Commentary

Changes in volume with age—consistency and interpretation of observed effects

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These two MR morphometric studies by Walhovd et al. and Allen et al. add important information to the existing literature about life-span changes in brain morphology. They are both relatively large studies with 73 and 87 individuals, respectively, and in both cases, the imaging and segmentation methods are carefully standardized and highly reliable. The methods themselves are quite different, of course, representing relative extremes in the continuum of automation; and the authors have chosen to model their data using different statistical techniques. However, both studies have two major strengths in common—they included subjects over the wide age range from the early 20s to 88 years, and the investigators tested for evidence of nonlinearity in the age-functions they observed. Because these authors show the age-distribution of individual datapoints for many of the volumes they measured, it is possible to compare directly the age-functions they observe. It should be noted that the data are presented somewhat differently in the two reports. Notably, the data reported in Allen et al. are shown graphically as plots of raw volumes with male and female subjects superimposed to show the gender differences. In this case the volumes exhibit the interindividual variability related to cranial volume (head size) and thus show larger scatter. In contrast, the datapoints shown graphically in Walhovd et al., are residual scores from which variability associated with an estimate of cranial volume has been removed. Thus, these volumes show less scatter and exhibit no gender differences. Nevertheless, comparisons of the overall shapes of the age-functions are informative.

Importantly, the inclusion of young adult subjects in these two studies served to clarify the impact of ongoing progressive volume changes that can be thought of as continuous with brain maturational effects. This is particularly clear for

the white matter volumes, known to continue to increase throughout childhood and into young adulthood. In these new studies the curvilinear form of these age-differences is clearly apparent, and the current results confirm that whether or not investigators have reported age-related volume reductions in white matter depends strongly on whether the ages of the subjects included were predominantly under 50 years, when the protracted adult myelination effects continue, or were over 60, after which these give way to the fairly precipitous losses observed in the present studies in the 70s and 80s. Combined data published previously in separate reports on brain maturation [5] and aging [2] are presented graphically in the figure below for comparison. They also exhibit a strongly curvilinear age-function. The quadratic function (shown as a dashed line) improves the fit markedly relative to the linear fit (solid line), though the addition of a cubic term adds little (dash-dot line). The volumes in the figure are presented as standardized residuals (removing variability associated with volume of the supratentorial cranial vault) to facilitate comparison to those shown in Walhovd et al. Taking into account differences in data presentation, the results across the three studies, using different morphometry methods, are very similar (Fig. 1).

The hippocampus data presented in the two new studies reported here, also showing a curvilinear age-function, are especially important, as the nonlinearity was less apparent in earlier studies. The evidence that hippocampal volumes increase significantly, perhaps until 40 years of age, has important implications for the interpretation of previous studies, and indeed for any evaluation of age-related volume loss in hippocampus. Previously, investigators have, either explicitly or implicitly, made the assumption that volume loss in this structure is best measured by comparison of volumes in elderly subjects with those of young adults. However, the present findings suggest that such comparisons may conflate mid-life increases with late-life decreases. The implication

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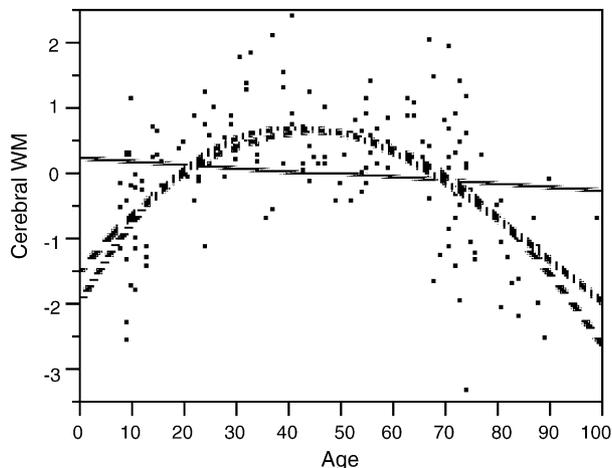*E-mail address:* tjernigan@ucsd.edu (T.L. Jernigan).

