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Structural Brain Changes in Aging: Courses, Causes and Cognitive Consequences

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SYNOPSIS

The structure of the brain is constantly changing from birth throughout the lifetime, meaning that normal aging, free from dementia, is associated with structural brain changes. This paper reviews recent evidence from magnetic resonance imaging (MRI) studies about age-related changes in the brain. The main conclusions are that (1) the brain shrinks in volume and the ventricular system expands in healthy aging. However, the pattern of changes is highly heterogeneous, with the largest changes seen in the frontal and temporal cortex, and in the putamen, thalamus, and accumbens. With modern approaches to analysis of MRI data, changes in cortical thickness and subcortical volume can be tracked over periods as short as one year, with annual reductions of between 0.5% and 1.0% in most brain areas. (2) The volumetric brain reductions in healthy aging are likely only to a minor extent related to neuronal loss. Rather, shrinkage of neurons, reductions of synaptic spines, and lower numbers of synapses probably account for the reductions in grey matter. In addition, the length of myelinated axons is greatly reduced, up to almost 50%. (3) Reductions in specific cognitive abilities—for instance processing speed, executive functions, and episodic memory—are seen in healthy aging. Such reductions are to a substantial degree mediated by neuroanatomical changes, meaning that between 25% and 100% of the differences between young and old participants in selected cognitive functions can be explained by group differences in structural brain characteristics.

KEY WORDS

magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), cognition, cross-sectional, longitudinal, neuropsychology, cerebral cortex

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INTRODUCTION

At least two reasons exist to study the brains of healthy elderly people: First, most people experience changes in specific cognitive abilities during aging /1/, especially related to performance on speeded tasks /2/, executive function /3/, and episodic memory /4,5/ (but see /6/). Such cognitive changes are likely partly caused by age changes in macrostructural brain properties. Magnetic Resonance Imaging (MRI) can be used to quantify the volume or thickness of specific brain structures in vivo, yielding a window into the human brain during aging. Thus, by comparing the brains of young and elderly participants, and the brains of the same individuals scanned repeatedly as they get older, we may achieve a better understanding of the neuro-biological foundation for age-related cognitive changes, and how changes in the brain may lead to changes in cognitive function. This knowledge may illuminate why some healthy people experience higher rates of cognitive decline than others, and ultimately, whether ways can be found to effectively counteract this process.

The second reason for studying the brains of healthy elderly people is that we must understand how the brain changes in normal aging to be able

to identify age-related pathology, especially Alzheimer's disease (AD). In what ways is the atrophy in AD qualitatively different from that seen in healthy aging? Recent research has shown that most brain areas that are atrophic in AD are also affected by healthy aging, although to a lesser extent /7/. Thus, attempts to differentiate AD from healthy aging at a very early stage can either be targeted at identifying accelerated atrophy in specific brain structures above atrophy seen in normal aging /8,9/, especially in the hippocampus and the entorhinal cortex /10-12/, or at identifying patterns of change across several brain regions that may indicate a pattern of atrophy characteristic of AD and not characteristic of normal aging /13-15/.

This paper has three major themes. First, we will present what is known about the effects of healthy aging on brain morphometry, and some factors that may modulate these, including genetic variations. A short review of the results obtained with a newer MRI technique, DTI, will also be given, as this is a very promising measure related to white matter (WM) integrity. We will also discuss how the morphometric effects seen in healthy aging are different from the atrophy seen in AD. Second, we will discuss possible neuro-biological foundations for the morphometric changes. What happens at the molecular level when a brain structure is reduced by e.g. 25% during the course of the adult lifetime? The final theme of this paper is the cognitive consequences of the macrostructural brain changes. We will review the studies that have directly targeted the cognitive correlates of age-related brain changes, and discuss to what extent morphometry can be used to explain the decrements in specific cognitive functions often seen among healthy elderly.

The advent of MRI yielded an opportunity to study macrostructural characteristics of the human brain in vivo for the first time. Incredible developments in MR scanners and software have made MRI a tool of increasing value in the study of the effects on the brain of healthy aging and age-related degenerative disorders. For instance, the thickness of the cerebral cortex can now be measured with sub-millimeter accuracy /16/, and changes in cortical thickness between two time points can be measured with an error as low as 0.5% /17,18/, enabling the identification and tracking of brain changes over short periods (See Figure 1 and Figure 2).

COURSE OF STRUCTURAL BRAIN CHANGES IN AGING

To date, more than 50 cross-sectional MR-studies have tested the effects of age on the volume or thickness of various brain structures (for a table of 31 cross-sectional studies reporting correlations between age and subcortical volumes, see /19/). Methodological differences related to scan quality, of 31 cross-sectional studies reporting correlations participant recruitment and screening, number of participants, brain structure measurement, and statistical choices make it challenging to directly compare results across studies. The general scientific consensus is that age influences total brain volume, but there are large differences between structures in how strong the effects are. Some structures are found to decline substantially in old age, while others appear better preserved. In addition, different brain structures show different age trajectories. Some brain areas are declining linearly from early in life, whereas others continue to increase in volume well into middle adulthood before eventually beginning to deteriorate in the later part of life.

Most studies of age-effects on the brain are cross-sectional, and only age-differences, not age-changes, can be observed in such studies. Especially, the issue of cohort effects is challenging when the age-span sampled often exceeds 50 years. Thus, the few longitudinal studies that exist are exceptionally important. Still, major methodological problems are also associated with longitudinal designs. First, scanner replace-ments and upgrades make it very difficult to follow the same group of participants over longer periods, e.g. 10 or 20 years. Thus, only exceptionally do longitudinal MR-studies span more than 5 years. Second, selective drop-out constitutes a challenge, and re-recruitment at each follow up may be necessary to counteract this. Finally, because longitudinal studies require much larger efforts and finances, the samples sizes are usually smaller than in cross-sectional studies. Even with these caveats

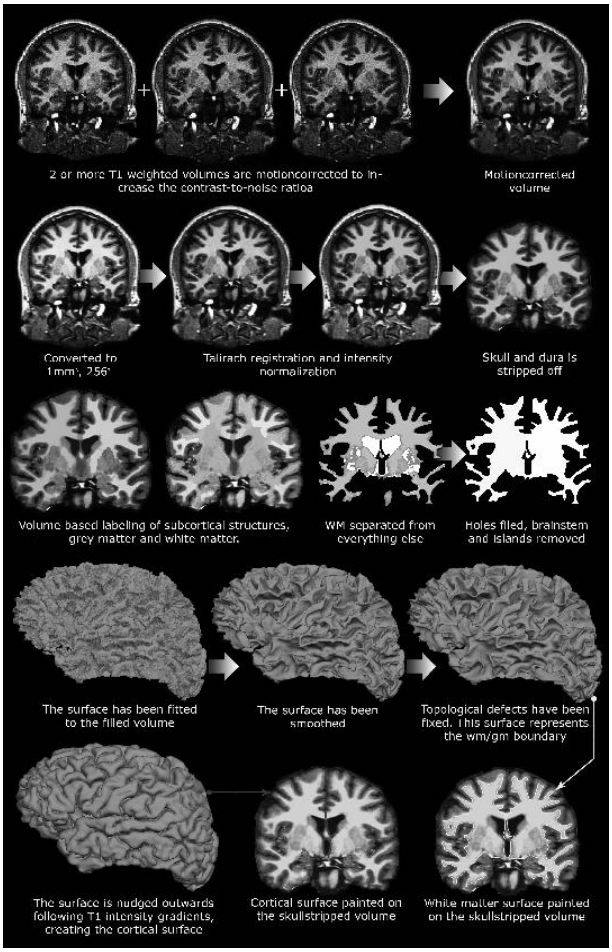

Fig. 1: Steps in processing of MRI scans. The figure illustrates the main processing steps in a freely available software package for calculation of brain volumes and cortical thickness based on magnetic resonance imaging (MRI) scans (FreeSurfer, see surfer.nmr.mgh.harvard.edu/). Figure made by Inge K Amlien.

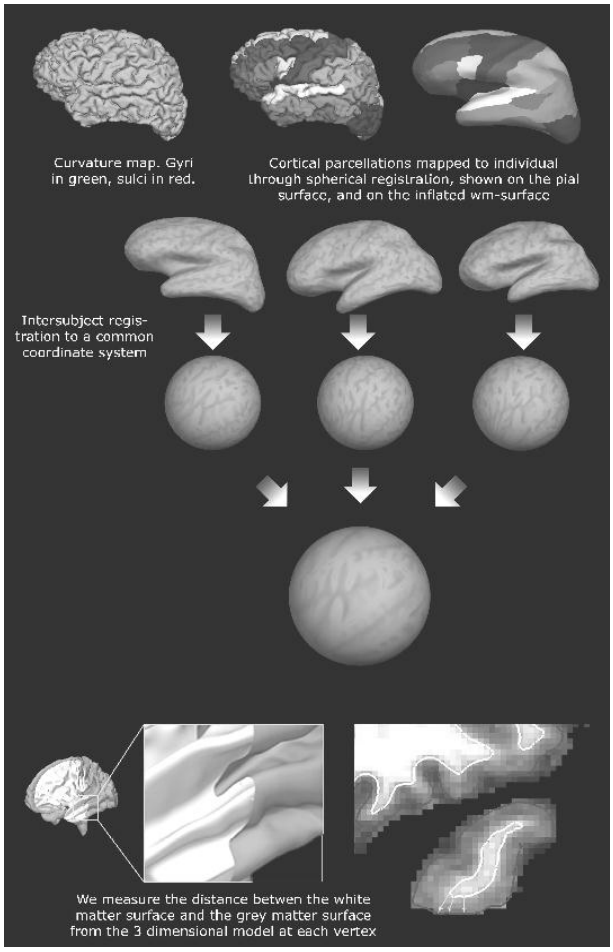

Fig. 2: Calculation of cortical thickness and comparisons among different brains. The figure illustrates output from processing of MRI scans, how different brains are registered and compared, and the calculation of cortical thickness at each point (vertex) of the brain surface. Figure made by Inge K Amlien

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in mind, longitudinal studies are very important additions to the cross-sectional studies. We will start by giving an overview of the extant cross-sectional MRI-aging literature, before comparing these results to the conclusions obtained by longitudinal designs.

CROSS-SECTIONAL STUDIES OF AGE-EFFECTS ON THE BRAIN

The consensus from cross-sectional studies is that grey matter (GM) is reduced with age /20-33/, and that this reduction begins early in life /20,34-38/.

