.

Experimental Design
Each subject underwent 12 consecutive scans (injections of H\(_2\)O\(^{15}\)) during a single PET session lasting approximately 3 hours. Three different conditions, each replicated 4 times, were performed in pseudorandom and balanced order: (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 responses\(^2\) 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 \(^{99m}\)Tc source before emission scans. The duration of each scan was 90 seconds. Approximately 7 mCi of H\(_2\)O\(^{15}\) 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.\(^3\) For subsequent data analysis, Statistical Parametric Mapping (SPM)

### TABLE 1. Activation Peaks (Corrected P<0.05) in the Young Group, Shown Separately for Right and Left TIT vs Rest

<table>
<thead>
<tr>
<th>BA</th>
<th>x, y, z</th>
<th>Cluster Size</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right TIT vs rest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensorimotor cortex, left</td>
<td>1–4</td>
<td>−40, −20, 52</td>
<td>5811</td>
</tr>
<tr>
<td>Rolandic operculum, left</td>
<td></td>
<td>−44, −6, 12</td>
<td>6.44</td>
</tr>
<tr>
<td>Parietal operculum, left</td>
<td>40</td>
<td>−52, −26, 20</td>
<td>5.67</td>
</tr>
<tr>
<td>Inferior parietal lobule, left</td>
<td>40</td>
<td>−54, −26, 34</td>
<td>5.20</td>
</tr>
<tr>
<td>SMA proper, left</td>
<td>6</td>
<td>−10, −10, 68</td>
<td>3.85</td>
</tr>
<tr>
<td>Dorsal premotor cortex, left</td>
<td>6</td>
<td>−26, −6, 44</td>
<td>3.40</td>
</tr>
<tr>
<td>Cingulate sulcus, posterior, left</td>
<td>31</td>
<td>−18, −20, 42</td>
<td>3.27</td>
</tr>
<tr>
<td>Cerebellum (hemisphere, dentatus, vermis), right</td>
<td></td>
<td>18, −48, −16</td>
<td>2585</td>
</tr>
<tr>
<td>Cerebellum (hemisphere, dentatus, vermis), left</td>
<td></td>
<td>−12, −58, −20</td>
<td>4.67</td>
</tr>
<tr>
<td>Parietal operculum, right</td>
<td>40</td>
<td>56, −24, 24</td>
<td>580</td>
</tr>
<tr>
<td><strong>Left TIT vs rest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensorimotor cortex, right</td>
<td>1–4</td>
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<td>4627</td>
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<tr>
<td>Parietal operculum, right</td>
<td>40</td>
<td>56, −24, 24</td>
<td>5.94</td>
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<tr>
<td>Inferior parietal lobule, right</td>
<td>40</td>
<td>64, −34, 22</td>
<td>4.99</td>
</tr>
<tr>
<td>Cerebellum (hemisphere, dentatus, vermis), left</td>
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<td>−14, −50, −18</td>
<td>2885</td>
</tr>
<tr>
<td>Parietal operculum, left</td>
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<td>−52, −26, 20</td>
<td>541</td>
</tr>
<tr>
<td>Rolandic operculum, left</td>
<td></td>
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<td>445</td>
</tr>
<tr>
<td>Cerebellum, right</td>
<td>20, −60, −18</td>
<td>317</td>
<td>4.75</td>
</tr>
<tr>
<td>Putamen, anterior, right</td>
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<td>286</td>
<td>4.10</td>
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<tr>
<td>Putamen, posterior, right</td>
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<td></td>
<td>3.69</td>
</tr>
<tr>
<td>Thalamus posterolateral, right</td>
<td>28, −16, 12</td>
<td></td>
<td>3.18</td>
</tr>
</tbody>
</table>

Clusters are listed in decreasing order of Z value; secondary peaks are shown in italic.
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 (\( P < 0.05 \), 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 2. Activation Peaks (Corrected \( P < 0.05 \)) in the Aged Group, Shown Separately for Right and Left TIT vs Rest |
|---------------------------------|-------|---------|--------|------|
| **Right TIT vs rest**           | BA    | \( x, y, z \) | Cluster Size | \( Z \) Score |
| Sensorimotor cortex, left       | 1–4   | \(-38, -26, 60\) | 3927           | 7.38          |
| Parietal operculum, left        | 40    | \(-60, -24, 20\) | 5441           | 5.54          |
| Cingulate cortex, anterior, left| 24    | \(-8, -10, 50\)  | 1055           | 5.01          |
| Cerebellum, right               | 14,   | \(-54, -14\)    | 1866           | 7.18          |

| **Left TIT vs rest**            | BA    | \( x, y, z \) | Cluster Size | \( Z \) Score |
| Sensorimotor cortex, right      | 1–4   | \(-44, -26, 54\) | 5511           | 7.87          |
| Cingulate cortex, anterior, right| 24    | 6, 2, 50        | 1233           | 6.22          |
| Parietal operculum, right       | 40    | \(-62, -28, 20\) | 5451           | 3.99          |
| SMA proper, left                | 6     | \(-2, 0, 74\)   | 1203           | 3.75          |
| Cerebellum, left                | \(-10, -54, -16\) | 2184           | 7.34          |
| Cerebellum, right               | 26,   | \(-60, -24\)    | 5441           | 3.98          |
| Rolandic operculum, right       | 4     | 54, 2, 12       | 424            | 4.44          |
| Putamen, posterior, right       | 24,   | 0, 14           | 450            | 3.98          |
| Anterior putamen, left          | \(-26, 12, 18\) | 310            | 3.89          |
| Posterior putamen, left         | \(-26, -8, 16\) | 300            | 3.81          |

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

Figure 2. Right TIT vs rest (a) and left TIT vs rest (b) activation patterns in the old group (P<0.05, corrected). See Figure 1 for details. When compared with the young subjects (see Figure 1), there is a clear common pattern of activations but with additional as well as absent foci (note, for instance, the additional activations in the anterior cingulate cortex for both tasks, and ipsilateral SMA proper for left TIT; see Results for details).

Figure 3. Old vs young comparison of activation patterns for right TIT vs rest (P<0.05, corrected). The significant voxels are projected onto a surface rendering of a standard MRI. Shown here are sagittal and superior views of the cortical surface. The neurological convention is used. The data show an overactivation in the right superior frontal sulcus (BA 6/8) in the old compared with the young subjects (see Discussion for interpretation of this finding, however).
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

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).
Understanding of the effects of aging in the group comparisons and limited the comparison of activations and deactivations. There were a number of minor differences in the activation patterns between the young and old groups, with, for instance, an activation of the anterior cingulate cortex in the old but not the young group for both tasks, but none reached statistical significance in the direct comparison between the 2 groups at the stringent cutoff chosen. Thus, the direct comparison revealed only an overactivation in the right superior frontal cortex in aged relative to young subjects during right TIT (see Figure 3) (note, however, that the overactivated area found here would fall very near or at area 6aβ, 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.

Likewise, area 8 is activated with finger sequence tasks that are either complex, very slow, new, free-choiced, or free-choiced, but also when information has to be maintained within working memory. 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).

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 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. How-
ever, 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
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 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. 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, 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
activation.

One could also speculate that the condition of immobility
during scanning requires some inhibition of motor
activity in the young, which tends to disappears with age.
Indeed, it is increasingly recognized that the resting pattern
of rCBF contains behavioral information.

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 fron-
tal overactivation in older subjects, suggesting the recruit-
ment 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.

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