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Effects of age and sex on volumes of the thalamus, pons, and cortex

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Abstract

Volumes of thalamus, pons, cortical gray matter, and white matter were derived from MR brain images of healthy men and women spanning the adult age range in order to delineate patterns of aging and to compare age and sex effects in thalamus and pons with such effects in cortical gray and white matter volumes. Men had larger intracranial volume (ICV) than women, but ICV did not correlate with age in either sex. Thalamic, pontine, and cortical white matter volumes did not differ between men and women once ICV differences were taken into account, but men had more cortical gray matter than women even after accounting for ICV. Volumes of pons and thalamus were associated, independent of ICV, in women but not in men. Thalamic volume declined linearly with age at a similar rate in both men and women, whereas cortical gray matter volume declined more steeply with age in men than women. Both pontine and cortical white matter volumes remained stable across the age span in both men and women.

Keywords: MRI; Age; Pons; Thalamus; White matter; Gray matter; Cortex; Sex

1. Introduction

The pons and thalamus are both critical nodes in circuits linking the cerebellum and basal ganglia to motor and sensory cortices as well as frontal and prefrontal cortex that subserve higher-order behavior [2,15,21,29,47,48]. The pons is primarily a white matter structure of the brainstem that has been identified, for example, as the site of an intermediate step in the feed-forward loop of the cerebrocerebellar circuit [48]. The thalamus is a highly differentiated gray matter structure, comprising many subnuclei, each with specialized functional links to different cortical, subcortical, and cerebellar sites and has been characterized as a dynamic conduit linking subcortical with cortical areas [14].

Age-related deficits in the gross volume of either of these structures may provide a non-specific indicator of damage in functional circuits underlying any of a number of distinct cognitive and motor functions. However, while normal aging effects on the pons and thalamus have been studied in separate samples, no report has covered normal aging effects on both pons and thalamus in the same sample or examined whether age effects on these subcortical gray and white matter structures parallel those found for cortical gray and white matter. Similarly, while sex differences for thalamus [59,60] and pons [45] have been studied in separate samples, no study has included both structures in a study of sex differences or sought to compare sex differences in rates of aging of subcortical and cortical gray and white matter structures.

In vivo MR imaging studies broadly concur that the pons does not show cross-sectional change in volume with age [25,45], although one report found age-related changes in men but not in women [33]. This lack of age-related change in the pons is consistent with reports of other white matter structures, including the corpus callosum (e.g. [54]) and cerebellum [52] and cortical white matter as a whole [35,39]. However, the extent of age-related loss of cortical white matter volume has been controversial and depends to some extent on whether the sample includes subjects in their 80s and 90s, whether global or regional cortical white matter is measured, and the approach used to segment and measure white matter. Thus, some investigators do report volume declines starting from the fifth decade [3,5,10], differences between

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young and old subjects [13], and between healthy elderly in their 60s and 70s and those in their 80s and 90s [46].

The thalamus generally shows cross-sectional reduction in volume with age [59,60], although one report did not find this effect [17]. Age-related decline in the volume of this gray matter structure is consistent with age-related decline in cortical [10,39,44] and cerebellar [52] gray matter volumes. Decline of gray matter volume in healthy aging brains, however, does not necessarily mean cell loss but rather cell shrinkage or compaction, an observation increasingly supported from postmortem studies [24,58].

The extent to which men and women differ in rates of change in brain structure volumes over the adult age span has been controversial, with some studies finding sex differences in specific structures (e.g. [31,60]), whereas others find no sex difference in rates of age-related change, particularly for global cortical volume (e.g. [10,57]). It is not clear whether these discrepancies reflect differences in populations tested or in measurement techniques used.

In order to investigate the topics discussed above, we measured volumes of the thalamus and pons in a sample of healthy men and women spanning the adult age range, tested sex-related differences in the relationships between regional volumes and age, and explored the relationship between volumes of thalamus and pons, the sites of two major structural nodes of the fronto-cerebellar circuit. We also report on age and sex effects on volumes of cortical gray and white matter, with the expectation that age-related changes in thalamus would parallel those in cortical gray, while a lack of age-related changes in pons would parallel that in cortical white matter.

