Published in final edited form as:

Ann N Y Acad Sci. 2007 February ; 1097: 84–93. doi:10.1196/annals.1379.018.

Brain Aging and Its Modifiers:

Insights from *in Vivo* Neuromorphometry and Susceptibility Weighted Imaging

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Abstract

Aging is marked by individual differences and differential vulnerability of cognitive operations and their neural substrates. Cross-sectional studies of brain volume reveal greater age-related shrinkage of the prefrontal cortex (PFC) and the hippocampus than in the entorhinal and primary visual cortex. Longitudinal studies of regional brain shrinkage indicate that when individual differences are controlled, larger and broader shrinkage estimates are evident, with most polymodal cortices affected to the same extent. The mechanisms of age-related shrinkage are unclear. Vascular risk factors may exacerbate brain aging and account for some of the observed declines as both the PFC and the hippocampus show elevated vulnerability to hypertension. MRI techniques that are sensitive to small vessels function, tissue oxygenation, and perfusion may be especially well suited to study brain aging and its vascular modifiers. We present an example of one such technique, susceptibility weighted imaging (SWI), that allows direct measurement of T2* values that reflect deoxy- to oxyhemoglobin fraction in blood vessels and iron deposits in cerebral tissue. The T2* shortening is associated with advanced age, but the effect is significantly stronger in the PFC and the hippocampus than the entorhinal and visual cortices. Moreover, T2* is shorter in hypertensive participants than in their matched normotensive counterparts, and the difference is especially prominent in the hippocampus, thus mirroring the findings of the neuromorphometric studies. Future research on brain aging would benefit from combining structural and metabolic techniques in a longitudinal design, as such studies will allow examination of leading–trailing effects of those factors.

Keywords

aging; MRI; brain; longitudinal; vascular risk; susceptibility weighted imaging; deoxyhemoglobin; iron

INTRODUCTION

Aging is marked by substantial variability across individual organisms, among organs and systems, and within organs' cellular elements. Postmortem (PM) studies reveal a plethora of age-related differences in human brain specimens: reduced brain size, expansion of cerebral ventricles and sulci, loss of myelin, region-specific loss of neuronal bodies, rarefaction of cerebral vasculature, and reduced synaptic density.^{1–3} However, PM methods preclude examination of longitudinal trajectories of aging and make study of cognitive correlates of brain differences rather difficult.

The advent of magnetic resonance imaging (MRI) created conditions for *in vivo* examination of brain structure and function in healthy behaving humans. Moreover, MRI methods enable longitudinal follow-up and afford an opportunity to gauge true trajectories of change in brain structure and function. Multiple questions of normal and pathological development in late adulthood can be addressed with the help of MRI, among them determining of brain changes in normal and successful aging, transition from normal aging to its pathological expressions, as well as studying the processes that modify the normal trajectory of aging and affect its cognitive expressions. Most current MRI methods still derive their indices from assessing states and vicissitudes of only one element, brain hydrogen. Nonetheless, they allow interrogation of a wide variety of brain structural and functional properties, including changes in volume, microstructure, hemodynamics, and metabolism. In this brief survey, we focus on two types of MRI-based assessment of the brain: regional volumetry (neuromorphometry) and evaluation of regional differences in resting state magnetic susceptibility.

In MRI-based neuromorphometry, there are multiple ways of measuring regional brain volumes. Significant effort and ingenuity are being devoted to the development of computerized and largely automated methods of image analysis that allow relatively fast processing of vast amounts of MRI data.⁴⁻⁷ However, the neuroanatomic validity of those approaches has not been clearly established, especially when measures are conducted on less than ideal MRI scans from samples with a great range of individual differences. Thus, for the time being, algorithmic methods of neuromorphometry occupy a position of an initial search tool that generates a list of candidate regions, in a way similar to microarray technology in genomics that allows narrowing the list to candidate genes with expectation of a more customized and specific follow-up investigation.

Manual methods, the gold standard of neuromorphometry, have face validity and have a close conceptual link to classic methods of neuroanatomy, in which a visualized cerebral region demarcated by clearly defined landmarks is measured. With the right amount of training and knowledge of neuroanatomy, operators using those methods can attain high a degree of inter-rater reliability.⁸ The hyperintense spots observed in the white matter on T2-weighted MRI scans appear in asymptomatic older adults at the fifth decade of life and reflect multiple neuropathological and benign causes, including altered myelin production cycle, expansion of perivascular spaces, and microinfarcts.⁹ Besides calendar age, WMH is predicted by an assortment of vascular disease factors.¹⁰ The volume of WMH can also be measured manually, separated by lobes and types of WMH.²²

Neuromorphometric studies vary in methods of measurement, rules of region demarcation, and criteria for sample selection. However, general trends in findings across the extant literature are discernable, especially when quantitative information from multiple studies is pooled together. Such a general trend in cross-sectional studies of regional brain volumes vis-à-vis age suggests that although calendar age is associated with generalized reduction of brain volume, the polymodal (especially prefrontal) cortical regions are more significantly affected than the rest of the neocortex, with primary (but not secondary) visual cortices maintaining their integrity.¹¹ The hippocampus evidences a remarkably wide range of estimated age-related differences, from zero to large effects, with some studies showing nonlinear age-accelerated trends.^{8,12,13} Although reasons for such inconsistency are unknown, it is plausible that they reflect the variability in sample admixture of preclinical pathology, vascular and Alzheimer's type.

