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Commentary

Neuroanatomical aging: Universal but not uniform

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1. Patterns in brain aging

At least two premises must be met for MRI techniques to be informative: (1) there must be a set of identifiable regularities that can be identified by means of such techniques and (2) these regularities must be of some significance for human functioning. During the last 15 years some inconsistencies have been reported in brain aging research, but the first premise has partly been shown to hold true. Two relatively large new morphometric studies, Allen et al., and ours, Walhovd et al. ([1,30], in this issue) show notable similarities in their main results: both studies found pronounced linear age decreases of cortex and amygdala in early adulthood and onwards, with relatively larger effect sizes for the former than the latter, while volumetric reduction of cerebral white matter followed a non-linear course and was not evident until middle age.

Of differences between Allen et al.'s and our results, it may be noted that Allen et al. identified several cubic functions, e.g. for cerebral white matter and hippocampal volume, where quadratic functions were found in our study. In addition, the effect sizes for age were generally more pronounced in our data, especially for cortical volume. This variance may partly be grounded in incidental sample differences, since normal individual differences only grow larger with age [25]. The use of different tissue classification techniques could also contribute to discrepancies across studies. We used an automated segmentation technique that is specifically designed to classify across many structures [10], and the stronger effects could partially be due to the specificity of this classification. However, as noted above, the overall pattern identified is largely similar.

Regarding the generally larger effect sizes for age in our results, it should be noted that the mode of data presentation and analysis may also have contributed to this. Allen et al. used raw volumes for their analyses, while we used residuals after the effects of intracranial volume (ICV) had been regressed out. The latter approach likely leads to larger effect sizes, because non-age variance, which in studies of age effects may be conceptualized as noise in the material, may then indirectly be controlled for. Besides gender, which Allen et al. otherwise adjusted for, non-age factors that have been found to be associated with ICV or related measures include, for instance, height [20] and cognitive ability (e.g. [18]). The cranial vault normally ceases to grow at around the age of 7 years and brain volume starts to decrease in the 20s, but intracranial volume is assumed to remain constant. As noted in our paper, cohort effects on ICV may exist, but when they do not, as in our material, regressing out ICV will likely leave one with neuroanatomical volume estimates that can more fully be explained by the age variable alone. Note that this is not equivalent to another common way of "controlling for" ICV, namely to proportionalize, i.e. divide the

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volume of interest by ICV. While such ratio measures may seem intuitively appealing, they do not, as noted by Van Petten [29], remove the variance associated with ICV, but may at worst cause noise in the data, as also noted by Sanfilipo et al. [24]. Only by regressing all volumes of interest on ICV, will one achieve a measure that is, by definition, perfectly uncorrelated with ICV. We believe that the use of such measures may help uncover systematic brain–age relationships by the control of non-age variance.

The neuroanatomical aging reports in this issue constitute two of the most comprehensive volumetric segmentation studies performed. However, Allen et al.'s study and ours are largely complementary rather than overlapping in focus: We report volume of the cerebellum, brainstem and multiple subcortical structures, as well as total volume of cortex and cerebral white matter. In contrast, Allen et al. exclude cerebellum, pons and subcortical gray matter volumes of the basal ganglia and thalamus and instead focus on gray and white matter volumes of the major cerebral lobes and different sectors of the temporal lobe. As such, these studies address partially different topics. Allen et al.'s report adds to the body of evidence suggesting an anterior–posterior gradient of volumetric reduction of gray matter in the cerebral lobes. Our data, on the other hand, indicate that while volumetric reduction may be most pronounced in the cortex and thalamus, additional subcortical structures are also dramatically affected by age.

Despite variation, every region of interest examined in Allen et al.'s study showed statistically significant volumetric age-related changes. This is to a large extent also the case in our study: despite heterogenic effects across structures, age was associated with a significant decline in 11 of 12 structures, including the subcortical areas not studied by Allen et al. These reductions were generally accompanied by an increase in ventricular compartments. Based on the currently presented studies, in conjunction with other large-scale MRI studies reporting widespread declines, it would be tempting to conclude that age effects are heterogenic, but ultimately universal throughout the brain.

Recently, however, there has been much focus on exceptions to neuroanatomical aging. For instance, a current study [27] of 128 healthy adults aged 20–85 years presented evidence of preservation of hippocampal volume throughout the life span. The authors suggested neurogenesis as a partial mechanism in volumetric maintenance, but it is unclear why similar mechanisms should not be at play also in other samples. As reviewed by Van Petten [29], estimates of age-related volume loss in this structure vary widely across studies, but nearly all report negative correlations between age and volume. However, as shown in the present study as well as others [11,12], there seems to be *relatively* less decline in hippocampus relative to cortical areas. Thus, there has been a focus on "relative sparing" of limbic structures compared to presumably later maturing cortical areas, especially frontal regions [ibid]. Such relative sparing and reduction would be in accordance with Jackson's [13] hypothesis that brain areas being the phylogenetically and ontogentically latest to mature, are the first to undergo "dissolution". However, in light of the present studies as well as others pointing to limbic and subcortical age effects (e.g. [14]), it seems important to remember that "sparing" is in most cases just relative, and not absolute: subcortical and limbic structures, including hippocampus and amygdala, do show considerable age-related reduction in the present studies, and even if these effects are smaller than those observed for gross (and hence also likely more reliably measured) volumes of cortex and cerebral white matter, it seems probable that such decline of specialized structures should have functional significance. There may be less agreement regarding whether cerebral white matter declines (see [11] for a large-scale study illustrating this). The present studies, as well as another current large-scale study [12], clearly show non-linear relationships for white matter and age. Thus, as also indicated by Jernigan and Gamst (in this issue), the use of statistical procedures assuming linear relationships only (e.g. correlations, linear regressions) may substantially weaken the observed age functions. In studies including few or no participants in the youngest (e.g. 20–30 years) and oldest age range (e.g. above 80 years), the true age relationships may even be disguised by use of such procedures. The present reports therefore serve as a strong indication to include a broad age range and not to exclusively use statistical analyses based on an assumption of linear or monotone relationships in aging studies. Bartzokis [2] also recently advanced a theoretical model incorporating protracted brain development driven by oligodendrocytes, which continue to differentiate into myelin producing cells late into the fifth decade of life. Such a model predicts a curvilinear white matter volume–age relationship. Longitudinal MRI-results on aging have recently become available, and hopefully, future long-term follow-ups will help determine if there are individual or structural exceptions to the often observed neuroanatomical age reductions.