2. Methods

2.1. Study participants

Data for this report were derived from 3D T1-weighted and dual-echo axial image sequences obtained on different occasions from a pool of healthy men and women, recruited from the community to participate in studies of normal aging and to serve as healthy comparison groups for patient populations with neuropsychiatric conditions also studied in our laboratory. Potential control subjects who scored below 25 on the Mini Mental State Examination [9] were excluded from the study. All subjects gave written informed consent after the nature of the study and procedures were explained to them. Three-dimensional scans, obtained from a sample of 51 men and 49 women, were used to measure the thalamus and pons. Pontine data have been published in separate comparisons with schizophrenic and alcoholic men [55] and alcoholic women [41], but a full analysis and sex comparison of the normative data have not been previously reported. Axial data were also available for a sample of 95 men (33 of whom were in the 3D scan dataset) and 48 women (47 of whom were in the 3D dataset). Cortical data from subsets of these healthy men and women have been used to provide norms for neuropsychiatric groups (e.g. [7,22,38,40,53], but a report on normal sex and age differences based on these subjects has not been previously published. Demographic characteristics of men and women of both samples are summarized in Table 1.

Subjects were screened for entry into normal comparison samples using the Structured Clinical Interview for DSM-III-R or DSM-IV [8,50], a medical history, physical examination, panel of blood tests and a structured interview assessing lifetime alcohol consumption [49]. Subjects were excluded if they had a history of medical or neurological illness or trauma that would affect the CNS, had ever met DSM-III-R or DSM-IV criteria for a major psychiatric disorder including substance dependence, substance abuse in the past year, or had reported a period exceeding 1 month during which they had drunk more than two (for women) or three (for men) standard drinks a day.

2.2. MR image acquisition and analysis

3D SPoiled Gradient Recalled (SPGR) MR images were used for quantification of thalamus and pons and were acquired on a 1.5 T General Electric Signa (TR = 24 ms; TE = 5 ms; flip angle: 40°; 124 slices; 24 cm field of view; 256 × 196 matrix, reconstructed resolution = 0.9 × 0.9 × 1.5 mm, acquired resolution = 0.9 × 1.2 × 1.5 mm). Image data were reformatted to 1-mm isotropic voxels and aligned along the anterior–posterior commissure plane and interhemispheric fissure. All images were coded to allow processing to be performed blind to subject identity, age, and sex.

Table 1
Demographic variables and unadjusted volumes for brain structures: mean, standard deviation and range

Subcortical group 3D SPGR protocol	Age (years)	Years of education	Intracranial volume (cc)	Thalamus volume (cc)	Pons volume (cc)
Men ($n = 51$)	45.2 (13.9) 23–72	16.4 (2.2) 12–23	1449 (125) 1190–1718	13.4 (1.7) 9.8–17.8	8.1 (1.1) 5.6–11.1
Women ($n = 49$)	50.2 (19.1) 20–85	16.2 (2.5) 12–22	1238 (113) 964–1475	12.3 (1.5) 9.1–15.4	7.0 (0.9) 5.1–9.1
Cortical group Axial spin-echo protocol	Age (years)	Years of education	Intracranial volume (cc)	Cortical gray matter volume (cc)	Cortical white matter volume (cc)
Men ($n = 95$)	49.2 (15.8) 21–81	16.5 (2.6) 9–23	1345 (118) 1129–1654	118.6 (17.5) 78–161	75.4 (12.6) 50–108
Women ($n = 48$)	49.6 (18.9) 20–85	15.8 (2.0) 12–21	1173 (114) 880–1418	99.6 (11.9) 76–123	66.6 (10.3) 47–94

