the females (M = 0.336, SD = 0.015) and males (M = 0.341, SD = 0.019). There was a significant interaction of age and gender on the nWM: $F[1, 273] = 9.52$, $p<0.05$.

In our direct comparison of the YM and OM subjects, the groups' average nWM values were 0.349 ± 0.013 and 0.332 ± 0.017 (MD = 0.017, $p<0.01$), respectively. However, there was no significant difference in the average nWM values of the YF and OF groups. Figure 2b shows the normalized WM box plots of the four age × gender groups.

Regarding the TIV, the main effect of age showed an F-ratio of $F[1, 273] = 5.54$, $p<0.05$, i.e., a significant difference between the young subjects (M = 1548.60, SD = 142.19) and the older subjects (M = 1512.40, SD = 149.93). The main effect of gender had an F-ratio of $F[1, 273] = 127.30$, $p<0.001$, revealing a significant difference in TIV between the female (M = 1449.80, SD = 119.08) and male subjects (M = 1613.90, SD = 124.77). The interaction effect was not significant: $F[1, 273] = 0.78$, $p = 0.37$.

In our direct comparisons between the YF versus OF subjects and the YM versus OM subjects, there were no significant differences in the average of TIV values. This absence of significant differences in TIV showed that the two female groups (YF and OF) were comparable with respect to head size, as were the two male groups (YM and OM). Figure 2c shows the TIV box plot for each group.

Table 2. The range of global volume measurements for the young and older female and male subjects

	Older females (n=69)	**Young females** (n=66)	**Older males** (n=71)	**Young males** (n=71)
GM (ml)	562.59 ± 50.08	689.66 ± 59.77	614.28 ± 60.11	739.58 ± 56.97
WM (ml)	476.56 ± 44.65	499.70 ± 52.09	533.98 ± 57.17	568.6425 ± 53.71
TIV (ml)	1425.90 ± 108.93	1473.12 ± 124.58	1602.91 ± 132.94	1624.20 ± 116.68
nGM	0.399 ± 0.02	0.468 ± 0.02	0.383 ± 0.01	0.455 ± 0.01
nWM	0.334 ± 0.01	0.339 ± 0.01	0.332 ± 0.01	0.349 ± 0.01

All data are mean ± SD. GM: gray matter; WM: white matter; TIV: total intracranial volume; nGM: normalized gray matter; nWM: normalized white matter.

The correlation between the global brain tissue volume changes and age

To determine the effect of age on brain tissue volume changes, we estimated the correlation between age and global brain tissue volumes among the subject groups. Figure 3a–f illustrates the results of the correlation analysis of nGM, nWM, and TIV values in accord with age and gender.

Regarding the nGM (Fig. 3A, B), there was a strong negative correlation between age and nGMV in the young subjects (females: r (n=71) = −0.42, $p<0.001$; males: r (n=71) = −0.33, $p<0.001$) and in the older subjects (females: r (n=69) = −0.60, $p<0.001$; males: r (n=66) = −0.58, $p<0.001$). In the comparison of the nGM changes, the statistical analysis revealed a significant linear reduction with age in the older subjects as well as in the young subjects. In comparison to the males, this decrease was steeper in the females in both the older and young groups.

Regarding the nWM (Fig. 3C, D), we observed a weak interaction between nWM and age in the young subjects (females: r (71) = 0.03, p = ns; males: r (71) = 0.15, p = ns). Notably, the Pearson correlation test revealed a significant negative interaction between nWM and age in the older subjects (females: r (69) = −0.25, $p<0.05$; males: r (66) = −0.62, $p<0.001$), and this decrease was significantly steeper in the males compared to the females. There was no significant relationship between TIV and age in the various groups (p = ns) (Fig. 3E,F).