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Aging

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Abstract The normal adult brain undergoes considerable morphological changes with aging. Studying these changes is paramount to differentiate normal age-related brain variations from the effects of neurodegenerative diseases affecting brain structure in the elderly. Considerable progress has been made in this research area during the past few decades, given the availability of noninvasive imaging tools such as magnetic resonance (MR). In recent years image acquisition devices, computer technology and software development have also advanced, allowing sophisticated methods for analyzing brain images, at both the macro- and microstructural level. In this article we will review studies assessing the effect of aging on global and regional gray and white matter volume using advanced MR techniques.

Keywords Magnetic resonance · Aging · Gray matter · White matter · Advanced imaging

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Introduction

Understanding volumetric changes occurring in the aging brain is important for differentiating normal age-related brain changes from the effects of diseases affecting brain structure in the elderly, such as Alzheimer's disease. Moreover, knowledge of normal rates of atrophy occurring in aging is needed for clinical trials in Alzheimer's disease, when rate of atrophy is employed as a surrogate marker of disease progression. In fact, an experimental drug designed to slow disease progression would be able to reduce the rate of atrophy up to that seen in normal aging.

Magnetic resonance (MR) is the ideal imaging technique to study brain morphological changes in aging because it is non-invasive and can obtain high-resolution brain images. Moreover, advances in image acquisition and software development have produced sophisticated methods for analyzing brain image data.

This review will focus on the results of studies using quantitative methods of MR analysis to assess brain changes in aging. First, volumetric studies assessing global and regional volume changes will be briefly presented and thereafter studies based on advanced computerized algorithms of MR analysis (voxel-based morphometry-VBM, cortical pattern matching-CPM, and radial atrophy mapping-RAM) and non-conventional MR techniques (magnetization transfer-MT and diffusion tensor, DT) will be more extensively discussed.

Whole-brain and lobar volumetric studies in aging

Consistent in volumetric studies are findings of decline in total brain volume [1] and segmented tissue volumes of white and gray matter [2] with age. In a longitudinal study of 79 older adults, the mean rate of whole-brain volume loss was estimated as -0.45%/year in nondemented persons, while the rate of atrophy was more than twice (-0.98%) in persons who showed early Alzheimer's disease at follow-up [3]. The pattern of age-related white matter volume decline might differ from that of gray matter. Indeed, gray matter volume seems to have a linear decline, while that of white matter volume is non-linear, with a trend to increase until adult midlife, probably reflecting ongoing maturational processes, followed by a phase of decline [2]. Regionally, gray matter decline appears more prominent in the frontal cortex than in other cortical areas [4]. As regards the hippocampus, longitudinal volumetric studies showed an age-related volume reduction, with rate of atrophy acceleration in the older ages [1, 5]

Advanced structural brain-mapping studies in aging

Mapping techniques, such as VBM, CPM, and RAM are superior to the more traditional volumetric studies because they provide a fine-scale topography of brain morphological alterations and can visualize changes occurring not only within the brain but also at the cortical surface. Moreover, they eliminate the effects of operator bias. According to the findings of volumetric studies, gray and white matter measured with VBM show a linear and non-linear (quadratic) age-related decline, respectively [6]. Large cross-sectional VBM studies have estimated the mean annual loss of gray matter at 0.11%–0.18% [7, 8]. In particular, in a longitudinal VBM study of 122 elderly, gray matter volume reductions occurred in posterior parietal areas, posterior superior and middle temporal gyri, and inferolateral frontal regions, but not in the medial temporal lobe or posterior cingulated gyrus, areas typically affected by Alzheimer's disease [8].

CPM methods can be used to assess the effects of aging or diseases on the cortical surface, accounting for the interindividual differences in the gyral patterns of the cortex and improving the statistical power to localize age-related changes relative to the VBM method. A variety of maps can be made with CPM, describing different aspects of cortical anatomy (cortical thickness, gray matter density, gyral pattern variability, hemispheric asymmetry). A few studies have been conducted with this technique in aging. In a study of 176 normal individuals aged 7 to 87 years [9], gray matter density declined mainly over dorsal frontal and parietal association cortices, with results that are generally consistent with VBM studies in which pari-