The ventral (basilar) *pons* and the *thalamus* were manually traced by K.L.S. following visible borders on every third, 1-mm thick sagittal slice with the medial slice at mid-sagittal plane. All measurements were completed twice, and the volume was the mean of the two measurements. The most lateral boundaries of both structures were first estimated by marking the limits on coronal and axial views. The shape of the *pons* was smooth and ovoid (Fig. 1). The dorsal borders were formed by the medial and lateral lemnisci that appeared as a strip of reduced signal intensity. The most lateral aspects were traced until partial voluming made it difficult to distinguish the ventral pons from the superior cerebellar peduncles, approximately 10 mm from the midline, where the brainstem is transected by the calcarine fissure. Visible borders of the left and right *thalamus* were first apparent at approximately 15–18 mm each side of the midline. The rostral border of the thalamus forms part of the floor of the lateral ventricles, and is bounded by the fornix and body of the caudate nucleus (laterally). Caudally, the sulcus hypothalamicus marks the boundary of the thalamus and the subthalamus. The dorsal surface of the thalamus, the pulvinar, forms a part of the floor of the third ventricle, and is clearly delimited by the retropulvinal (subarachnoid) cistern. The ventral boundaries of the thalamus are the third ventricles (medially) and the internal capsule (laterally). The left and right thalami were randomly reversed in orientation to prevent measurement bias. Intrarater reliability was estimated with intraclass-correlations (ICC) between two scores of 40 subjects. ICC for the pons = 0.92, left thalamus = 0.93, and right thalamus = 0.92.

Intracranial volume (ICV) for 3D scans was estimated by modeling the head as an oblate spheroid. This analysis was based on the distance between inner skull margins on three brain slices derived from the SPGR sequence to represent *x*-, *y*-, and *z*-axes. The *x*-axis length was defined as the left and right extreme from an axial slice at the level of the AC-PC line; the *y*-axis length was defined as the anterior and posterior extreme from the midsagittal slice, defined above; and the *z*-axis length was defined as the superior margin of the parietal lobe/dura and the inferior margin of the temporal lobes/dura from a coronal slice at the anterior commissure. The resulting voxel count was then transformed into a volume (cc) measure (volume $= (4/3) \times \pi \times (x/2) \times (y/2) \times (z/2)$).

Fig. 1. Outlines of thalamus and pons on the 11 sagittal slices used for delineating these structures in a 42-year-old healthy man.

Axial spin-echo MR images were used to quantify cortical gray and white matter and were 5-mm thick, 2.5-mm skip; field of view = 24 cm; 256 × 256 matrix; TE = 20 and 80 ms; cardiac cycle gated effective TR > 2400 ms; 256 phase encodes; oblique plane perpendicular to sagittal plane crossing through anterior and posterior commissures. Analysis, which has been previously described in detail [39], encompassed seven consecutive sections, beginning at an index section (the most inferior section above the level of the orbits, where the anterior horns of the lateral ventricles could be seen bilaterally) and proceeding superiorly. Each slice was segmented into CSF, gray matter, and white matter compartments using a semi-automated image analysis technique [23]. Pixel counts for gray and white matter within a geometrically defined cortical rim (the outer 45% of each slice) were transformed into cubic centimeters (cc) to provide estimates of their absolute volume. These estimates, thus, provide a sample of total cortical gray and white matter limited by the number of slices included in the analysis and the geometrically defined boundary within the cortical rim.

ICV for axial scans was also estimated by modeling the ICV as a sphere using the area of the index slice and head height as the diameter of the sphere. Head height was derived from a slice passing through the temporal lobes at the anterior commissure in a plane oriented perpendicular to the AC-PC line from a separate coronal scan [26].

2.3. Statistical analysis

Group differences were analyzed using analysis of variance (ANOVA), analysis of covariance (ANCOVA) with ICV as a covariate, and two-group *t*-tests (two-tailed, alpha = 0.05). The effects of age and sex differences in aging were tested with Pearson product moment correlations and slopes tests applied to assess differences in pairs of regressions for men versus women. Association between pontine and thalamic volumes, independent of shared variance due to ICV, was assessed using multiple regression for the total sample and for men and women separately.