2. Neuroanatomical aging in a neuropsychological perspective: how does it add up?

We agree with Allen et al. [1] in that data on volumetric brain aging ultimately should help us understand normal age-related changes in cognition from a biological perspective. As noted above, this is a premise, which must be fulfilled for MRI techniques to be truly informative in aging. However, in view of the age functions observed for structures such as the hippocampus, which is assumed to support memory capacity, this seems to be a highly complex task. De facto, sharply curvilinear or cubic functions such as those observed here do far from characterize the major neuropsychological or cognitive functions in aging. Rather, normative studies point to relatively steady age reductions of memory capability from young adulthood onwards [7,8,28]. Thus, as also pointed out by Grieve et al. [12], hippocampal age reductions cannot drive age-related memory decline. While hippocampal volume obviously is important in long-term memory

capability [3,16,26,31], such a specific and small structure is of course not the sole support of mnemonic abilities [29], and there is no reason why it should be in aging. Abilities generally depend on distributed networks, so it seems natural also to focus on larger structures in this regard. In a comment to Bartzokis' model on protracted myelination, Jernigan and Fennema-Notestine [15] point out that the years of life between the end of adolescence and extending through middle age that have previously been viewed as years of "stability" in brain development, are probably more accurately viewed as a period during which progressive and regressive changes happen to be in relative balance. From a neuropsychological perspective, this may have some validity, since certain cognitive scores may drop somewhat more rapidly in the latter half of the adult life span (e.g. [17]). However, age decrements are seen already from the mid-20s onwards, and scores are often reported to decline steadily (e.g. [6]). Thus, in neuropsychological normative samples, as in our sample, substantial performance decline is clearly evident prior to the point at which white matter volume decline is reported to begin (see Fig. 1). However, it is evident that the age relationship of performance abilities observed here resembles the average age function of the two major neuroanatomical volumes (the sum of cortical volume and cerebral white matter volume, divided by two). Oversimplified, one could speculate that when the increase in white matter volume no longer can approximate compensation for the decrease in gray matter in midlife, performance abilities start to decline more sharply.

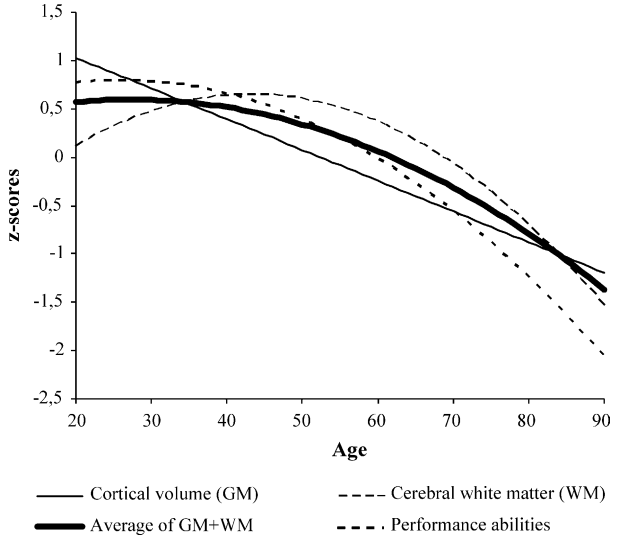

Fig. 1. Cross-sectional age functions observed for cortical volume (GM), cerebral white matter volume (WM), and the average of the *z*-scores of cortical volume and cerebral white matter volume as well as performance abilities as measured by the Wechsler Abbreviated Scale of Intelligence (WASI) [32], in our sample ($n = 73$). The volume and performance scores are not age-corrected, but have been converted to *z*-scores based on the mean and standard deviations of the sample in order to achieve the same scale across measures. It is evident that the age relationship of performance abilities resembles the average age function of the two major neuroanatomical volumes (cortical volume plus cerebral white matter volume divided by 2).

Human cognitive ability is necessarily determined by a complex interplay of brain structures and their characteristics. There has recently been much focus on the role of subcortical structures and cortical–subcortical interactions in cognition (e.g. [4,5,19,21,22]). The present data point to large and heterogeneous age effects on both cortical and subcortical volumes. Semi-automated and automated techniques for quantification of specific cortical areas and structures in neuroimaging studies have been and are being developed (e.g. [9,23]). Such techniques will enable more comprehensive and detailed whole-brain segmentations and in combination with functional and behavioral measures they will likely lead to further knowledge on the role of subcortical and cortical characteristics in cognitive aging.

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