Cross-sectional design has many advantages but its main weakness is inability to measure true change. Longitudinal studies that would allow measurement of true change and evaluation of individual variability of brain-aging trajectories are still rare. To date, most of the longitudinal investigations with a few notable exceptions¹⁴⁻¹⁶ (see Ref. 11 for a review) evaluated global

brain parameters, such as ventricular volume (relatively large, age accelerated expansion noted) and total brain volume (very modest decline observed), as well as change in WMH burden (modest expansion). As far as regional volumes are concerned, longitudinal follow-ups were by and large limited to the medial temporal structures and to the samples restricted to older adults. Such studies have typically reported hippocampal and sometimes, entorhinal shrinkage at a rate of 1–2% per annum (e.g., Ref. 17). Although longitudinal investigations confirmed many of the estimates based on cross-sectional studies, some notable discrepancies were found.

The advantages of the longitudinal approach can be illustrated by a recent study of 72 generally healthy adults (with exception of several individuals with controlled hypertension), who were assessed twice within a 5-year interval.¹⁵ In that study, we found longitudinal change in the prefrontal cortex (PFC) and the hippocampus commensurate with the cross-sectional estimates. In contrast, inferior parietal lobule volumes that consistently appeared age-insensitive on cross-sectional measures^{8,18} and revealed no age-related differences at baseline and follow-up alike, evidenced the same rate of longitudinal shrinkage as did the PFC.¹⁵ The findings in that study are summarized in Figure 1. The observed discrepancy reinforces the need for longitudinal assessment and verification of age-related change estimates based on cross-sectional studies.

Despite inter-study discrepancies with respect to the estimated shrinkage rates, it is clear that even in healthy adults, the brain loses volume. Nonetheless, the biological meaning of such loss observed on MRI is unclear as are the mechanisms underlying the phenomenon. In all likelihood, multiple factors play significant and complementary roles in creating a pattern of preservation and decline of the aging brain. An important group of factors that probably shape and modify the trajectories of normal aging consists of various correlates of vascular disease and vascular risk. The brain's dependence on steady delivery of blood-borne nutrients and neuroactive substances makes it exceptionally vulnerable to age-related declines in vascular functions and to alterations of its own vascular properties. As blood-borne oxygen is critically important for brain work, measures of tissue oxygenation may hold promise as predictors of brain atrophy. Transition of blood from an unstable oxygenated to a default deoxygenated state (i.e., from relatively high concentration of unstable oxyhemoglobin to increased concentration of deoxyhemoglobin) can be monitored with *in vivo* MRI by measuring T2* relaxation times.^{19,20} Although T2* is sensitive to many factors that introduce local inhomogeneity of the magnetic field, in the cerebral cortex it provides an indirect index of metabolism via rate of clearance of oxygenated blood.

Recent findings in older humans and a rodent model by Small and his colleagues suggest that basal rate of tissue oxygenation at rest may be associated with regional deterioration of the specific hippocampal regions of the medial temporal system of older adults and related to declarative memory performance.^{20,21} However, Small and his colleagues examined only hippocampal and entorhinal regions and did not compute true T2* values. Thus, it is unclear whether the observed effects are unique to the hippocampal–entorhinal system and whether they reflect true differences in relaxation rates. If such differences are observed in other regions, it is important to establish whether their regional pattern mirrors the pattern of age-related shrinkage.

To determine whether differential effects of age on basal brain oxygenation indices are restricted to the medial–temporal structures, we studied age differences in neocortical (superior frontal gyrus and primary visual cortex) and medial–temporal (hippocampus and entorhinal cortex) T2* values. The latter were computed from a multi-echo susceptibility weighted imaging sequence (SWI; axial plane, eight echoes, TE = 10 – 80 ms, voxel = $1 \times 1 \times 2 \text{ mm}^3$, slice thickness = 2 mm) for each voxel. Regions of interest were identified on the true T1-weighted image (first echo, TE = 10 ms) and marked with a standard-size probe. The mean

T2* within the probe was measured with test–retest reliability of regional measures for one (fixed) rater was ICC(3) ≥ 0.90 across the ROIs.

Inasmuch as shorter T2* reflects higher deoxyhemoglobin to oxyhemoglobin ratio, advanced age was associated with higher basal deoxyhemoglobin concentration (main effect of age: $F(1, 68) = 46.23, P < 0.001$). Some regions evidenced greater T2* values than others (main effect of ROI: $F(3, 204) = 11.39, P < 0.001$). Most notably, age-related differences in basal oxygenation rate varied across the examined ROIs: Age $\times$ ROI: $F(3, 204) = 10.22, P < 0.001$. Specifically, significantly lower T2* was observed in PFC and hippocampus of the older adults, whereas little or no age differences were evident in the entorhinal and primary visual cortices (see Fig. 2). Comparison of correlations with Steiger's Z^* , which takes into account dependence between the correlated variables, revealed that HC and SFG correlations with age were significantly larger than EC–age correlation: $Z^* = 2.37$ and $1.88, P < 0.01$ and $P < 0.05$ one-tailed, respectively. They were also significantly larger than the correlation between age and VC T2*: $Z^* = 3.51$ and 3.04 , both $P < 0.001$, one-tailed. There were no differences in strength of association with age for SFG versus HC and EC versus VC. Thus, the pattern of age-related difference in resting T2* values seems to mirror the pattern of age-related shrinkage. In a longitudinal study currently under way in our laboratory, we will assess the possibility that local changes in tissue oxygenation may precede structural decline in the selected brain locales.