3. Results

3.1. Volumes of thalamus and pons

3.1.1. Effects of sex

A two-group by two-hemisphere ANOVA for thalamic volumes yielded a significant group effect ($F(1, 98)$ =

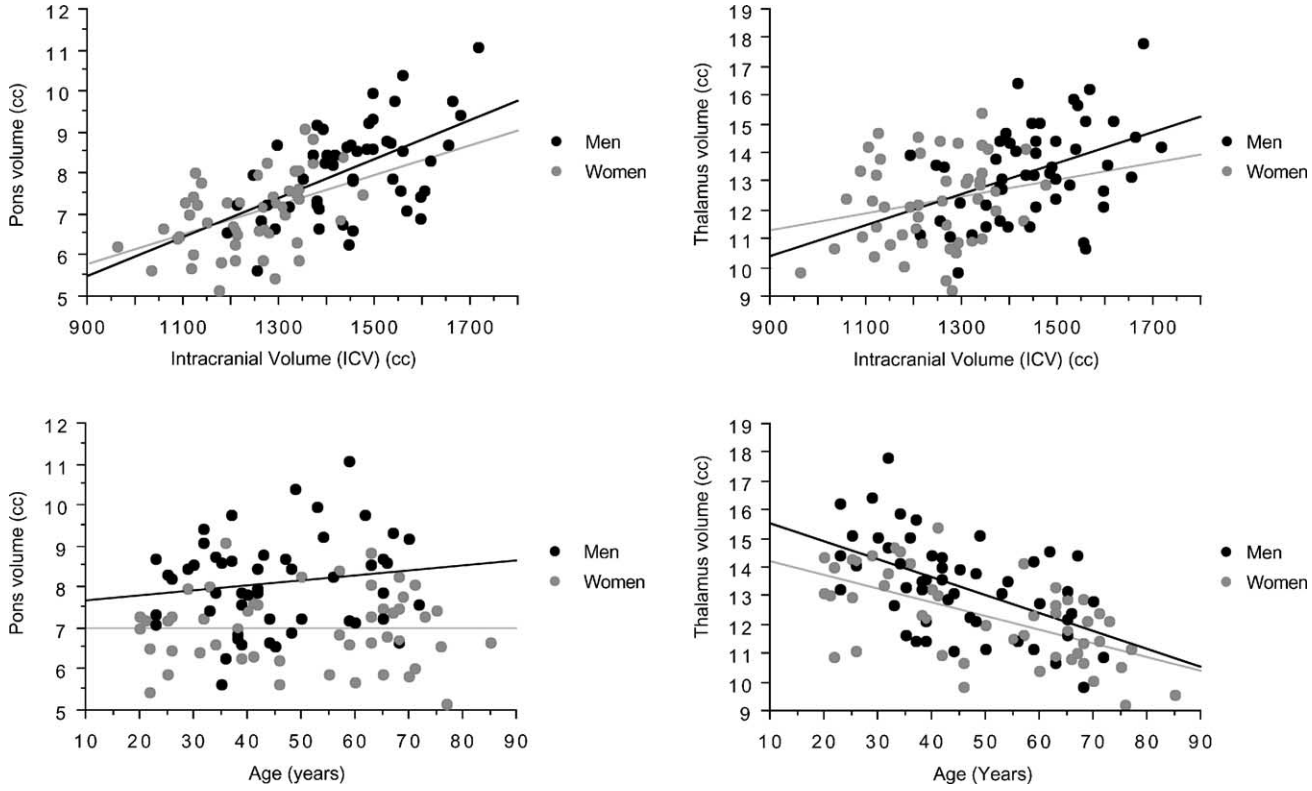

Fig. 2. Volumes for thalamus and pons plotted as a function of ICV (upper row) and age (lower row) for 51 men and 49 women. ICV is estimated by modeling the head as an oblate spheroid using the distance between inner skull margins in *x*-, *y*-, and *z*-axes on the image. Thalamic volume and ICV were significantly correlated for men ($r = 0.41$, $P = 0.0025$) but not for women ($r = 0.22$, $P = 0.12$). Pontine volume and ICV were significantly correlated for both men ($r = 0.53$, $P < 0.0001$) and women ($r = 0.45$, $P = 0.0012$). Thalamic volume and age were significantly correlated in both men ($r = 0.53$, $P < 0.0001$) and women ($r = 0.59$, $P < 0.0001$). Pontine volume was not associated with age in either men or women. The slopes of the regression lines describing the relationship between age and each structure in men and women did not differ significantly.

