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Citation for published version (APA):

Tisserand, D. J., van Boxtel, M. P. J., Gronenschild, E. H. B. M., & Jolles, J. (2001). Age-related volume reductions of prefrontal regions in healthy individuals are differential. *Brain and Cognition*, *47*(1-2), 182-185.

Document status and date:
Published: 01/01/2001

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

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47. Age-Related Volume Reductions of Prefrontal Regions in Healthy Individuals Are Differential

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During the aging process cognitive functions are differentially affected. Especially 'complex' attentional and long-term memory capacity decrease with advancing age. These cognitive changes may be the result of reductions in the volume of the prefrontal cortex. We used magnetic resonance imaging (MRI) to measure prefrontal regions of 60 healthy subjects with a broad age range (21–81 years). Here we present a method for determining the volume of the prefrontal lobes and their gross functional subregions (dorsolateral, medial, orbital) based upon the stereotactic coordinate system of Talairach. Advancing age was found to be associated with marked reductions in dorsolateral and medial and less outspoken in orbital prefrontal volumes. This decrease was disproportional compared to the more global age-related brain atrophy. © 2001 Academic Press

Introduction

It is well established in the field of neuropsychology that aging affects cognitive functions in a differential way. For example, in a large cross-sectional study (n = 1900; Jolles et al., 1995) it was shown that especially 'complex' attentional functions and the ability to learn and retrieve new information tend to decrease with advancing age. What causes these changes? Are there regions in the brain that can be designated to mediate this age-related cognitive deterioration?

Advancing age is clearly accompanied by decreases in global brain volume (Tisserand et al., 2000). It is tempting to examine to what extent brain regions implicated in cognitive functions also show this age-related volume reduction. Our assumption is that decreases in brain volumes may be reflected on a functional level. Magnetic resonance imaging (MRI) provides a useful tool for studying the human brain *in vivo*. To date, most attention has been focused on regions in the medial temporal lobe (e.g., Tisserand et al., 2000) as they have a key function in long-term memory. However, not much research has been performed on the volume of the prefrontal cortex despite its role in many higher cognitive functions. This may be because this brain region is fairly difficult to delineate because of large variability in sulcal and gyral neuroanatomy. Here we present a method for measuring the prefrontal lobes and their gross functional subregions (dorsolateral, medial, orbital) based upon the stereotactic coordinate system of Talairach and Tournoux (1988). The hypothesis was that ad-

vancing age is associated with decreases in prefrontal volumes and that these volume reductions would be more pronounced than global age-related brain atrophy. Furthermore, we examined whether the three prefrontal regions were differentially affected by the aging process.

Method

Subjects. The study sample consisted of 60 healthy and cognitively normal persons, aged 21 to 81 years (mean 55.7). Subjects were excluded if there was a history of cerebrovascular (e.g., stroke) or chronic neurological disease (e.g., dementia, epilepsy, head trauma), systemic disorders (e.g., diabetes mellitus), or major psychiatric illnesses using health questionnaires and a semistructured interview.

MRI acquisition and analysis. All subjects were imaged using a 1.5-T Gyroscan ACS-II MRI scanner (Philips, Best, The Netherlands). T1-weighted images were acquired in the coronal plane (perpendicular to the anterior commissure–posterior commissure line). A 3D gradient fast field echo (FFE) sequence was applied with TR = 23 ms, TE = 7 ms, and a flip angle of 30°. Slice thickness was 1.5 mm with no interslice gap. The image matrix was 256 × 256 and the field of view was 230 mm. The first step in image analysis consisted of removing the skull from the brain. This was done using locally developed software. Next, the brains were realigned for placement within the stereotactic coordinate grid as originally proposed by Talairach and Tournoux (1988; see Fig. 1). For this purpose the BrainImage software was used