GM loss in the cortex appears to be somewhat greater than in subcortical structures /19,24,32/. When specific structures have been studied in detail, the results have unfortunately diverged substantially across studies, and differences in how a structure is defined and how the scans were segmented complicate comparisons. Adding to this problem, in several studies only a few structures are segmented, making it difficult to assess the relative age-effect of different structures. Fortunately, recent studies have addressed the issues of comparisons between different brain structures and samples directly, strengthening the general view that most brain structures decline in volume with age, but at

TABLE 1

Overview of cross-sectional studies of age-effects on brain morphometry

Brain structure	Main results	Conclusion
Limbic structures		
Hippocampus	***Effects*** 10 of 17 studies reviewed found that hippocampus shrank with age [24, 32, 39-46], five found no change [30, 47-50], one found reductions for men but not women [51], and one found reductions in right posterior but not anterior hippocampus [52]. Age effects on hippocampal volume normalized to global GM loss were not observed in two large studies [22, 53]. In a large multi-center study including five independent samples, significant age-correlations were found for all but one sample [19]. ***Course*** Four studies found non-linear effects [32, 41, 42, 46], and non-linear relationships were found for all five samples in a large multi-center study [19].	The variability among studies is high, but part of the discrepant findings may stem for failure to account for non-linear effects. Likely affected by age, but not especially affected by normal aging compared to other structures.
Amygdala	***Effects*** Has received less attention than the hippocampus, but reports indicate age effects of comparable size. Four studies found reductions [32, 39, 41, 54], three did not [24, 51, 52], and in two were reductions relative to global GM loss not observed [22, 53]. In the multi-sample study, significant age-correlations were found for four of five samples [19]. ***Course*** Linearly related to age.	Variability among studies, and effects comparable to hippocampus. Likely affected by age, with linear reductions.
Basal ganglia		Heterogeneous effects across different constituent structures.
Striatum	***Effects*** All eight studies found reductions in caudate [23, 24, 32, 43, 55-60], and significant effects in four of the five samples in the multi-sample study [19]. Four studies found reductions in putamen [32, 43, 56, 58], and in one additional study was reductions found in men but not women [61]. The effects are generally stronger for putamen than caudate. Age effects were not found on the lenticular nuclei in one study [24], but this include the globus pallidus in addition to the putamen, which may explain why age effects were not found. ***Course*** Caudate generally non-linearly related to age, while recent studies of putamen indicate linearity.	Consistently found to be affected by age. Generally larger effects for putamen than caudate. Caudate non-linearly affected by age (decelerated decline in higher age), while putamen is likely linearly affected.
Pallidum	***Effects*** Previous reports found weaker effects than for striatum, with none of four studies finding linear reductions [24, 56, 58, 62], while a quadratic reduction was found in a fifth [32]. Recent studies have reported significant age-reductions also for pallidum [19, 63, 64] or for the basal ganglion in general [65]. ***Course*** Likely mainly linear	Inconsistent findings, but the most recent studies indicate age-effects. The course of change is likely linear.
Thalamus/ diencephalic structures	***Effects*** Six studies found reductions [31, 32, 64, 66-68], two did not [23, 24] and three found lack of age effects relatively to global GM or whole brain loss [22, 52, 53]. Thalamus declined in all samples in the multi-sample study [19]. ***Course*** Linear	Consistently related to age, and the course of change is linear.
Accumbens	***Effects*** Two studies found linear reductions [24, 32], and all but one sample in the multi-sample study showed large and significant linear effects [19]. ***Course*** Linear	Accumbens is a primitive and phylogenetically old structure, but is still subject to substantial and linear age-decrements.
Brainstem	***Effects*** Relatively robust to effects of age, with small reductions found in one study [32], while the ventral pons has been found to be well preserved in another [69], no significant age-change was observed in pontine structures in a third study [47], and significant linear effects found in two samples only in the multi-sample study [19]. ***Course*** Not related to age	The brainstem is probably the best preserved of all brain structures in healthy aging.
Cerebellum	***Effects*** Eleven studies found reductions in total cerebellar volume, cerebellar GM, cerebellar WM, or other cerebellar compartments [24, 32, 48, 52, 62, 64, 66, 69-72], one study found no effects on cerebellar WM [70], in contrast to a more recent study [73], one study observed that the age changes were exponential [62], and cerebellum cortex declined with age in all samples in the multi-sample study [19]. ***Course*** Cerebellum GM mainly linearly related, while WM are best characterized by a non-linear function of prolonged volume increase and accelerated decrease in high age	Consistently found related to age, but not very large effect sizes. GM linearly reduced, while WM follows a non-linear pattern of accelerated decrease in high age
CSF and the ventricular system	***Effects*** There is agreement across studies that CSF compartments increase in volume with age [22, 24, 30, 32, 43, 45, 74-76], and some have also found non-linear age changes [19, 22, 30, 32]. ***Course*** Some degree of non-linearity (accelerated increase in high age)	Consistent increases. May partly be caused by atrophy in other brain areas, e.g. deep WM, and partly from mild versions of normal pressure hydrocephalus.

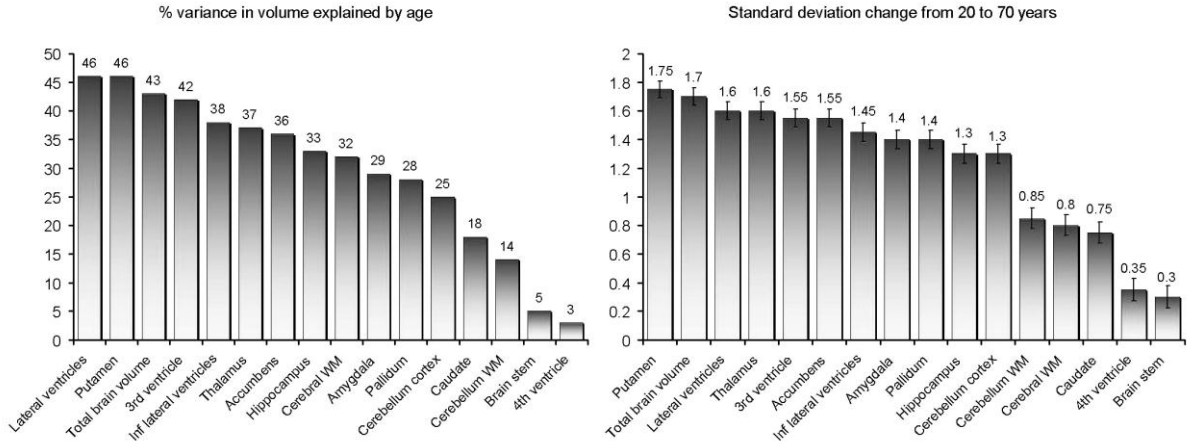

Fig. 3: Effects of age on volumes of different brain structures. The bar charts to the left show percentage of the variance that can be explained by age. The bar charts to the right show how many standard deviations in volume that change over 50 years (decrease for all structures expansion for the ventricles). The sample consists of 1143 healthy participants between 18 and 94 years, pooled from several independent studies /39/.

highly different rates, and probably following different courses. In Table 1, an overview over status of knowledge of the effects of age on brain morphometry for several subcortical structures is given.

Figure 3 (left) depicts the amount of variance in volume that can be explained by age in a series of brain structures. The data material is identical to that used in /39/, and consists of 1143 healthy participants between 18 and 95 years, pooled from several independent research projects /32;40-44/. All volumes were regressed on ICV, and the residuals used in the calculations. As can be seen, age explained between 3% and 46% of the variance in volume, with a median of 32.5%. cerebral spinal fluid (CSF) and the ventricular system are to a large extent affected by age, while putamen tops the list of the brain tissue structures. The hippocampus is also substantially affected, but does not stand out from the rest of the structures as especially vulnerable to effects of normal aging. The 4th ventricle, brain stem, cerebellum WM, and caudate were the structures least related to age in these data.

Figure 3 (right) gives the estimated number of standard deviations (SD) change from 20 to 70 years (error bars represents standard error of the regression coefficient used to estimate the change). The estimated change across 50 years was between 0.3 (brainstem) SD to 1.75 SD (putamen), with a median of 1.4 SD. Thus, the age-related changes are profound in terms of both explained variance and magnitude of change.

Several subcortical structures increase in volume throughout most of adolescence and well into adulthood, e.g. the thalamus, brainstem, amygdala, hippocampus, and cerebral and cerebellar WM /45/. In contrast, thinning of the cerebral cortex starts at an early point in life /20, 46/, approximately at five to six years of age, but with substantial variations across different regions. This thinning continues throughout the adult part of the lifespan /20-32;47-50/. Within this general picture, however, a heterogeneous pattern of age effects on different parts of the cortex exists /27,29,41,51/. Unfortunately, interpretations have been hindered by inconsistency among the results from different studies /52/. However, as the quality of MR scans and the methods used to analyze them have undergone steady improvements over the last years, stronger agreement across different studies and samples is seen.

Traditionally, regional cortical volume has been measured in vivo by the manual drawing of region of interests (ROIs) on MRI scans. In studies using such manual approaches, age has large effects on the frontal cortex, with significant but more moderate effects in temporal areas, posterior

association areas and occipital areas, and relative preservation of the primary sensory regions /41, 48,52/. New segmentation tools have more recently given the possibility to study age effects continuously across the cortical mantle without pre-defining ROIs. Automated methods may have weaknesses, e.g. registration of morphologically different brains to a common stereotactic space and the need for smoothing, but they are still important in studies of aging. First, such methods require less manual intervention, which increases the reliability across raters and labs, and they are also much less time-consuming. Second, without the use of ROIs, differences in anatomical definitions and placement of anatomical borders will not preclude comparisons. Third, the spatial resolution is not restricted to the size of the ROIs. The localization of the effects cannot always be known beforehand, and ROIs may thus hinder discovery of unexpected effects.

From the results of cortical studies using automated techniques, the general consensus now is that the effects of age are strong in frontal and especially prefrontal areas /22,29,50,53-58/. This is in accordance with the 'last in, first out' hypothesis, according to which the brain areas that are the latest to develop phylogenetically and ontogenetically are the first to be affected by normal aging. This view corresponds well with neuropsychological studies showing that executive functions, which depend heavily on frontal neural circuits (e.g. fronto-striatal circuits), are among the cognitive functions to be most affected by advancing age /59,60/ (more about this later). Several studies also find the occipital lobes to be negatively affected by age /29,50,53,54,56,58/. Finally, most studies demonstrate age effects on parietal cortex /22,29,53,55,58/, with some variations in localization.