Fig. 1. Cerebral white matter volume (standardized residuals) as a function of age. Solid line is linear, dashed line is quadratic, and dash-dot line is cubic fit.

is that a similarity between volumes in 70 year old and 20 year old individuals does not imply "preservation" of hippocampal volume (Fig. 2); rather such values are consistent with fairly dramatic age-related losses after age 50 as suggested in both Walhovd et al.'s Fig. 2 and Allen et al's Fig. 7. Again, the combined data from our studies is shown here for comparison, confirming the consistency of this later drop in hippocampal volumes across the three studies. These findings do not imply that age-normative volume assessments cannot be used profitably in the evaluation of aging individuals, simply that these must be derived from more appropriate nonmonotone models of normal age-variability. The evidence for protracted increases in hippocampal volume raises very important questions for future studies. For example, it is important to determine whether this is due to neurogenesis or to dynamic changes within existing neuronal populations in adult subjects; and whether increases are present in (perhaps more circumscribed) gray matter regions elsewhere in

the brain. Although similar increases in gray matter volumes elsewhere were not demonstrated in these studies, in which only large cortical regions were examined, the age-functions given for the temporal lobe (particularly the temporal pole) in the Allen et al. report appear to deviate from those in other cortical regions, and this could be due to later volume increases in some areas within these temporal lobe regions. In any event, it will also be important to determine how the volume increase in hippocampus relates to learning and memory functions of mid-life adults; and, of course, what processes lead to the sharp reversal in hippocampal volume changes after age 60.

Previous results regarding age-differences in subcortical gray matter structures have been inconsistent. For example, in Jernigan et al. [2] we reported modest age-related decreases in volumes of the caudate nucleus and the nucleus accumbens, but could not detect significant volume loss in a region including the amygdala and adjacent cortical structures of the uncus, nor in thalamus or lenticular nucleus. The amygdala was measured in our previous study and in both of the present studies. Because the amygdalar region measured in Jernigan et al. [2] included uncal cortex, while Allen et al. carefully separated the amygdala from adjacent cortex, it is difficult to compare the findings of these two studies. Interestingly, despite different measurement approaches, the effects of age on amygdalar volumes were similar in the two new studies reported here. Nevertheless, the likely functional distinctions between the amygdala and adjacent rhinal cortices would seem to warrant more detailed examination of the anatomy of this region in future studies.

Basal ganglia structures were not measured by Allen et al. However, Walhovd et al. provide data for the accumbens area, caudate nucleus, putamen, and pallidum. We reported modest age-related loss in the caudate and accumbens in adults from 30 to 99 years of age in Jernigan et al. [2]; however, the present findings appear to show stronger effects. One factor contributing to this difference could be the inclusion of younger subjects in the study by Walhovd et al., since previous work suggests that developmental volume reductions in the basal ganglia continue into adulthood [4]. For comparison, we provide plots of our data across the age-range from 7 to 99 years for the nucleus accumbens (Fig. 3) and caudate nucleus (Fig. 4). With the extended age-range, Spearman's rho increased from -0.33 to -0.59 for the nucleus accumbens, and from -0.35 to -0.64 for the caudate nucleus, and the quadratic term significantly improved the fit for both measures over a linear fit, i.e., the losses over the lower age range appeared to be more rapid. These comparisons emphasize that the estimates of the magnitude of age-effect vary considerably depending on the age-range included, and that nonlinear, and even nonmonotone, functions further complicate extrapolation from linear estimates. However, the degree of age-related caudate and accumbens loss apparent in our data still appears to be less than is observed by Walhovd et al. over the same age range.