11.55, $P = 0.001$), hemisphere effect (with right larger than left thalamus) ($F(1, 98) = 32.16$, $P < 0.0001$), but no interaction ($F(1, 98) = 0.22$, ns). Men had larger pontine volumes than women ($t(98) = 5.39$, $P < 0.0001$). Because men as a group had significantly larger ICV than women ($t(98) = 8.85$, $P < 0.0001$), we re-examined group differences in regional volume with ANCOVAs, using ICV as a covariate. Group differences for thalamus and pons were no longer significant, once ICV was taken into account.

Fig. 2 (upper row) plots thalamic and pontine volumes for men and women relative to ICV. Correlations between thalamic volume and ICV were significant for men ($r = 0.41$, $P = 0.0025$) but not for women ($r = 0.22$, $P = 0.12$). Correlations between pontine volume and ICV were significant for both men ($r = 0.53$, $P < 0.0001$) and women ($r = 0.45$, $P = 0.0012$). In both men ($r = 0.38$, $P = 0.0059$) and women ($r = 0.41$, $P = 0.0035$), correlations between thalamic and pontine volume were significant; however, when the shared variance with ICV was accounted for using multiple regression, the association between regional volumes was no longer significant in men ($P = 0.15$) but remained significant in women ($P = 0.013$).

3.1.2. Effects of age and sex

Thalamic volumes were significantly correlated with age in men (left: $r = 0.42$, $P = 0.0023$; right: $r = 0.55$, $P \leq 0.0001$) and women (left: $r = 0.50$, $P < 0.0001$; right: $r = 0.60$, $P \leq 0.0001$), yet pontine volume was not associated with age in either men ($r = 0.15$, ns) or women ($r = 0.009$, ns) (Fig. 2, lower row). Linear regression provided the best fit of the data in all instances. No differences between men and women emerged from the slopes of the regression lines describing the relationship of age with either structure (pons, $F(1, 96) = 0.84$, ns; thalamus, $F(1, 96) = 0.81$, ns).

3.2. Volumes of cortical gray and white matter

3.2.1. Effects of sex

Men had significantly more cortical gray ($t(141) = 6.79$, $P < 0.0001$) and white ($t(141) = 4.19$, $P < 0.0001$) matter than women. Because men as a group had a larger ICV than women ($t(141) = 8.32$, $P < 0.0001$), we re-examined group differences in regional volume with ANCOVAs, using ICV as a covariate. These analyses showed that group differences for white matter were no longer significant, once ICV was