Within the frontal cortex, the findings across studies are not coherent. In some studies /29, 53/, thickening of the anterior cingulum is found, whereas it is found to be preserved or reduced in others /22,55,56,61,62/. A study comparing the effects of age on cortical thickness in six different samples found a significant thickening in the left cingulum in three samples from the USA (overlapping with the one used in /29/), but not in three samples from Nordic countries /58/. Further, some studies find sparing of the medial orbito-frontal cortex /29/, whereas others report age effects throughout most of the anterior part of the brain /50,53/. Tisserand et al. /62/ suggested that the effects to some degree depended on the method of choice. Semi-automated and voxel-based approaches yielded the most prominent age effects within the lateral frontal and cingulate regions, whereas a manual approach yielded the strongest reductions in the lateral and orbital cortices.

In aging research the temporal lobes are of special importance because they include and are functionally related to the hippocampi and other structures important for declarative memory. Thinning of the temporal lobes is seen in MCI and AD /63/. Further, it has been argued that the medial temporal volume (i.e. hippocampus) differentiate between healthy and pathological (e.g. AD) aging /15/ (see below). A relative sparing of the temporal and parahippocampal cortices was found in one study /29/, and another found that age affected the entorhinal cortex relatively less than the rest of the cortex /22/. Other studies, however, have found thinning in temporal cortical areas /50,53-55,58/. Also, co-occurring volume reductions and increases in different parts of the temporal cortex have been reported /56/. Targeting morpho-metric effects in the temporal lobe with a newly developed semi-automated technique, one study found that entorhinal and perirhinal cortices, but not the posterior parahippocampal cortex, were reduced in volume with age /63/. This reduction in volume could be attributed mainly to reduction of the surface area of these regions, not the thickness of the cerebral cortex.

Figure 4 (top) illustrates estimated thinning of the cerebral cortex based on a cross-sectional sample of about 684 healthy participants between 18 and 94 years, drawn from previously published data samples /13,39,44/. As can be seen, thinning is seen throughout most of the cortex and is especially pronounced in the superior and inferior frontal areas, medial and superior temporal areas, and supramarginal cortices. The anterior medial temporal cortices, including entorhinal, as well as the anterior cingulate and medial orbitofrontal cortices, seem relatively spared. We believe that the age effects around the central sulcus, as well as the lack of effects in anterior parts of the cingulum, may be artefacts of the cross-sectional design.

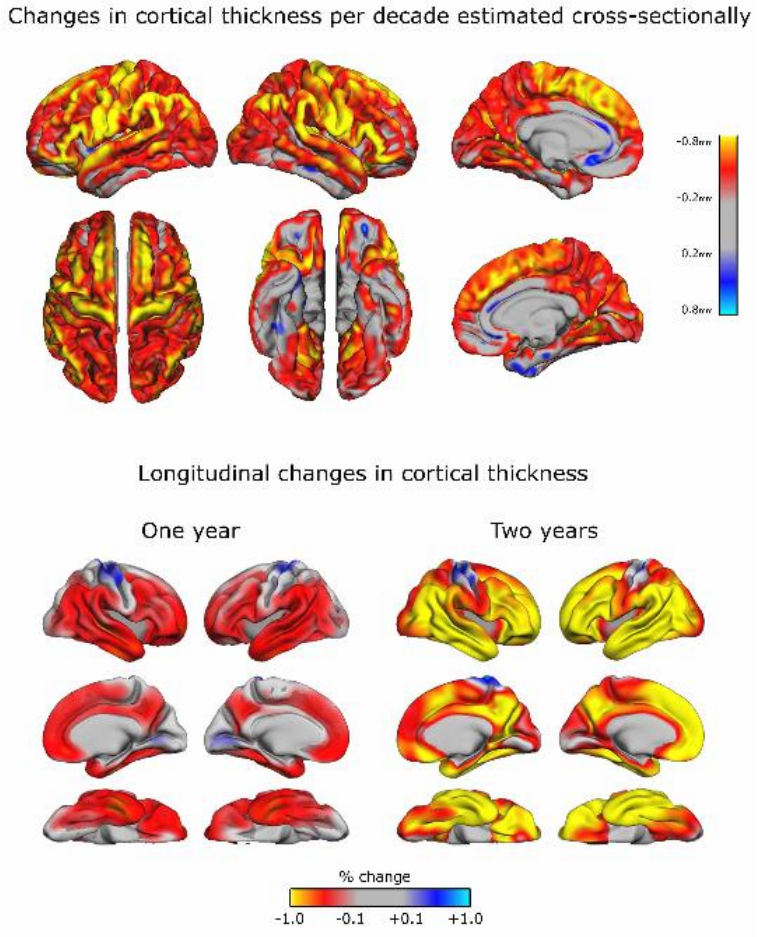

Fig. 4: Regional changes in cortical thickness per decade. *Top*: Reductions in cortical thickness in mm per decade estimated from a cross-sectional sample of 688 healthy participants between 18 and 94 years. (Figure made by Inge K Amlien.) *Bottom:* Percentage change in cortical volume over one and two years in 142 healthy elderly (60-81 years of age) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database of MR-scans. Annual change of ≈ 0.5% can be seen across large sections of the brain surface, e.g. in temporal and prefrontal areas. The figure is a modified version of Figure 2 in Fjell et al, J Neurosci 2009, 29, 15223-31.

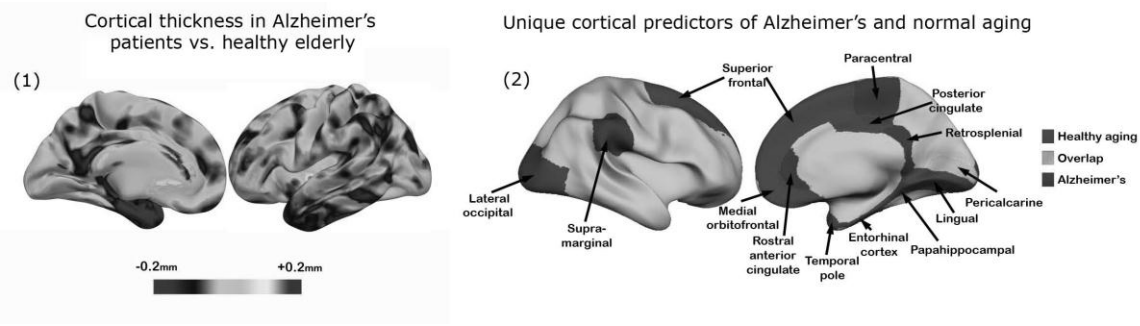

Fig. 5: Differences between normal aging and Alzheimer's disease. Panel 1: Differences in cortical thickness between 96 patients with mild to moderate Alzheimer's disease (AD) and 93 healthy age-matched controls. All participants are drawn from the Open Access Series of Imaging Studies (OASIS). As can be seen, the AD patients have substantially thinner cortex in anterior temporal cortex, including entorhinal cortex, and in other parts of the so-called medial temporo-parietal episodic memory network, e.g. posterior cingulate/ isthmus of the cingulate and precuneus. Panel 2: Cortical areas that were statistically unique predictors of AD vs healthy elderly (red), or of healthy elderly vs. young (blue), in addition to areas predicting both (green). The data material consists of 96 AD patients, 93 healthy elderly and 137 young.

Age-effects on white matter

The integrity of the brain's WM is postulated to be significant for cognitive function in health and disease /64-70/. The WM consists largely of myelinated long distance axonal projections of neurons and is important for the integration and coordination of neural activity between brain areas (see below). The effects of age on WM volume are different from those seen for much of grey matter, especially the cerebral cortex. The volume of WM increases in childhood and adolescence /20,26,34, 35,71,72/, but for many years it was assumed that the WM volume was relatively stable throughout most of the adult lifespan /21-23,26,31,73/. Some studies found that the total WM volume was negatively related to age /24,32,48,74/, but the discrepancy among studies was substantial. Over the last few years, it has been acknowledged that substantial changes in WM volume characterize also the adult part of the lifespan. WM changes are non-linear and may not be detected if only linear relationships are tested. Typically, a pattern is seen in which WM volume grows until 40-50 years before accelerating volume reductions set in /19,20, 32,44,47,48,75-78/. Thus, the use of samples of varying ages could be a reason for the discrepant findings in the early literature. For instance, one study /20/ reported WM to be negatively related to age only from 70 years, but this age range had not been consistently included in aging studies. Jernigan and colleagues /24,75/ found that despite its later onset, WM loss was more rapid than grey matter loss, and ultimately exceeded it. As for grey matter, results indicate somewhat less age-related loss in deep subcortical regions than in the cerebral lobes /24/. Little or no decline is often observed in brainstem volume /19,32/, and several studies report sparing of the pons in aging /79-83/. Salat and colleagues /76/ recently published the most comprehensive study of WM volume changes to date, and found WM volume-age-relationships in several regions, including strong effects in frontal and temporal areas.

The advent of DTI has yielded new opportunities for studying age-effects on WM in vivo. DTI is sensitive to the degree and directionality of water diffusion in the brain /84,85/, and this information can be used to make inferences regarding the microstructural properties of the tissue. Because the diffusion will be stronger parallel with, rather than perpendicular to, myelinated nerve fibers, DTI can be used to gain information about the integrity of nerve fibers. The information that can be obtained about WM by DTI is complementary to volumetric measures /73, 86/. Early studies by Salat and colleagues /87,88/ demonstrated that the diffusion parameters of WM changed with age, especially in the frontal areas of the brain/. Age-related decreases in the directionality of diffusion, the fractional anisotropy (FA), is now well documented /65,68,87,89-97/.

For a long time, however, large-scale regional analyses focusing on the trajectories of changes in diffusion properties across the lifespan were lacking. Recently, Westlye and colleagues /44/ compared the lifespan trajectories for both regional WM volume and DTI measures in a large sample of 430 participants. Inverted U-shaped WM development was found for both volume and FA, as was expected because the study included children and adults of varying ages. The total WM volume peaked at approximately 50 years of age, which supported earlier findings of volume growth until middle age /19,24,48/.