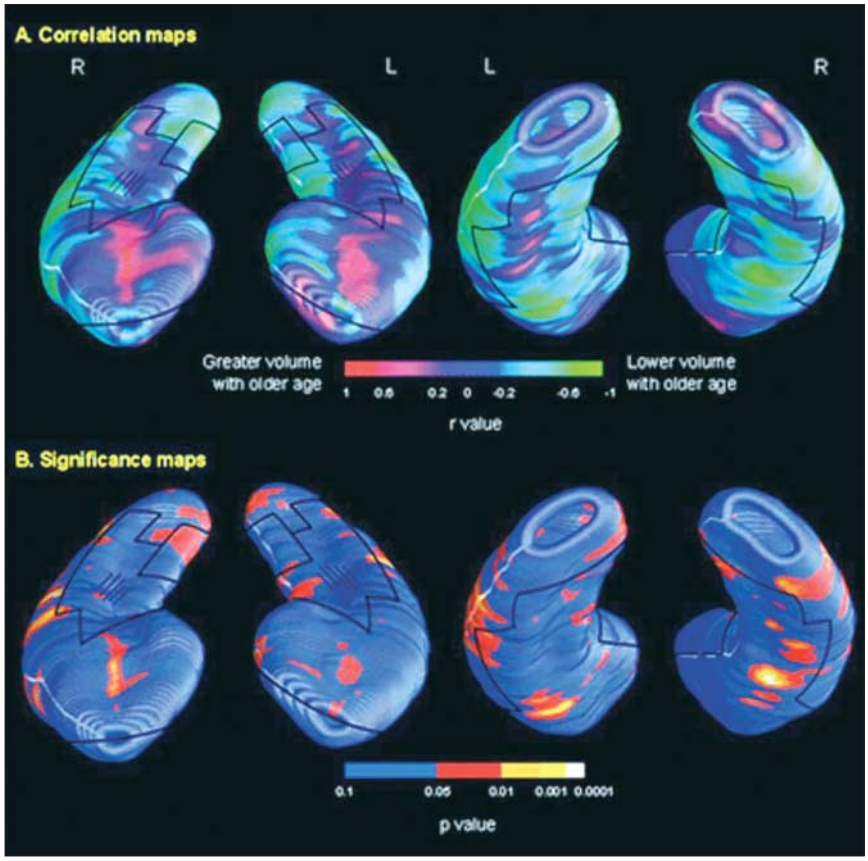

Fig. 1 Statistical maps of the correlation between age and regional hippocampal volume in 14 older healthy controls. **a** Pearson's r and **b** statistical significance

etal and frontal regions were more involved in aging. The peak loss occurred between the ages of 50 and 70, and thereafter decline was much more gradual [9].

RAM is a recently developed algorithm sensitive to local surface changes of closed structures, such as the hippocampal formation, and is superior to volumetric techniques in that it can accurately localize where atrophy occurs in the hippocampus – except grossly in the head, body, and tail. In a 2-year longitudinal study of 18 patients with very mild Alzheimer's disease and 26 older controls, hippocampal volume loss to the right side was 10% and 5%, respectively. In the older subjects small amounts of shape change were evidenced. These changes were confined to the head of the hippocampus and subiculum, while in the Alzheimer's patients most of the head and the CA1 subregion, as well as the subiculum, were involved [10]. Personal data based on high resolution magnetic resonance images at 3 Tesla are consistent with the above. Data showed that hippocampal volumes were inversely correlated with age in 14 older healthy controls (r=0.53 and 0.56 to the right and left, $p<.05$, corresponding to 14% lower volume for every 10 years of older age from ages 65 to 85) (Fig. 1). Ageing-associated atrophy mapped to medial and lateral areas of the tail and body corresponding to the CA1 subfield and ventral areas of the head corresponding to the presubiculum.

MR-based diffusion imaging studies in aging

Conventional MR provides information only on macroscopically visible decreases in brain tissue volume, even when sophisticated algorithms of MR analysis are used. However, macroscopic changes only represent the end-stage phenomenon of the aging process and the underlying microstructural modifications remain unknown, being beyond the spatial resolution of conventional MR. DT and MT imaging are nonconventional MR-based techniques able to detect the amount and direction of the movement of water molecules (DTI) and the exchange of proton magnetization between water molecules and macromolecules (MTI) in living tissue. Parameters measuring diffusion properties (mean diffusivity and fractional anisotropy) and the efficiency of magnetization exchange (MT ratio) are related to the integrity of the brain tissues at a microstructural level. In particular, mean diffusivity measures the amount of water diffusion in biological systems that normally is impeded by tissue structures, such as cell membranes, myelin sheaths, intracellular microtubules and proteins. Fractional anisotropy measures the direction of diffusion that normally occurs parallel, rather than perpendicular, to an axon or myelin sheath.

The MT ratio has been shown to decrease in the aging brain. In a study of 52 healthy volunteers aged between 20 and 86 years MT ratios were computed for gray and white matter. The findings showed that the mean MT ratio was significantly lower in the older (subjects aged 50 years or more) than in the younger group for both brain tissues. Moreover, the relation between MT ratio means and age showed a nonlinear pattern, with gray and white matter starting to decline only after the age of about 40 years [11].

A more recent study evaluated the influence of aging on gray and white matter with both MT and DT imaging [12]. In 85 healthy subjects aged 11 to 76 years undergoing conventional and nonconventional MR, Benedetti et al. found that gray and white matter mean diffusivity peak significantly correlated with age after correction for number of white matter hyperintensities, gender and the corresponding normalized tissue volumes. MT ratio correlated with age only in gray matter and in the uncorrected analysis. In a multiple regression analysis only gray matter volume and gray matter diffusivity were independent predictors of age.