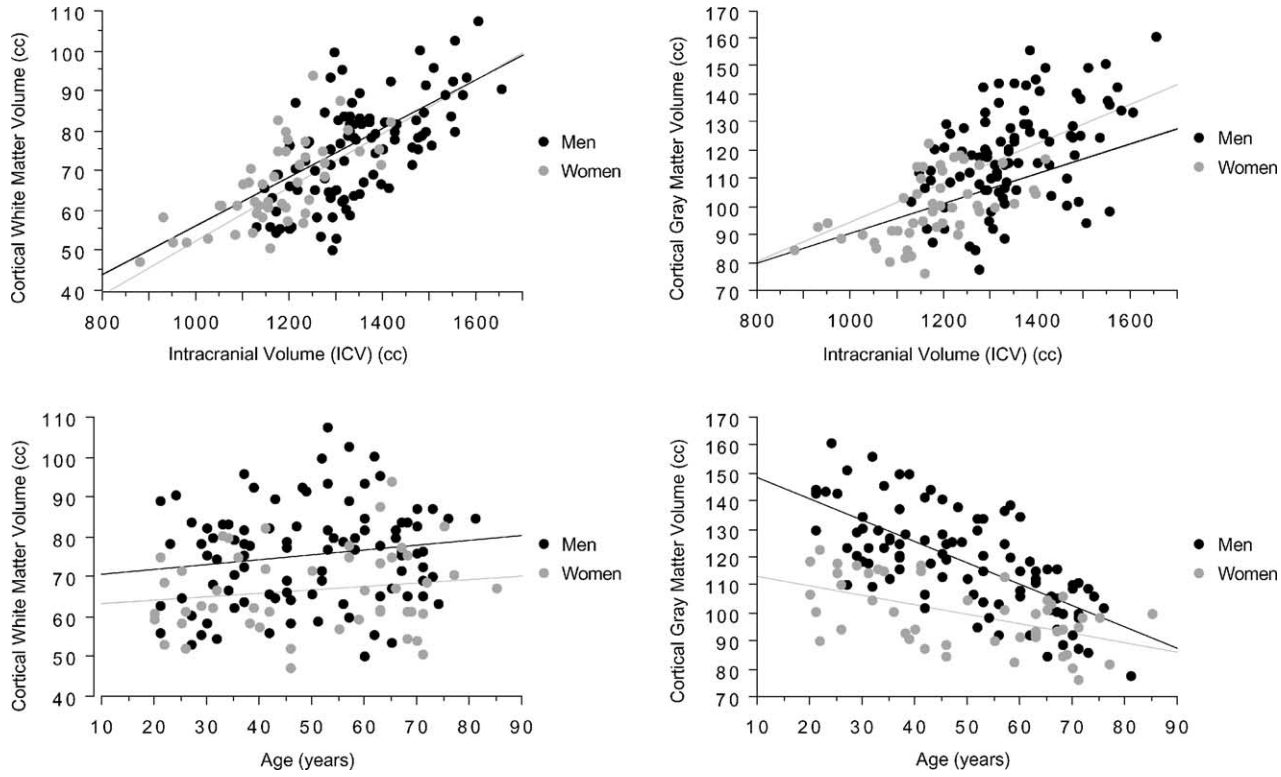

Fig. 3. Volumes of cortical gray and white matter plotted as a function of ICV (upper row) and age (lower row) in 48 women and 95 men. Cortical gray and white matter volumes represent only the outer 45% of seven axial slices. ICV is estimated by modeling the head as a sphere using the area of an index axial slice and head height, derived from a separate coronal image, as the diameter of the sphere. Cortical gray matter volume and ICV were significantly correlated for men ($r = 0.47$, $P < 0.0001$) and women ($r = 0.52$, $P = 0.0002$) as were cortical white matter volume and ICV (men, $r = 0.63$, $P < 0.0001$; women, $r = 0.68$, $P < 0.0001$). Cortical gray matter volumes were also significantly correlated with age in men ($r = 0.69$, $P < 0.0001$) and women ($r = 0.54$, $P < 0.0001$), and the slope describing the relationship was significantly steeper ($F(1, 139) = 11.83$, $P < 0.001$) for men than for women. Cortical white matter volume was not associated with age in either men or women.

taken into account, but that the difference for gray matter persisted ($F(1, 140) = 6.90$, $P < 0.01$).

Fig. 3 (upper row) plots cortical gray and white matter volumes for men and women relative to ICV. Correlations between gray matter volume and ICV were significant for men ($r = 0.47$, $P < 0.0001$) and women ($r = 0.52$, $P = 0.0002$). Correlations between cortical white matter volume and ICV were significant for both men ($r = 0.63$, $P < 0.0001$) and women ($r = 0.68$, $P < 0.0001$).

3.2.2. Effects of age and sex

Cortical gray matter volumes were significantly correlated with age in men ($r = 0.69$, $P < 0.0001$) and women ($r = 0.54$, $P < 0.0001$) yet cortical white matter volume was not associated with age in either men ($r = 0.16$, ns) or women ($r = 0.16$, ns) (Fig. 3 lower row). Higher-order polynomials did not improve the fit of the age regression of either structure. The slope of the regression lines describing the relationship between cortical gray matter and age was steeper in men than women ($F(1, 139) = 11.83$, $P < 0.001$). There was no difference between men and women in the relationship between cortical white matter and age ($F(1, 139) = 0.11$, ns).