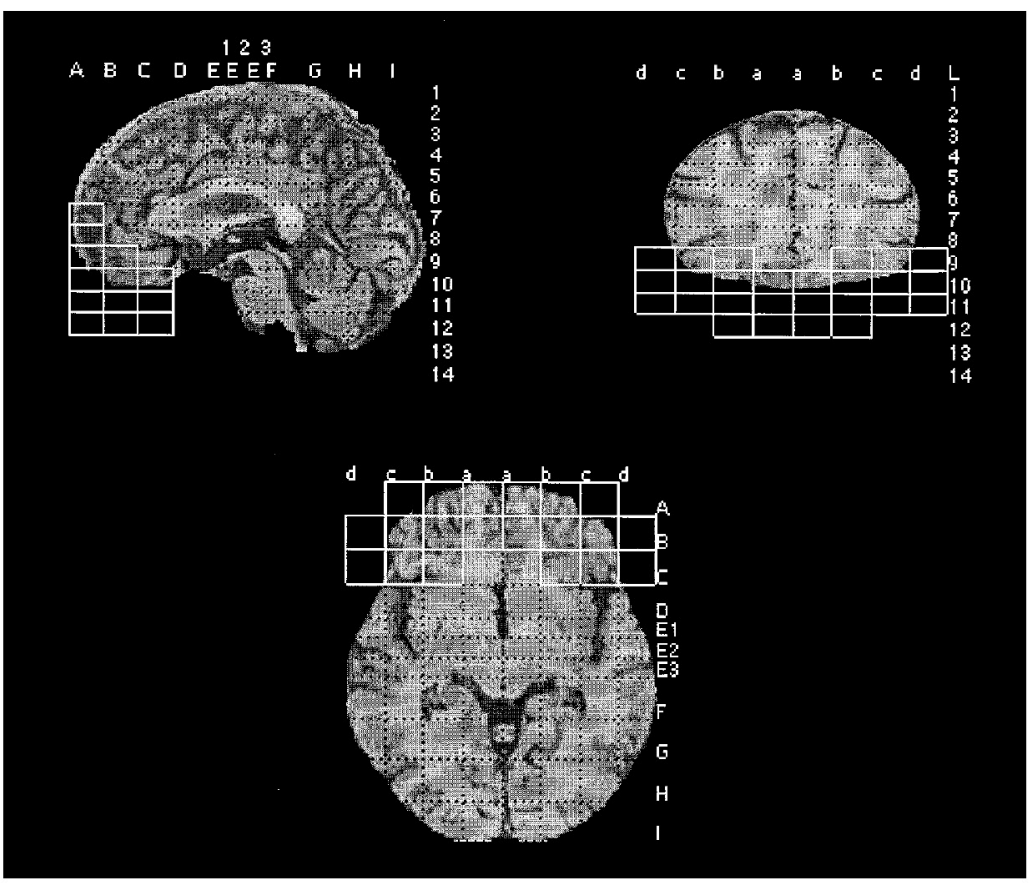


FIG. 1. Multiplanar view of a 3D MRI volume within the Talairach stereotactic grid. The boxes drawn in white represent the orbital prefrontal region.

(Subramaniam et al., 1997). The Talairach coordinate system is based upon three landmarks: the anterior and posterior commissures (AC and PC) and a point above the AC–PC line within the interhemispheric fissure. The anterior, posterior, superior, inferior, and left and right cerebral boundaries are then designated automatically, which ensures the comparability of head position across subjects, irrespectively of brain size and form.

Using this approach, brain areas can be defined based upon their relationship to the specified neuroanatomical landmarks. We assigned the boxes of the Talairach grid to prefrontal areas, defined as Brodmann areas:

—Dorsolateral prefrontal (DLPF): areas 9, 45, and 46;
—Medial prefrontal (MPF): areas 8, 24, and 32; and
—orbital prefrontal (OPF): areas 10, 11, and 47.

In cases where a box included two different regions, it was assigned to the region that comprised the majority of the tissue within the box. As a reference area (where no age-related changes were expected; Scheibel, 1996) we measured the cerebellum. Care was taken to include only those boxes where no cerebral tissue was present.

Finally, a segmentation procedure was applied in order to divide pixels into three classes: gray and white matter and liquor. Intracranial volume (ICV) was defined as the sum of these three classes, and total brain volume as the sum of gray and white matter.

Statistical analysis. Gender differences in prefrontal brain volumes were examined using multiple regression analyses (with ICV as a covariate). The effect of age on the prefrontal areas was investigated in two multiple regression models, one with ICV as the only covariate and another with both ICV and total brain volume as covariates.

Results

A significant sex difference was found for ICV (men, 1071 cm^3; women, 955 cm^3, $p < .001$). Age and ICV were not related ($r = -.16$, ns). After accounting for ICV, none of the brain regions were found to differ between men and women. Higher age was associated with reduced total brain volume ($r = .78$, $p < .001$). A strong relation was also found between age and prefrontal tissue (DLPF, $r = .62$; MPF, $r = .75$, $p < .001$; OPF, ns.), and age and gray matter (DLPF, $r = .60$; MPF, $r = .71$, $p < .001$; OPF, $r = .32$, $p < .01$). Age and volume of the cerebellum were not related ($r = .19$, ns).

Next, we examined if the age-related prefrontal atrophy was disproportional compared to the total brain volume reductions. After correcting for ICV and total brain volume, no significant associations were found between age and prefrontal tissue, but a relation between gray matter and age was found for the DLPF ($r = .70$, $p < .05$) and MPF ($r = .78$, $p < .001$).

Discussion

In this cross-sectional study it was demonstrated that advancing age is associated with marked reductions in total and prefrontal brain volumes, but not in that of the cerebellum. This is in line with the literature (e.g., Scheibel, 1996). Furthermore, we expected that the reductions in prefrontal volumes would be more pronounced than the total brain atrophy. Indeed, the volume of the medial and dorsolateral (but not orbital) prefrontal cortex was found to be related to advancing age, even when accounting for global atrophy. To conclude, prefrontal regions seem to be very sensitive to the aging process. Moreover, the effect of age appears to be differential within

the prefrontal cortex; i.e., the dorsolateral and medial areas are more affected than the orbital region. These volume reductions are mainly the result of decreases in gray matter. Since many higher cognitive functions are dependent on the integrity of areas within the prefrontal cortex, these volume changes may play a causal role in age-related cognitive decline. In the near future we will investigate the relation between these prefrontal measures and performance on specific cognitive tests.

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