This study suggests interesting conclusions. First, not taking into account the presence of white matter hyperintensities can lead to the misinterpretation of MT results. Benedetti et al. did not find a correlation between white matter MT ratio and age, but they considered only normal appearing and not total white matter. Thus, decrease in the white matter MT ratio observed in the previous studies [11, 13] could be due, in part, to the presence of white matter hyperintensities, having a lower MT ratio than normal-appearing white matter. Second, changes in gray and white matter microstructure with age seem independent of corresponding tissue atrophy and suggest that both macro- and microstructural measures should be acquired to obtain a more complete picture of the aging brain. Lastly, the finding that gray but not white matter volume and diffusivity are predictors of age suggest a different vulnerability of gray and white matter to aging.

A recent study used voxel-based analysis to investigate the regional effects of age on gray and white matter volumes, and on diffusion properties (mean diffusivity and fractional anisotropy) in 73 healthy women aged 22 to 70 years [14]. The results showed a positive correlation between mean diffusivity and age. Local areas of increased mean diffusivity were observed bilaterally across widespread regions of the brain, particularly in anterior regions, such as gray and white matter frontal, temporal, and parietal lobes, insula and corpus callosum. Voxel-based direct comparison of volume and DT data showed that mean diffusivity was more strongly correlated with age in areas (bilateral thalamus and caudate nucleus) different from those where the strongest correlation was found between volume and age (bilateral frontal lobes, insula, basal ganglia), suggesting that diffusion properties and brain volume are complementary markers to the effect of aging.

Voxel-based analysis has been used in another recent study to assess the topographical distribution of age-related white matter volume changes in 84 healthy persons aged 13 to 70 years [15]. Results showed that aging has a heteroge-

Table 1 Cross sectional and longitudinal studies assessing the effect of aging on brain morphology

Study	Design	n	Age	MR method	Results
Fotenos et al. 2005 [3]	Longitudinal	79	65–97	Total brain volume with semiautomated technique	Total brain volume declined by -.45% per year
Ge et al. 2002 [2]	Cross-sectional	54	20–86	Gray and white matter volumes with semiautomated technique	Gray and white matter declined with a linear and quadratic pattern, respectively
Jernigan et al. 2001 [4]	Cross-sectional	78	30–99	Lobar volumes with semiautomated technique	Brain volume decline was localized mainly in the frontal lobe
Scahill et al. 2003 [5]	Longitudinal	39	31–84	Hippocampal volume with semiautomated technique	Hippocampal volume declined by -.82% per year, with acceleration after 70 years
Smith et al. 2007 [8]	Longitudinal	122	58–95	Voxel-based morphometry	Regional reduction in gray matter occurred in posterior parietal areas, posterior superior and middle temporal gyri, and inferolateral frontal regions
Sowell at al. 2003 [9]	Cross-sectional	176	7–87	Cortical pattern matching	Regional reduction in gray matter occurred in dorsal frontal and parietal association cortices
Wang et al. 2003 [10]	Longitudinal	26	66–80	Radial atrophy mapping	Shape changes of the hippocampus was localized in the head and subiculum
Benedetti et al. 2006 [12]	Cross-sectional	85	11–76	Magnetization transfer and diffusion tensor imaging	Gray and white matter mean diffusivity correlated with age. Only gray matter diffusivity was independent predictor of age
Abe et al. 2008 [14]	Cross-sectional	73	22–70	Diffusion tensor imaging and voxel-based analysis	Local areas of increased mean diffusivity occurred in gray and white matter frontal, temporal, and parietal lobes, insula and corpus callosum.
Pagani et al. 2008 [15]	Cross-sectional	84	13–70	Diffusion tensor imaging and voxel-based analysis	Regional reduction in white matter volume occurred in the fronto-parietal lobes and the superior cerebellar peduncle

neous topographical effect, with a predominant involvement of regions located in the frontoparietal lobes and the superior cerebellar peduncle. The increased vulnerability to aging of association cortices supports the theory that the impact of aging is predominant in the frontal lobes. Moreover, the shape of the relation between age and white matter volume differed depending on the region, being linear in the frontoparietal bundles of the corona radiate, the anterior cingulum, the fornix and the superior cerebellar peduncle, and non-linear in the genu of the corpus callosum. These results suggest that aging of the white matter is regionally heterogeneous, probably reflecting maturational aspects of the different white matter fibre bundles.

Conclusions

We have reviewed a variety of studies that assess the effects of aging on the morphology of the human brain in vivo using MR imaging (Table 1). Postmortem studies in aging have shown neuronal shrinkage and reduction in axon density and number and length of myelinated fibres. *In vivo* MR studies have confirmed regional changes in gray and white matter tissues, at both the macro- and microstructural level, which vary depending on the age studied and the method used to measure age-related changes. Future studies with a longitudinal design might best characterize the time course of underlying tissue changes in the aging brain.

Conflict of Interest statement The Authors declare that they have no conflict of interest related to the publication of this manuscript

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