4. Discussion

This study compared two subcortical structures that form part of the ponto-thalamic cerebellar circuit and showed that, at least in cross-sectional analysis, the gross volume of the thalamus declines over the adult age range, while the volume of the pons remains stable. Further, we found no evidence for sex differences, either in absolute volumes or in rate of change with age, once ICV differences were taken into account. A parallel analysis was performed on measures of cortical gray and white matter obtained from a larger sample of men that included 33 of those in the subcortical structures analysis, and all but two of the women. Although ICV was measured differently in axial and 3D datasets, both approaches yielded comparable differences between men and women that are consistent with published norms. In particular, on axial images, women's mean ICV was 87% that of men; on 3D images, women's mean ICV was 85% that of men. Cortical gray matter, like the thalamus, was strongly affected by age, while cortical white matter, like the pons, was not. Cortical gray matter differed from the thalamus, however, in showing a steeper decline with age in men than women and greater volumes in men than women, even after their larger ICV was taken into account.

Our finding of lack of age effects on the pons is consistent with other studies of this white matter structure [25,45] as well as with studies of other white matter structures such as the corpus callosum [37,54]. The thalamus, by contrast, does lose volume throughout the adult age range, similar to gray matter in the cortex (this study, [10,16,39]) and cerebellum [52]. Our finding of no sex differences in the age-related decline of the thalamus is consistent with a recent study using volumetric measurement [59]. The volume of combined left and right thalamus is roughly twice that of the pons and both structures are related in size to ICV. One structure declines in volume over the adult age span while the other remains constant. In women, both structures are related to each other in size even when the shared variance of ICV is taken into account. In men, this is not the case. It is not known however, whether this sex difference in association between pons and thalamus size has any functional significance.

The cortical white matter measure reported in this study showed a lack of relationship with age. This finding is consistent with some studies (e.g. [11,18,35]), but not others (e.g. [3,5,10,13,17,46]). Indeed, postmortem studies also generally report age-related changes in white as well as gray matter volume [19,28,30,56]. Furthermore, while white matter volume loss with age may not be apparent using in vivo MRI in healthy elderly up to their eighth decade, diffusion tensor imaging studies are demonstrating alterations in the microstructure of white matter fibers [32,42,43,51] that may reflect demyelination and deterioration of microtubules and microfibers.

A number of methodological variables may account for different findings on white matter. These include the technique used to segment white matter from gray matter (some may be more vulnerable than others to decreasing signal intensity and gray/white signal contrast with advancing age [20]), the regions of white matter examined (local or global), how they are defined, and the statistical approach (group comparison versus regression analysis) used. For example, some studies that found white matter volume reduction with age examined only frontal or temporal white matter [3,46]. Finally, the age range and health status of individuals studied is critical: although white matter volume decline may not be universally apparent prior to the eighth decade, it is more likely to appear after age of 80 years. Our report included only two individuals over the age of 80 years. However, the measure used in the current report, a geometric estimate of white matter that encompassed only seven 5-mm slices with a 2.5-mm skip and sampled only part of the cortical white matter rim, is not likely to explain the lack of white matter volume decline over the age range studied. We have observed a similar lack of white matter volume decline with age when using an anatomically defined measure of cortical white matter that yielded volumes approximately twice those reported here [40].

MRI studies differ in extent of change observed and the stage of life at which age-related cortical white matter volume decline begins. There is a stronger consensus, however, on loss of gray matter volume with normal aging [3,5,10,11,17,18,35], but see others [13,46] and some pathological [19,34] reports. The greater change with age in men than women has been reported before, both for absolute gray matter volume [10,11] as well as for cortical tissue [4,6,12] and sulcal CSF [27]. When expressed as a percentage of ICV, however, sex differences in cross-sectionally estimated

rate of cortical gray matter decline were eliminated in one study [10]. Loss of gray matter volume, as measured with MRI, most probably indicates shrinkage rather than elimination of neuronal cells. This would be consistent with postmortem cell-count studies [58], as well as in vivo spectroscopic studies that find stable gray matter concentrations of *N*-acetyl-aspartamate, a marker of neuronal integrity [1,36], over the adult age range in healthy subjects.

Thus, changes in the thalamus and pons over the adult age span parallel global changes in cortical gray and white matter volume. Whether associations exist between age-related changes in volume of thalamus and in specific cortical gray matter regions to which it is functionally linked has not been addressed in this report. Nor has the possibility that age-related changes in the microstructure of the pons and specific cortical or cerebellar white matter regions to which it is functionally linked may be associated. These are new directions for future studies.

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