However, global FA peaked at around 30 years, followed by a small, yet stable, linear decrease until approximately 65 years, with a subsequent accelerated decline. This did not fit well with the notion of continuous WM maturation extending into middle-age, but rather a three-phasic lifespan model of WM development with accelerated alterations in the earliest and latest phases of life /78/. This pattern is supported by developmental studies indicating an asymptotic maturation from childhood to early adulthood /37, 38,98/, and accelerating WM volume decreases in the latest part of the lifespan /19/. A large study by Kochunov and colleagues /99/ also confirmed the non-linear pattern of developmental and age-related changes in FA. In a recent review, Madden and colleagues showed that both anterior-posterior and superior-inferior gradients of FA-changes are likely present in normal aging. We will discuss the implications of this for cognitive function in a later section of this review.

LONGITUDINAL STUDIES OF AGE EFFECTS ON THE BRAIN

Longitudinal studies have reported annual gross brain volume decreases on the order of 0.2% to 0.5% /47,100-102/. The most studied structure is the hippocampus, due to its relevance in Alzheimer research. The hippocampus shows annual atrophy rates from 0.79% to 2.0% /7,11,78,100,101,103/, which tend to be somewhat higher than cross-sectional estimates /51, 100, 103/. For instance, in a large study conducted by Raz and colleagues /78/, the annual hippocampus shrinkage estimated from cross-sectional data was 0.35%, whereas the shrinkage estimated from longitudinal data was 0.79%. This finding indicates that rather than overestimating age-changes due to cohort effects, cross-sectional studies may actually underestimate real brain changes. Noteworthy, however, is that the interpretation of percentage change is often difficult for the hippocampus, as percentage change tends to show a non-linear age relationship. Thus, the estimated change will likely depend heavily on the age of each participant. In the Raz et al study, a quadratic function was not significant for hippocampal volume, but this will often constitute a challenge that needs to be taken into account. Entorhinal cortex shows decline rates somewhat smaller than those seen for the hippocampus, usually in the range of 0.3% to 2.4% /7,51,101, 103,104/. As for the hippocampus, longitudinal estimates tend to be larger than the cross-sectional. In the Raz et al study, the cross-sectionally estimated annual atrophy for entorhinal cortex was 0.11%, whereas the longitudinal data indicated 0.32%.

Atrophy rates in other parts of the brain have seldom been studied, with a few important exceptions /51,105-107/. These studies describe atrophy in several regions, with prominent decline in prefrontal cortex, as well as in caudate, cerebellum, hippocampus, and association cortices /78/ and parietal areas /106/, in addition to expansion of the ventricles /105/. In a recent study, significant atrophy was found in all 25 regional brain volumes tested, over periods extending as long as 10 years in some cases /107/. An earlier study found significant ventricular enlargement over one year, but no detectable change in total or regional brain volumes /28/. In a final study change over one year was tested in 142 healthy elderly in 48 ROIs /7/. This study used a newly developed and very sensitive algorithm for detecting longitudinal brain change /17/. A significant volume decrease or ventricular expansion was found over 1 year in 39 of the ROIs. The only areas that did not show significant change was caudate, 4th ventricle and ROIs around the central sulcus and in the occipital lobe. Over 2 years, only the postcentral gyrus and the pericalcarine sulcus did not decline significantly. The hippocampus (–0.81%) and the amygdala –0.81%) showed the largest reductions, and the median 1-year atrophy was –0.38% (not including the ventricles). Cortical atrophy typically ranged between –0.2% and –0.6% annually. The most atrophy was seen in frontal cortex, especially the superior frontal, lateral temporal (inferior, middle and superior temporal gyri), and supramarginal cortices. Relative sparing was seen around the central sulcus and in occipital cortex. Figure 4 (bottom) shows the annual percentage change in cortex in a sample of 142 healthy elderly. The results mimic those from cross-sectional analyses to a substantial extent. In contrast to the cross-sectional results, however, no effects were seen around the central sulcus. Further, thinning was seen in most of cingulate, which is also contrary to the cross-sectional effects. These differences may be due to variations in sample characteristics, for instance the higher mean age in the longitudinal vs. the cross-sectional sample, differences in the algorithms used to compute the age effects, differences in the age span sampled (cross-sectional age span of about 70 years, compared with longitudinal measures over 1 and 2 years), and/ or artefacts from the cross-sectional design. For instance, cross-sectional designs are based on the assumptions that the only relevant difference between participants at different ages are their age, but the possibility that sampling bias may be different for various parts of the age-span cannot be excluded a priori.

The results indicate that brain changes in healthy elderly are prominent even after short time intervals and that by using modern techniques for analyzing MR images, these changes can reliably be detected. Such methodological advances make

possible the use of MR technology to study relatively small changes in brain structures also in clinical settings, e.g. by monitoring atrophy in specific brain regions over time in individual patients at risk for various degenerative conditions, e.g. AD, or to monitor the effects of administered medications over short periods. Further, the results from longitudinal studies indicate that the effects seen in cross-sectional investigations are valid, and not artefacts from e.g. cohort effects.

THE TRAJECTORIES OF AGE-CHANGES IN BRAIN STRUCTURES

Brain volume increases during the first years of life and generally decreases during the last. The shapes of the trajectories that connect these two ends of the lifespan are not uniform across the brain. A brain structure can follow five basic courses. First, a structure can be relatively immune to the effects of age, which often is seen for areas around the central sulcus, medial occipital areas, and possibly the cerebellum and 4th ventricle. Second, a structure can undergo a linear volume reduction, i.e. the effect of age is similar across all ages. This reduction is typically seen for e.g. the thalamus, accumbens, and pallidum. Also, most cross-sectional studies find that the relationship between regional cortical thickness and age is linear or almost linear in the adult part of the lifespan /58/. Third, a linear development or a plateau can be seen for the first part of the lifespan, and then accelerating decline may characterize the latter part. This picture can be seen for cerebellar WM. Interestingly, this pattern of change is likely to represent a common belief about brain changes, but is seldom reported in the cross-sectional literature. In longitudinal studies, however, correlations between age and rate of atrophy have been reported for selected cortical regions, indicating a pattern of accelerated atrophy among the oldest participants /7,78/. It is, however, challenging to rule out that this accelerated decline in old age is not related to effects of higher rates of incipient degenerative disorders in the oldest participants. The alternative version of this path is where linear changes are followed by deflations of effects in high age. Fourth, the course of change for a structure during the adult lifespan can follow a quadratic path, in which volume growth is prolonged before accelerating atrophy is seen in the latest part of the lifespan. Cerebral WM is the most typical example of this type of development. Finally, a cubic trajectory is theoretically possible, where for instance initial growth is followed by atrophy, followed by additional volume increase. This pattern is rarely observed, but may the case if external agents, e.g. iron depositions in higher age, should increasingly influence neuroanatomical volumes in old age /32/.

The most commonly used statistical approach to describe the trajectory of brain change in cross-sectional studies is a regression equation on the form $\beta 0 + \beta 1 age + \beta 2 age^2 + \varepsilon$. If $\beta 2$ is significant, then the relationship can be said to be non-linear. This approach is valid, and the use of such higher order polynomials in research on brain aging was a huge step forward from testing only linear relationships. Unfortunately, this approach is more suitable to reject a hypothesis of a linear relationship between age and brain structures than to yield an accurate description of the relationship itself. For instance, by this approach describing a situation in which relative stability or linear decline through middle age is followed by accelerating decline in higher age is impossible. Thus, at present, we can not rule out that progressive decline in brain volumes can be the case after a certain age, e.g. 70 years, for some of the structures that usually are reported to be linearly related to age. Other statistical methods, e.g. the smoothing spline or locally weighted polynomial regressions (LOESS), may be better alternatives to describe the trajectory of change for a brain structure across the lifespan /108/. Thus, it is our belief that more research with large samples and sophisticated statistical methods is needed in this area before a more realistic picture of the course of brain changes in healthy aging can be given.

The question of which curve best characterizes the age-changes of a specific structure is critical and relates to the question of whether brain age changes are continuingly going on through the adult lifespan, or whether adulthood in general can be characterized by essentially a preserved, stable brain, with structural changes occurring only in advanced aging. Additionally, the first question

also relates to the question of for how long the brain develops. For instance, the often reported increase of WM volume until 40-50 years of age has been taken to support a view of positive development, possibly serving increased cognitive functions, across large parts of the adult lifespan. Clinically, knowing whether accelerated decline of the volume of a specific structure can be taken as evidence of neurodegenerative conditions is important. If structures of known importance for e.g. AD follow a linear pattern of change in healthy aging, accelerated decline in e.g. the hippocampus, entorhinal cortex, or precuneus, could be used as a marker for neurodegenerative disease. Unfortunately, the hippocampus and WM volume, both vulnerable to AD /10,11,109,110/, seem to show non-linear age relationships /19/. The course of change of these structures per se may be more challenging to use as biomarkers to distinguish AD from healthy aging than if linear changes were expected in normal aging, and accelerated volume loss was seen only in disease.

GENETIC FACTORS MODULATING BRAIN AGING

General trends in brain aging are established, but individual variability is substantial. Whereas some persons show large decrements, others are able to maintain higher cognitive function and relatively intact brain structures well into advanced age. Knowledge of the factors that contribute to this variability is very important. Several conditions impact the aging of the brain, including physical and cognitive activity, nutrition, cerebrovascular health, and hypertension. The present review will focus on the effects of genetic variability. For a review of other modifying factors, please consult e.g. /111/.

Twin-studies have shown that the characteristics of both GM /112/ and WM /113,114/ are highly heritable and that the observed relationships between brain morphometry and cognitive function to a substantial degree are mediated by genetic factors /113,115,116/. About two-thirds of the genes in the human genome are directly related to brain function /117/.Thus, there is currently a huge interest in studying the effects of inter-individual genetic variations on brain function and structure. Especially, much interest has emerged in mapping the effects of substituting one nucleotide, the so-called single nucleotide polymorphisms (SNPs), on brain structure. Knowledge about contributing SNPs will help us to understand the neurobiological mechanisms involved in aging. For instance, if a SNP involved in myelin maintenance modulates the relationship between DTI parameters in a specific WM tract, aging and cognitive function, then this modulation will indicate that the integrity of the myelin sheaths in this tract indeed have an impact on a specific cognitive function in aging. This possibility has previously been tested only for a small number of specific candidate genes, e.g. apolipoprotein E (APOE).