Jernigan et al. [2] measured only the combined lenticular nucleus (i.e., the putamen and part of the pallidum), and
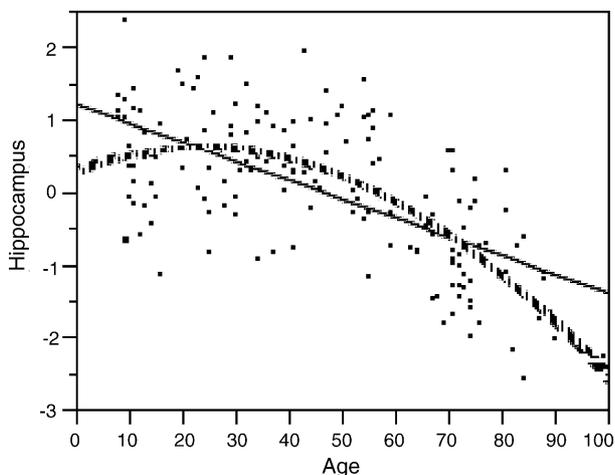

Fig. 2. Hippocampal volume (standardized residuals) as a function of age. Solid line is linear, dashed line is quadratic, and dash-dot line is cubic fit.
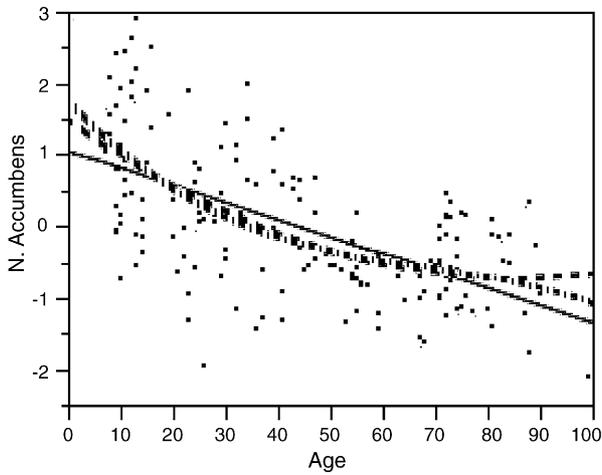
Fig. 3. Nucleus accumbens volume (standardized residuals) as a function of age. Solid line is linear, dashed line is quadratic, and dash-dot line is cubic fit.

thus direct comparisons with Walhovd et al. are not possible. The closest comparison is between the lenticular nucleus of Jernigan et al. and the putamen of Walhovd et al., since the latter structure makes up a large proportion of the lenticular measure. Although we reported no significant age-effect on the lenticular nucleus in subjects aged 30–99 years, it is clear (Fig. 5) that we do observe age-related loss in this structure over the wider age-range (Spearman's rho is −0.58). However it is also interesting that there is some evidence, both in the Walhovd et al. putamen data and in the Jernigan et al. [2] lenticular data, for an anomalous increase in the volume after age 60. We have been struck by the fact that this unexpected increase occurs at approximately the same age as does a steep increase in the volume of cerebral white matter with abnormally high MR signal [2]. As we speculated in the 2001 article, it is possible that these signal alterations, either associated with perivascular spaces around lenticulostriate vessels or in white matter within or adjacent to the putamen,

Fig. 5. Lenticular nucleus volume (standardized residuals) as a function of age. Solid line is linear, dashed line is quadratic, and dash-dot line is cubic fit.

could lead to spurious increases in apparent volume. Higher resolution anatomical studies may be helpful in resolving this issue.

A final comparison can be made between the results for thalamic volume in the Walhovd et al. and the Jernigan et al. [2] studies. The present results suggest much stronger dependence of these volumes on age than was observed by Jernigan et al. [2]. Although we observe definite age-related loss in thalamus across the wider age-range shown in Fig. 6 (Spearman's rho = −0.65), the effect we observe over the range studied in Walhovd et al. is clearly smaller (with very little or no change observed after 40). This may also be related to changes in the signal of the extensive white matter that courses through the thalamus, and if so, our methods may be more strongly affected by such changes.