Multiple factors affect brain aging and among the most important are those that alter its vascular function.^{9,22} Arterial hypertension accelerates age-related shrinkage of the PFC and the hippocampus and modifies the nonlinear trajectory of hippocampal aging.^{15,17} Hypertension-related HC shrinkage is exacerbated by presence of lacunar infarcts, whereas no such influence on EC atrophy rates was found.¹⁷ Persons with hypertension and other vascular disease factors show longitudinal declines in the regions that are usually stable in normal aging, such as the primary visual cortex.²³ In the resting T2* study (Fig. 3), we found reduced T2* values in 13 hypertensive participants compared to 13 normotensive controls matched on age, sex, and education. The difference, presumably reflecting reduced oxygenation, was observed across all examined ROIs: main effect of HBP: $F(1, 24) = 8.36, P < 0.008$; no HBP $\times$ ROI interaction ($F[3, 72] < 1$, ns).

At this stage the interpretation of T2* findings is unclear. The major determinant of T2* signal in the brain tissue is local deposition of various iron-related compounds, that is, heme and nonheme iron.²⁴ As heme iron is blood born, its abundance is related to perfusion of the cortical tissue, mainly through a dense network of small vessels. On the other hand, the presence of nonheme iron in the brain is unrelated to blood flow, blood volume, or oxygen metabolism. In the absence of direct measures of brain oxygen metabolism, we can offer only circumstantial evidence in favor of the oxygenation interpretation of our T2* finding. Nonheme iron is especially plentiful in the basal ganglia and myelinated axons, not in the neocortical regions examined here, although, in degenerative disease, the hippocampus may also be prone to iron accumulation.^{25,26} Nonheme iron may also accumulate in some (though not all) amyloid plaques and contribute to a reduction of T2* signal.²⁷ In the cerebral cortex, however, with notable exception of the primary motor regions, nonheme iron content is relatively low and relaxation rates do not show high correlation with iron concentrations assessed from postmortem studies.^{28,29} Thus, it is likely that the observed T2* variations in the cortical regions reflect concentration of deoxyhemoglobin in the local vasculature more than that of nonheme iron. Disentangling those sources of age-related T2* shortening is a challenge we are currently addressing in a longitudinal study of healthy aging and its modifiers.

CONCLUSIONS

The extant literature provides clear evidence that even “normal” (“successful”) aging is associated with significant brain shrinkage. Such shrinkage is differential and affects polymodal association cortices, striatum, and cerebellum more than primary sensory cortices. Hippocampus and the white matter evidence nonlinear shrinkage that accelerates with age. The mechanisms of differential brain shrinkage are unclear, but vascular risk factors, even at moderate levels, may significantly accelerate its pace. Imaging modalities that interrogate local inhomogeneities of the magnetic field created by vascular phenomena, such as susceptibility weighted imaging,²⁴ are sensitive to metabolic and microvascular properties of brain tissue and may be well suited for evaluation of the effects of aging on the brain.

ACKNOWLEDGMENT

This work was supported in part by a grant R37-AG-11230 from the National Institute on Aging. We thank Y-C.N. Chang for stimulating discussion of the topics covered in this article.

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FIGURE 1.

Summary of 5-year changes in cortical regions (based on Raz *et al.*, 2005).¹⁵ The effects size (Cohen's *d*) is the difference between the baseline and 5-year follow-up measures in standard deviation units. PFC = lateral prefrontal cortex; HC = hippocampus; IPL = inferior parietal lobule; OFC = orbitofrontal cortex; IT = inferior temporal cortex; FG = fusiform gyrus; EC = entorhinal cortex; VC = primary visual cortex. The *bars* indicate 95% confidence limits of *d*. Lack of overlap between the confidence limits indicated by the bars is tantamount to statistically significant difference at $P < 0.05$, two-tailed.

FIGURE 2.

Regional T2* values as a function of age in four cortical regions. Note significant age-dependent shortening of T2* (corresponding to prolongation of relaxation rate) in prefrontal cortex (SFG) and hippocampus (HC). In contrast, susceptibility dependent relaxation rate in the primary visual cortex is unrelated to age. Correlations with age were significantly stronger for HC and SFG than for EC and VC.

Regional T2* and Treated Hypertension

FIGURE 3.

Comparison of regional T2* values between normotensive and hypertensive demographically adults. Vertical *bars* correspond to standard errors of the mean. Solid *circles* are normotensive and empty circles are hypertensive participants.