'Imaging genetics' is the term used for the field of research that aims to connect genetic research with imaging studies of brain structure and function. Mattay and colleagues /118/ describe imaging genetics as a form of genetic association analysis, in which the phenotype is a measure of brain structure, chemistry or function, based on the assumption that these are closer to gene function than trait differences in overt behavior. In the field of cognitive aging, the application of imaging genetics has been surprisingly limited. Here, the primary goal would be to identify genes that accelerate age-changes in brain structure and function, and genes that make individuals more resilient to the effects of aging. However, this task is challenging, and Petrella and colleagues /117/ argue in a review that most studies are limited by small convenience samples, cross-sectional in contrast to longitudinal design, an exploratory nature, and lack of long-term clinical correlations. Adding to the complexity, almost certainly several genes affect each brain structure. In their seminal review of genetic effects on cognitive aging, Deary and colleagues /119 point out that age-related cognitive change is a continuous trait that, if it is affected by genes, is probably influenced by a large number of genetic differences (polygenic effects), and a smaller but unknown number of larger effects (oligogenic effects). Thus, studies correlating a single gene with e.g. hippocampal or prefrontal volume will likely see only part of the big picture in terms of interactions among various genes. For example, while both APOE4 and the BDNF Val-

Met polymorphisms appear to affect hippocampal volume, it is not known if and how these two genes interact /117/. In the following, we are going to describe a small selection of SNPs that may affect age-related structural brain changes, with special focus on APOE as this gene has received by far the most focus in imaging genetics research.

Effects of APOE on brain aging

The ε4 allele of APOE constitutes the major genetic risk factor for AD /120-122/. Multiple interacting mechanisms are probably involved, many of which may also have an impact on brain aging in healthy persons. APOE functions as the primary transporter of endogenously produced lipids /123,124/, necessary for repair, growth, and maintenance of myelin, and the ε4 alleles are related to greater and faster myelin breakdown in later-myelinating brain regions /125,126/. APOE may also be involved in brain plasticity /124,127/, possibly in amyloid clearance, and we can speculate that APOE ε4 reduces the ability to cope with damage in the central nervous system (CNS). Supporting this hypothesis, (a) CSF biomarker levels were in one study found to correlate with memory performance in ε4 carriers only /128/, (b) ε4 carriers are more likely to develop AD after mild head injuries /129/, and (c) ε4 with concurrent changes in CSF biomarkers increase the risk of conversion from MCI to AD /130/. Further, many of the risk factors for AD, including APOE, have been suggested to contribute by impacting myelin breakdown /131/. Several recent neuroimaging studies have shown reduced WM integrity in patients with mild cognitive impairment (MCI) and AD /92,110,132-139/, in accordance with histological findings of partial loss of myelin, axons, and oligodendrocytes, as well as reactive astrocytic gliosis, in AD /140/. The ε4 allele has also been found to be associated with other biomarkers for AD, especially CSF levels of amyloid beta (Aβ42) /128/.

Due to its general functions, APOE may have an impact on both GM and WM in healthy aging as well /141,142/. Nevertheless, although the basic functions of APOE in the brain are known, the direct effects of APOE on brain structure have not been easy to establish in healthy populations. Some studies have found negative effects of APOE ε4 alleles on brain volumes in elderly, with most focus and strongest effects generally found in the hippocampus /143-149/. Shaw and colleagues /150/ showed thinner entorhinal cortex in young children and teenagers who were ε4 carriers, indicating possible life-long influences of APOE on brain structure. Still, we must note that the effect size in this study was small, and significant only at $p = .03$, even with more than 530 scans included in the analyses. Adding to this, several studies have not identified hippocampal volume differences between healthy APOE ε4 carriers vs. non-carriers in non-demented aging samples /151-154/. In any case, volume differences do not show whether APOE exerts an influence through the aging process, or whether such differences are related to neurodevelopmental deficits. Based on cross-sectional data, Espeseth and colleagues /43/ found thicker cortex and steeper estimated decline in several areas in healthy middle-aged ε4 carriers. If this result can be replicated, then a thicker cortex in ε4 carriers could be related to developmental deviations, e.g. related to suboptimal myelination of U-fibers in areas directly beneath the cortex, causing the cortex to appear thicker on Mr scans. This picture fits less well, however, with the findings of a thinner cortex in children with ε4 /150/. Honea and colleagues recently used cross-sectional data to show increased GM atrophy in ε4 carriers, i.e. hippocampus and amygdala, as well as WM diffusion (reduced FA) in left parahippocampal gyrus. Still, a scattered pattern of opposite effects was also seen, in which APOE ε4 carriers had a larger volume, e.g. in middle temporal and inferior frontal gyri.

Several longitudinal studies have found greater rates of hippocampal atrophy in APOE ε4 carriers compared with non-carriers in non-demented elderly /155,156/. Crivello and colleagues /157/ published the largest study to date on the effects of APOE on brain aging, based on a longitudinal cohort of 1186 healthy elderly persons. The longitudinal analyses showed a relationship between age and the rate of GM and hippocampal loss. The greatest volume decline was seen in the ε4 homozygotes only, with no evidence for a dose effect. Thus, although a premature conclusion, possibly longitudinal studies are capable of identifying the subtle effects of APOE on brain

structure that are usually hidden in cross-sectional studies due to large interindividual variability. This view is supported by the findings of Jak and colleagues, in which cross-sectional comparisons revealed no effect of APOE on hippocampal volume, whereas longitudinal atrophy was significantly greater for the participants with at least one APOE ε4 allele.

Fewer studies have addressed the effects of APOE on WM characteristics, even though the function of APOE as involved in lipid transportation indicates that the effects on WM may be as likely as those on GM. recent research has shown reduced WM integrity /110/ and volume in patients with MCI or AD /76,137,158-160/, and some studies have shown the effects of APOE on diffusion properties of the posterior corpus callosum and medial temporal lobe /161/, parahippocampal gyrus /162/, and fronto-occipital and inferior temporal fascicule, splenium of the corpus callosum, subcallosal WM, and the cingulum bundle /163/. A recent study also showed higher correlations between the volume of different parts of the corpus callosum and age in ε4-carriers than in non-carriers, whereas no effects on GM were seen /164/. Interestingly, the volume of the different rOIs was generally not different between the APOE groups, only the age-slope, indicating that APOE exerts its effects on WM volume through life, and is not necessarily present at an early age. Although the latter was not explicitly tested, the data seem to indicate an opposite relationship between APOE status and WM volume in the early (ε4 > ε3) versus the late (ε4 < ε3) phase of adult life. Thus, the results are promising so far, and future research will settle the issue of whether effects of APOE are larger on WM than on GM in aging. Longitudinal studies will be especially important. To our knowledge, no longitudinal study has yet looked at the effect of APOE on WM integrity in aging.

Effects of other candidate genes and brain aging

Neurotrophins: Another set of variables of potentially great importance for individual variation in brain structure are the neurotrophins, a class of proteins that include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5). Neurotrophins are important for brain plasticity and development and are involved in the regulation of neuronal survival /165,166/, axonal growth /167, 168/, synaptogenesis /169,170/ and neurotransmission /171/. Neurotrophins induce the survival /172/, development, and function of neurons /173/; are capable of signaling particular cells to survive, differentiate, or grow /174/; and prevent apoptosis and induce the differentiation of progenitor cells. The most studied SNP of the BDNF gene is Val66Met, which is expressed throughout the brain but particularly in the hippocampus where it plays a key role in long-term potentiation and long-term memory. Compared with Val-carriers, Met-BDNF carriers show larger age-related reductions of prefrontal cortical /175/ and amygdala volume /176/, and generally smaller hippocampal and prefrontal volumes independent of age /177/. Additionally, BDNF helps to stimulate and control neurogenesis, which occurs in humans postnatally and in adulthood primarily in the hippocampus and olfactory area. The differences in hippocampal volume between Val and Met carriers could be due to differences in dendritic complexity, fewer neuronal and supporting cells, and increased cell death or decreased neurogenesis during embryologic development or over the lifespan, as BDNF and its receptors can mediate all these processes /178/. For instance, one study of striatum in transgenic mice lacking postnatal BDNF found that both cell soma size and dendritic number and thickness were reduced, and later on, the number of neurons was 35% lower /179/. In adults, variation in BDNF is related to human memory and brain volumes /180/. Yet, how allelic variations in genes coding for neurotrophins affect cognitive abilities through normal variations in brain structure, e.g. how BDNF affects the relationship between memory consolidation and hippocampal structure is largely unknown.

Neuregulin 1: Of possible relevance for the lifespan trajectories of WM is a specific variant of the Neuregulin 1 (NrG1) gene, associated with reduced WM density and anisotropy. As WM development is a very slow process continuing throughout childhood, adolescence and well into adulthood /37,181/, the genes regulating myelin may be very important for cognitive development

and aging. A few cellular studies have related NrG1 to myelination /182/, and some DTI studies exist /183-185/. NrG1 has also been related to reaction time measures in a attention task, which can be interpreted to mean that this gene is related to the capacity for the fast transfer of information in the brain, probably though its effect on myelin/183/.

Genes modulating inflammatory processes: 'Proinflammatory' cytokines affect apoptotic, neurodegenerative and excitotoxic processes, modulate neurotransmitters, and neuroendocrine responses, and have been associated with risk for AD /186/. A few studies have tested the effects on cognitive function in the elderly of polymorphisms within this set of genes—interleukin-1b (IL-1b), tumor necrosis factor alpha (TNF-α), and Interleukin-1b-converting enzyme (ICE)—and relationships to cognitive functions, e.g. memory, speed, and executive function have been found /117/. Nevertheless, we know of no attempt to relate these SNPs to brain structure.

Other genes of established or likely importance for cognitive functions are catecholaminergic genes (e.g. catechol-O-methyl; COMT), serotonergic genes, KIBrA and GrM3 (glutamate receptor, metabotropic), but the significance of these genes for brain structure, or whether they modulate the relationship between changes in brain structure and changes in cognitive abilities in aging, is not known /117/. Also the ancestral allele of one ADrB2 SNP was associated with corpus callosum integrity and cognitive function in aging in one study, in which some evidence that ADrB2 partially mediated cognitive function via corpus callosum splenium integrity was also found /187/. Interestingly, one study found this polymorphism to be inversely related to cognitive abilities in younger and elderly participants /188/, which suggests that the polymorphism is more closely related to individual differences in normal cognitive aging than to lifelong cognitive ability differences /187/.