Finally, in Jernigan et al. [2] we attempted to compare the effects observed in different regions. We argued there and elsewhere [3] that if one wants to infer that the effects of age (or any other variable) differ across brain structures it is
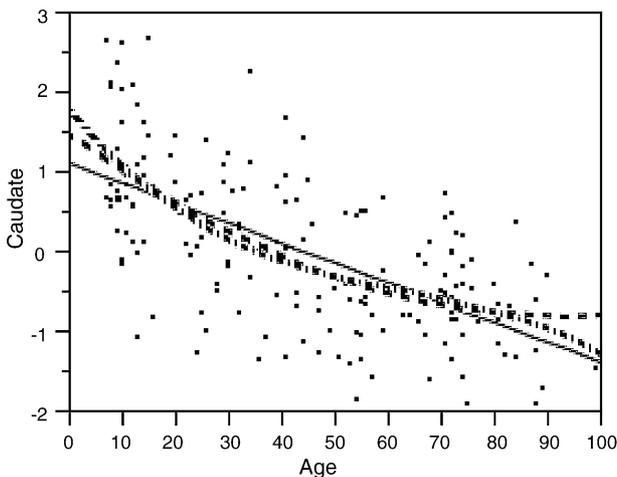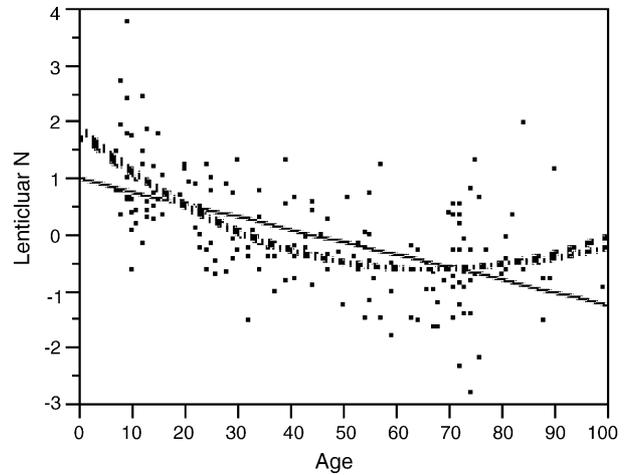

Fig. 4. Caudate nucleus volume (standardized residuals) as a function of age. Solid line is linear, dashed line is quadratic, and dash-dot line is cubic fit.
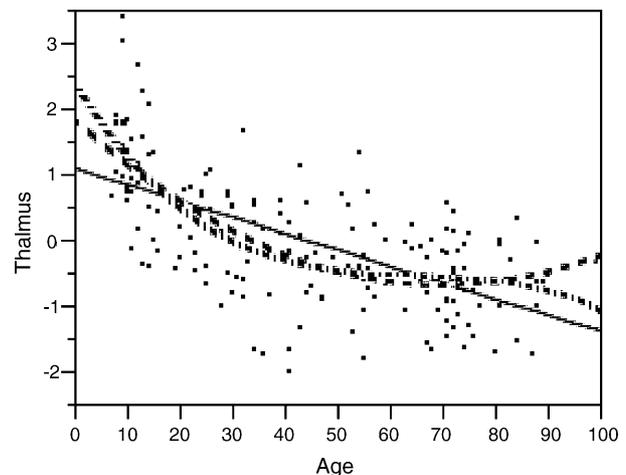

Fig. 6. Thalamic volume (standardized residuals) as a function of age. Solid line is linear, dashed line is quadratic, and dash-dot line is cubic fit.

necessary that proper statistical comparisons be performed. The test we applied was designed to detect a more rapid change over some part of the age range in one region relative to another (with no less rapid change in other parts of the age range). The method took into account the compositional nature of such volumes, i.e., although individual volumes vary, they are non-negative and sum to the total brain volume. Ratios were used in the comparisons of rate of change to reflect the fact that a uniform percent loss per year will be a larger absolute volume loss in a large structure than in a small structure. Ratios are useful for characterizing compositional data [1] and avoid some of the problems inherent in comparing structures with volumes on different scales (floor effects, etc.). We continue to feel that statistical comparisons of effects in different brain regions are important; however, the evidence presented here for quite differently shaped age-functions across regions further complicates this process. The analyses for comparing age-effects in Jernigan et al. [2] are most meaningful when one can assume monotonicity in the (age) trends being compared. This is clearly not a safe assumption, and thus more meaningful ways of comparing the effects are needed. Whatever methods are applied, they should be appropriate for use with compositional data such as these, and the interpretation should include a discussion of the importance of the specific age-range examined. Most importantly, methods assuming linearity or even monotonicity of the age-functions to be compared should be used with appropriate caution.

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