Although APP (amyloid precursor protein) and Presenelin 1 and 2 (PSEN 1 and PSEN2) have been implicated in familial AD, there does not seem to be evidence linking these to differences in brain structure and cognition in aging /117/.

As seen from the above, relatively scarce evidence exists for the effects of specific SNPs on brain aging. There may be several reasons for the relatively weak gene-brain relationships that have been observed so far. One is that even though a large proportion of our genes are expressed in the brain, to distinguish pure genetic influence from gene × environment interactions is difficult. Thus, such factors as nutrition, physical exercise, cognitive activity, etc may affect brain morphometry and how the brain is affected by aging; individual differences at the level of these factors may be affected by genetic variations. Thus, possibly a substantial amount of the genetic influence on brain structure may be indirect through influence on modulating factors. Second, different brain parameters may be related to different genes. For instance, a recent study of the Vietnam Era Twin Study of Aging (VETSA /189/) sample found that both cortical surface area (0.89) and thickness (0.81) were highly heritable but were essentially unrelated genetically /190/. This finding means that cortical volume, the typical measure in studies of heritability of GM, combines two distinct sources of genetic influences that may confound the underlying genetic architecture of brain structure. For instance, a recent study found that common sequence variations in a region in and around *MECP2* were associated with cortical surface area but not with cortical thickness, were specific to male gender, and were restricted cortical regions (cuneus, fusiform gyrus, pars triangularis) /191/. The finding was replicated across two independent samples, one including participants with psychiatric disorders, the other including patients with Alzheimer's dementia. Third, as highlighted by several authors /118,119/, the effect on brain aging is almost certainly polygenetic, with several genes each accounting for a small proportion of the variance. As mentioned above, interactions between different genes and between genes and environmental factors are likely.

Large samples are needed if better genetic models of brain aging are to be obtained, probably consisting of several thousand participants. Also difficult to ascertain is whether a SNP affects the trajectory of cognitive aging per se, or whether the effect is secondary to a degenerative condition /119/ (see below for a discussion of healthy aging vs. AD). Finally, most studies of the effects of specific SNPs on brain aging are cross-sectional.

Due to the large inter-individual variability in brain morphometry, most likely SNPs affecting the age-trajectories of different brain areas will be much stronger predictors of brain *change* than of brain *differences*. This pattern seems to appear when effects of APOE are studied in cross-sectional vs. longitudinal samples.

DIFFERENCES AND SIMILARITIES BETWEEN THE EFFECTS OF NORMAL AGING VS ALZHEIMER'S DISEASE

One important line of research in the field of AD is the identification of biomarkers than can be used to aid early detection and diagnosis, and to monitor disease progress and possibly the effects of therapeutic trials. AD is associated with a range of structural brain changes that can be measured in vivo /8-12,192,193/. Recently, structural MrI was suggested as a research criterion for AD diagnosis in a consensus paper /194/. Nevertheless, as even healthy aging affects most of the brain, being able to identify brain areas that are affected only in AD and not in healthy aging is not realistic. AD is an age-related disease, and the brain changes in AD are seen on top of the brain changes observed in healthy aging, which makes it difficult to distinguish atrophy that is related to AD from atrophy that is common among the elderly, whether they have AD or not. Thus, a recent line of research has focused on whether the pattern of change across different brain structures can be used to dissociate AD from normal aging. The effects of AD are especially prominent in a medial temporoparietal neural network involved in episodic memory function /195/, which includes the hippocampus /8,10,196, 197/, entorhinal, retrosplenial, posterior cingulate, and precuneus cortices, whereas frontal effects are more moderate in the early stages of the disease /9,192,198-204/. Additionally, in the lateral temporal cortex, especially in the medial and superior temporal gyrus, large effects of AD are seen /9, 192,205,206/. As reviewed above, morphometric brain changes in these areas are also seen in the healthy elderly of advanced age /7,19,32,58,207/, even though at a much smaller scale. For instance, one longitudinal study found an annual atrophy of hippocampus of –0.84% vs. –3.75% in healthy elderly vs AD, and of –0.47% vs. 2.87% for the middle temporal gyrus.

Still, while degeneration of the medial temporo-parietal memory network has been suggested as a signature for AD, change in a frontostriatal network supporting executive functions has been proposed as a hallmark of healthy aging /4,15/. To clarify the question of how unique the effects of AD are, comparisons of the effects of AD with those of healthy aging across several areas and circuits simultaneously have been necessary. A few recent studies have addressed this issue directly. Head and colleagues /15/ found accelerated hippocampal volumetric reductions in mild AD compared with healthy aging. In addition, age-related differences were found to be greater in anterior than in posterior callosal regions, and these differences were not augmented by mild AD. In one study, age-related decline was observed in the volume of the prefrontal cortices, insula, anterior cingulate, superior temporal gyrus, inferior parietal lobes, and precuneus, and AD-patients had additional reductions of volume in the hippo-campal formation and entorhinal cortices /208/.
In one of our own studies, we found that the medial temporoparietal memory network distinguishes AD patients from controls better than the frontostriatal network, whereas the fronto-striatal network distinguishes healthy elderly from young participants better than the medial temporo-parietal network /13/. In Figure 5, millimeter difference in cortical thickness between the patients and healthy elderly are shown, as well as the cortical areas that uniquely distinguished AD patients from healthy elderly, the areas that distinguished healthy elderly from young, and the areas that distinguished both AD from healthy elderly, and healthy elderly from young (overlap).

This result was supported in a later longitudinal study based on the large ADNI (Alzheimer's Disease Neuroimaging Initiative) database. In healthy aging, larger than average atrophy was seen in the frontal cortex as well as the temporal cortex, whereas a larger than average atrophy was seen in the temporal cortex only of AD patients /7/. Similar findings were obtained by Raji and colleagues /14/ who showed that age and AD exerted independent atrophy patterns, but with substantial overlap of effects in hippocampus and entorhinal cortex.

Driscoll, Resnick, and colleagues /107/ analyzed 1017 scans of 138 participants from the Baltimore Longitudinal Study of Aging, followed annually for up to 10 years. The authors concluded that an age-related regional volume loss was apparent and widespread in normal participants, but that MCI was associated with a unique pattern of structural vulnerability reflected in differential volume loss in specific regions. Together, these studies support a view of healthy aging characterized by changes in the fronto-striatal network, whereas AD may be relatively characterized more by changes in the medial temporoparietal circuitry.

An alternative approach was used in another study based on the ADNI database. McEvoy and colleagues /9/ used stepwise linear discriminant analysis to identify regions that best discriminated between healthy controls and Alzheimer patients. The authors then used a classifier trained on these data to determine whether presence of phenotypic AD atrophy at baseline was predictive of clinical decline and structural loss in an independent group of patients with mild cognitive impairment (MCI). They found that atrophy in mesial and lateral temporal, isthmus cingulate, and orbitofrontal areas aided discrimination of controls and Alzheimer patients, with fully cross-validated sensitivity of 83% and specificity of 93%. Further, patients with MCI who had phenotypic AD showed significantly greater one-year clinical decline and structural loss than those who did not, and were more likely to have progression to probable AD. Thus, even though it is not possible to identify a single brain structure that is preserved in healthy aging and atrophic in AD, the pattern of change across structures seems to be different.

Causes of brain changes in aging: molecular and cellular basis

As shown above, the overwhelming evidence from MRI-research indicates age-related volumetric brain changes. Structural MRI, however, tells us less about the molecular underpinnings of the observed morphometric effects. For instance, while thinning of the cerebral cortex is almost linearly related to age 6-7 years of age to old age, the neurobiological foundation of the thinning is likely to be at least partly different in children and elderly. Thus, obtaining a better understanding at the molecular level of the neurobiological mechanisms responsible for the morphometric changes seen would be beneficial. Further, as noted by Esiri, it is interesting and possibly no coincidence that the major age-related neurodegenerative diseases, AD and Parkinson's disease (PD), particularly affect cells that are selectively vulnerable to aging itself—cortical and hippocampal pyramidal cells in the case of AD and pigmented brain stem neurons in PD /209/. Loss of neurons that form long cortico-cortical projections in the association neocortex is probably directly related to AD, but the same circuits that are vulnerable to degeneration in AD are vulnerable to synaptic alterations short of neuron death, likely impacting cognitive function also in normal aging /210/. Thus, this information makes the case that if we want to understand these diseases, then we have to understand the brain changes that occur in normal aging. Further supporting this view are recent studies showing that the CSF levels of Aβ peptides that are related to AD /211/ is just as strongly related to atrophy in the healthy elderly as in patients with MCI or AD /18,212/.

In a recent review, Esiri /209/ highlighted the great demand of neurons for oxidative metabolism in the generation of energy as a key factor in brain aging. A neuron demands an exceptional amount of energy through a lifetime. The transmission of impulses requires ion gradients to be maintained over long stretches of axonal membrane, which is extremely energy consuming. Further, some neurons are very large, which leads to high energy demands related to maintaining a very large surface membrane and transport of molecules and organelles to distant parts of the cell. Oxidative metabolism requires mitochondrial activity, which again will generate oxygen free radicals that have the capacity to damage proteins, nucleic acids, and lipids, and interfere with many aspects of normal cell metabolism and function /209/. Among the consequences are both reduced and increased gene expressions. One study found that genes involved in synaptic plasticity, vesicular transport, and mitochondrial function showed reduced expression after 40 years /213/. This decrease was followed by an induction of the stress response, antioxidant and DNA repair genes. The authors speculated that

DNA damage may reduce the expression of selectively vulnerable genes involved in learning, memory, and neuronal survival, thus initiating a program of brain aging that starts early in adult life /213/.

Rutten and colleagues /214/ suggested that the modulation of the nuclear DNA (nDNA) damage response by eliminating neurons with a high amount of unrepaired nDNA damage in the aging brain may lead to a functional improvement in networks of these neurons and to a better functioning of the aging brain in general. The authors argue that if the nDNA repair mechanisms become insufficient to repair the damage during aging due to decreased repair capacity or to an increased amount of nDNA damage, then nDNA damage will remain unrepaired and will accumulate, possibly resulting in cellular dysfunction. As aging may reduce the apoptotic response to genotoxic stimuli, this deficiency may contribute to increased nDNA damage and mutation with age /215/. Thus, the aging brain may benefit from an age-related loss of neurons, which would otherwise lead to dysfunction /214/. Most likely, a substantial amount of neurons must be lost before clinically detectable functional or cognitive decrements are seen, with a loss of up to 60% of the dopaminergic neurons in the substantia nigra before Parkinson's disease is manifested /216/.

Neuronal loss was earlier believed to be a major factor in volumetric reductions and cognitive decrements in normal aging. Research has demonstrated that hippocampal volume is proportional to the neuronal number /217/, that larger brains generally contain more neurons /218/, and that some studies have identified negative relationships between neuronal number and age in certain brain regions /219/. Nevertheless, it now seems clear that age-related decreases in the number of neurons in the healthy human brain cannot account for the observed reductions in neuroanatomical volumes /20/, with less than a 10% reduction in neuron number from 20 to 90 years of age typically being seen. In addition, contrary to the hypothesis that neuronal death in aging causes age-related changes in cognitive function, studies of memory in rats have suggested that age-related cognitive decline occurs in the absence of significant neuron death in any major, cytoarchitectonically defined component of the hippocampal system /220/. The evidence indicates that this decline is likely to be true for cerebral cortex as well. Terry and colleagues /221/ found age-related decrements in brain weight, thickness of certain cortical regions, the neuron-glia ratio midfrontally and inferior parietally, and a shrinkage of large neurons, but concluded that neuronal density was relatively unchanged. The authors found that the most salient change was shrinkage of the large neurons with a consequent increasing numbers of small neurons, i.e. constant neural density coupled with diminished cortical volume. In a review paper, Peters and colleagues /222/ conclude that no strong evidence was found to support the concept that significant numbers of neurons are lost during normal aging from the human cerebral cortex while keeping open the possibility that regional losses of neurons from one architectonic area or cortical layer with age are possible. Presently however, no strong case has shown that (1) the neuroanatomical volumes reductions in normal aging are caused by loss of neurons, or that (2) if loss of neurons occurs in specific regions, this deficit causes cognitive decrements. A recent study showed cortical thinning in the frontal and temporal neocortex, despite relatively constant neuronal count numbers across a 50 year age-range /223/. Other studies have reported that glial cells were not significantly reduced in number either /224/.

The question of neuronal loss has been difficult to settle, but as reviewed above, agreement has been greater that neuron size decrease modestly with age, especially in the neocortex /209/ and hippocampus /225/. Neuron size likely reflects dendritic and axonal aborization of the cell. More extensive cells require more energy, more protein synthesis etc, which again will require a larger cell body to support these processes /209/. In line with this, an overall decrease in synaptic density is observed with age, with a special focus on dendritic spines in the cerebral cortex /209/. For instance, significant reductions in dendritic neuropil and an almost 50% reduction in spine number and density have been reported in humans above 50 years of age /226/. Still, dendritic values were found to be relatively stable after 40 years of age, and the authors suggested that dendritic and spine degeneration in the elderly may not be an inevitable

consequence of the aging process /226/. Still, dendritic degeneration may be a major factor causing the volumetric brain reductions seen in both autopsy and MR-studies. Freeman and colleagues /223/ recently provided evidence for this view and suggested that a loss of neuronal and dendritic architecture, rather than a loss of neurons, underlies neocortical volume loss with increasing age in the absence of AD. A series of studies by Small and colleagues /227/ have also shown that normal aging vs. AD likely affect specific cells in specific brain regions. The authors ague that entorhinal cortex is especially vulnerable in AD, while normal aging primarily targets the granule cells of the dendate gyrus.

Studies of dendritic trees have also revealed some indications of neuronal plasticity in aging. For instance, one study found some compensatory increases in the branching pattern in a subset of the dendrites in parahippocampal gyrus in response to the loss of other dendrites /228/ and suggested a model in which the aging cortex contains both regressing dying neurons and surviving growing neurons. The same groups of researchers later refined the picture by replicating the findings of increased dendritic extent in the dendate gyrus granule cells between middle age and early old age /229/. In the oldest old (nineties), however, dendritic regression was found, indicating some degree of regional specificity.

As described above, WM is known from morphometric studies to exhibit a pattern of protracted growth until middle adulthood, before accelerating decline is seen in the latter half of the lifespan. Histologic studies in general support the morphometric findings and provide insight into the neurobiological correlates to the morphometric reductions. Postmortem studies of humans and primates have confirmed WM loss /230/ and myelin breakdown in normal aging with loss and shrinkage of myelinated fibers /231-235/. For instance, one study found the total myelinated fiber length in males to be 176.000 km at the age of 20 years, and 97.200 km at the age of 80 years, with corresponding length for females being 149.000 and 82.000 km /231/. Similar findings were obtained in independent studies /224/. Thus, myelinated fibers seem to be extensively affected by normal aging processes. Still, a simple relationship between degeneration of myelin and WM atrophy in aging has not been definitively established /232,236/. Among complicating factors are redundant myelination, sometimes observed with higher age /232/. The same may be true for fluid bubbles in the myelin sheet, which also have been observed with age /236/. Further, we should bear in mind that even though WM consists of myelinated fibers, the fibers are of different types depending on the neurons of origin, of different axon diameters, and are affected by age to different degrees. Axons that are myelinated later in life often have smaller diameters and seem more vulnerable to age changes /231,235,237/. Further, a large part of WM consists of glial cells, i.e. oligodendrocytes and astrocytes, which may be differentially affected by age /238/. Thus, many features of WM are not directly related to myelin and may be related to the morphometric age-reductions seen. Still, there seems to be a consensus that myelin break-down is an aspect of healthy aging, and that this breakdown contributes to the loss of WM volume detected in morphometric MRI-based in vivo studies.

CONSEQUENCES: EFFECTS OF BRAIN CHANGES ON COGNITIVE FUNCTION

As reviewed above, little doubt remains that the brain undergoes substantial structural changes during healthy aging, and that a regionally heterogenous pattern is seen, with different structures affected to different degrees. Further, although much more research is definitely needed, we also have some knowledge about the neurobiological underpinnings of the macro-structural changes. The last topic of this review is the question of to what degree the brain changes seen lead to altered cognitive performance. The causality embedded in this question is of course very hard to isolate, but much effort has been made to pinpoint how the age-cognition relationship may be explained by age-related morphometric changes. Most researchers agree that normal aging is associated with reduced cognitive abilities within several domains, especially mental speed, episodic memory function, executive and flexible cognition, and non-verbal problem solving. As the volume and thickness of the frontal

cortex decline with age—and this area is known to support executive functions and flexible cognition—it is tempting to speculate that the former is responsible for the latter. Likewise, there are moderate morphometric changes in the hippocampus and medial temporal cortex, and moderate reductions in episodic memory.

In research, the general hypothesis of reduced regional brain volume causing reductions in specific cognitive abilities is often framed as "*brain structure X mediates the relationship between cognitive function Y and age*". Nevertheless, what is very often reported is a correlation between brain structure X and cognitive function Y, with or without age included as a covariate. A significant correlation between brain structure and cognitive function without controlling for age is the first step to yield support for the general claim of structural changes mediating cognitive changes. Yet, we must bear in mind that if both brain structure and cognition are expected to correlate with age, a relationship between the two would not be surprising, and neither would a correlation between either of the two and hair loss. If the correlation is significant when effect of age is statistically accounted for, then this is interesting because it indicates a relationship between structural properties of the brain and cognitive function. However, such a result does not tell us anything about the role played by aging. If the brain structure and the cognitive function are both highly correlated with age, then regressing out the shared variance with age may even leave them uncorrelated. In our opinion, the most important question regards how likely it is that age-related structural brain changes play a causal role in age-related cognitive changes. Indirectly, this statement can be framed as the question of to what extent age-related variability in cognitive abilities is shared with age-related variability in brain structure.

Although a plethora of studies have looked at the relationships between brain structure and cognitive performance in aging, few have addressed the question in this way. Madden and colleagues /239/, in a review paper on the role of WM integrity in cognitive aging, argued that to justify that structural brain changes may cause cognitive changes, three conditions should be considered: (1) A test of the age-related difference in the relation between the WM and cognitive measures (2) the WM measures should have a significant relation to the measures of cognition that is independent of age, and (3) the age-related variance in the cognitive measure should be attenuated by including the WM measures in the regression model predicting cognition from age. Madden and colleagues argue that individual studies have addressed a variety of different, although related issues that do not always map directly onto the fundamental question of the possible causal role of WM changes as observed with DTI on cognitive performance in aging. We suggest that the same, to a substantial degree, is true for morphometric studies of both cortical and subcortical structures. Still, there are several notable exceptions. In this review, we focus on studies that have tried to answer the question of what causal role brain changes in aging may play for the observed cognitive decrements, and not studies that only have shown that a relationship between brain structures and cognitive performance exists with or without the influence of age statistically controlled for.

A moderate relationship between gross measures of cognitive functions (e.g. IQ) and gross measures of brain volume (e.g. total brain volume) is established, with correlations typically around 40 /240,241/. As previously argued, this relationship seems to be mainly of genetic origin /115/. Yet, positive correlations between specific cognitive functions, e.g. episodic memory and executive functions, and the morphometric characteristics of specific brain areas, e.g. hippocampus/temporal lobe and prefrontal cortex, have been more difficult to establish /242-246/. Still, several recent studies have found relation-ships between, for instance, episodic verbal memory and brain structures implied in the temporoparietal memory network /247-249/, recall and hippocampus, recognition and entorhinal cortex /250/, and between different brain areas and speed of processing /251, 252/, executive functions /251,253,254/ and attention /252/. Studies identifying brain structure-cognition relationships may serve as an indication that the changes in brain structure in healthy aging can contribute toward explaining the decrements in cognitive performance. However, if cognitive decrements to some extent are related to structural

reductions in aging, then it is possible that the relationships gradually will be stronger with advanced age, or that some relationships with cognitive function will be found only in aging. Such a view is advocated by Cyma van Petten /242/, who coined it '*the neuropsychological perspective*', according to which volume decreases due to normal aging or disease, are accompanied by memory decline, whereas brain structure-cognition correlations are not necessarily found among young participants. One study found that elderly persons with high performance abilities (Wechsler' Abbreviated Scale of Intelligence, performance score /255/) had a thicker cortex than that of the elderly with average performance scores /256/. No corresponding group differences were identified in the young. The observed effects were ascribed to age-related brain changes being different in higher vs. average functioning participants, and were likely not only due to characteristics that are observable early in life.

Naftali Raz and colleagues /257-260/ published a series of studies using path analysis to test the role of brain morphometry in mediating age-related cognitive changes. In one study, the prefrontal volume was found to account for 25% of the age-associated variance in perseveration, while frontal WM hypointensities accounted for 49% /257/. Also, age showed an initial correlation of –.28 with working memory, which dropped to –.20 when neuroanatomical variance was accounted for. Thus, this study directly addressed the question of how much of the age-related decline in cognition that could be accounted for by morphometric differences. With a similar approach, the same group showed that age-related deficits in working memory were mediated by decreased prefrontal volume, that smaller prefrontal cortical volume increased perseveration indirectly through working memory /258/, and that neural and cognitive factors completely mediated age differences in episodic memory /259/ and perceptual skill learning /260/. Thus, this series of studies demonstrate that structural brain characteristics can explain a substantial proportion of the age-related decline in a wide range of cognitive abilities, and that a certain functional anatomical specificity exists, in that specific cognitive abilities are related to specific brain areas. Along similar lines, Kochunov and colleagues /261/ found that structural brain measures fully captured age-related variability in executive function. As the neuro-anatomical variables in all these studies were measured on a region of interest basis, the authors could not test for brain-cognition relationships outside the few selected regions. Bartzokis and colleagues /262/ provided evidence for a relationship between transverse relaxation rates (R2) of frontal lobe WM and finger tapping speed in aging. The two measures correlated .45 in an adult lifespan sample. Most convincingly, however, the two measures showed almost indistinguishable quadratic age-trajectories, with peaks at 39 years in both cases. The authors argued that speed of movement requires high-frequency action potential bursts and is associated with myelin integrity. Thus, they speculated that because myelination is quadratically related to age, this may be the neural substrate for similar trajectories of transverse relaxation rates and cognitive processing speed.

The studies reviewed above are cross-sectional. Cardenas and colleagues /263/ showed that baseline morphometry predict longitudinal decline in neuropsychological performance, i.e. left entorhinal cortex and cerebellum predict a longitudinal decline in memory, left anterior temporal white matter and cerebellum predict object naming abilities, and frontal WM and cerebellum predict longitudinal changes in executive functions. Rabbitt and colleagues /264/ showed that baseline levels of CSF, interpreted as a proxy for life-long brain atrophy, predict decline over the previous 8-20 years on speed and marginally of WAIS, but not on three different tests of memory.

Very few longitudinal studies exist that relate atrophy rates as measured by brain scans at at least two time points, to changes in cognitive function over time. One exception is a study published by Rodrigue and Raz /265/, who found that a greater annual rate of shrinkage of entorhinal cortex, but not hippocampus and prefrontal cortex, was related to poorer memory performance. Another study found greater reduction of hippocampal volume over time in elderly persons with declining episodic memory compared with those with stable memory performance /266/.

A substantial amount of research has focused on functional brain changes in aging, e.g. differences

between young and elderly in cognitive activation patterns measured with functional MRI (fMRI), positron emission tomography (PET), or electrophysiological recordings (EEG/ERP) /267-269/. These studies showed changes in activation patterns between young and elderly participants, and between participants of different cognitive abilities. For instance, Cabeza and colleagues /268/ found that the high-functioning elderly recruited bilateral brain areas in a retrieval task, whereas the lower functioning elderly showed a more asymmetrical pattern that was more similar to that of young participants. Such findings have lead to the idea that age-related changes are more functionally than structurally based /249/. Still, most researchers would probably agree that changes in activation patterns between younger and elderly participants are rooted in structural brain changes, even though such changes may be subtle. Cabeza and colleagues /249/ and Logan and colleagues /270/ suggest that age-related activation changes have a neurogenic origin, i.e. that they are associated with physiological age-related brain changes. Possibly these changes are not detectable by structural MR scans even though several studies have shown that structural and functional changes often accompany each other in aging /266,271/.

THE IMPACT OF WHITE MATTER AGING ON COGNITIVE FUNCTION

Due to the modular nature of the human brain, so to speak, all cognitive tasks require the integration of information from relatively distant brain areas. Most likely, inter-individual variation in the integrity of the myelinated long-distance axonal projection fibers that constitute the major part of the brain's WM is related to cognitive abilities. DTI studies have shown that the micro-structural properties of WM are continuously developing and changing throughout the entire lifespan /37,38,44,99/, which necessitates a thorough examination of the possible role of WM microstructural changes in cognitive aging. The basic processing speed has long been known to decline with aging, with reductions starting in the twenties or thirties. Because processing speed is important for performance of most cognitive tasks, this decrease has even been proposed as a fundamental mechanism behind cognitive decline in healthy aging /2/. One cause of this age-related slowing is likely to be WM integrity, which is correlated with reaction time measures in both young and elderly participants /272/. The hypothesis of disconnection in aging has been proposed to accommodate such findings /65,237,239,273/, according to which cognitive decline in aging is related to decreased efficiency in communication between different brain areas, in a sense leading to a disconnection problem. In a review published in December 2009, Madden and colleagues /239/ stated,

> *"The integrity of cerebral white matter is critical for efficient cognitive functioning, but little is known regarding the role of white matter integrity in age-related differences in cognition"* (p 415).

Kennedy and Raz /96/ note that many discrepancies are found in the literature on WM-cognition effects in aging, and propose several possible explanations, including differences in methods of measurement, e.g. whole brain voxel-wise analyses, use of large ROIs, or localized and specific, sometimes fiber-tract specific, regional measures. Further, selection of cognitive measures also varies widely across studies and is often limited to single global measures differences in sample composition exist, and substantial differences between studies exist regarding the definition of what constitutes a healthy older adult /96/.

In their recent review, Madden and colleagues /239/ conclude that independent of age, variation in WM integrity is correlated with cognitive performance, particularly in tests relying on speed of information processing and executive functioning. An important question regards how specific are the cognition-WM effects. Given that the individual differences in WM microstructure are related to cognition due to the role of WM in enabling speeded and efficient transfer of information between distant brain structures one could expect the effects on cognitive performance to be general and unspecific. Madden and colleagues argue that even though the general trend of DTI studies suggests that WM integrity is related to processing speed and executive functioning, whether age-related differences in these aspects of cognitive

functioning can be fully separated at the behavioral level is not clear. If age-related differences in executive abilities are partly independent from age-related decrements in speed of processing, this would fit with the suggested anterior-posterior gradient in WM aging /87,88/. Speed of processing and executive functioning share substantial age-variance /274/ but give independent contributions to the variance in fluid intelligence in elderly /59/. Madden and colleagues /239/ argue that interpreting age-related variation in WM integrity in terms of the anterior-posterior gradient and executive functioning may be a useful starting point, but that this approach is unlikely to account for all results.

Kennedy and Raz /96/ have argued that age-related differences in executive functions do not depend only upon intact prefrontal WM, but rather reflect the integrity of a widely distributed network of connections, including fronto-parietal and cerebellar connections. Based on these premises, the authors suggest that the term "*associative regional aging*" may be more appropriate than "*frontal aging*", and that,

> *"If maintenance of optimal cognitive performance in older adults depends upon compensatory "rerouting" of the information flow, then such a process is significantly jeopardized by reduced anisotropy and increased diffusivity in these regions (p. 925)".*

In their study, Kennedy and Raz found multiple dissociations among specific age-sensitive cognitive skills and the regional relationships with WM integrity, i.e. relationships between age-related degradation in anterior brain areas and processing speed and working memory, decline in posterior areas and inhibition and task switching costs, and central WM regions and episodic memory. Still, widely distributed pathways were involved, and reduced integrity of these in aging is likely to have wide-reaching effects on cognitive performance.

As emphasized by Madden and colleagues /275/ in their review paper, an important question independent of that related to identifying age-cognition relationships per se regards whether interactive effects occur in aging-white matter and cognition-white matter relationships. Few studies have addressed this issue directly, but the evidence for the role of WM in mediating age-related decrements in cognition is starting to emerge. Madden and colleagues found that the age-related variance in a response-time derived measure (drift rate) is substantially attenuated by individual differences in FA in frontoparietal WM pathways. Gold and colleagues /276/ observed that FA of the left superior longitudinal fasciculus mediates age-related variance in task switching. Zahr and colleagues /277/ found that diffusion properties of the genu and fornix mediate the age-related changes in working memory, motor performance, and problem solving, whereas the age-related differences in motor performance are influenced by several pathways, including splenium and uncinate fasciculus. Additionally, Charlton and colleagues /278/ provided evidence for the view that WM diffusion properties mediate age-related changes in cognition. Thus, although the number of studies to date is not substantial, evidence is accumulating supporting the role of WM microstructure in cognitive age-changes. More studies are needed, however, especially on the relationships between WM microstructure and morphometry, e.g. cortical thickness, in explaining age-related changes in cognition.

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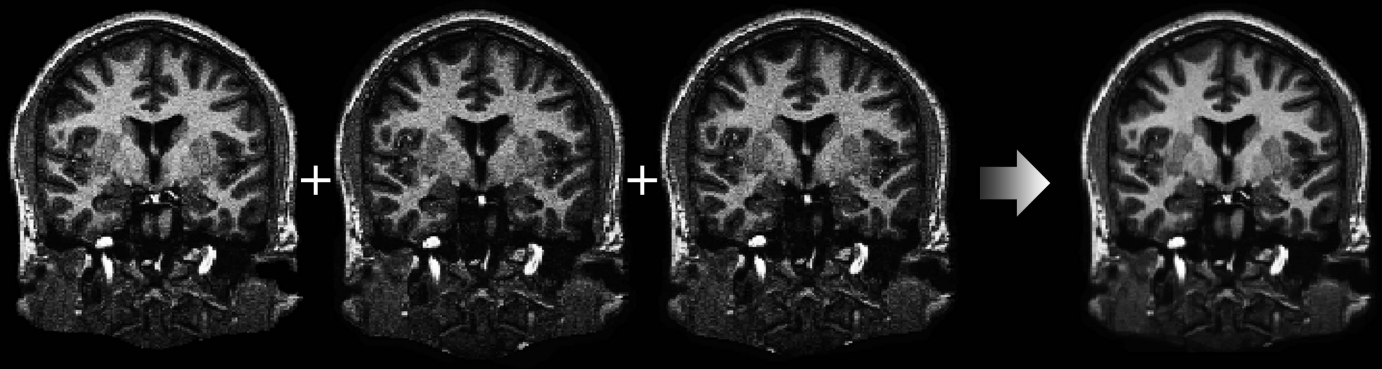
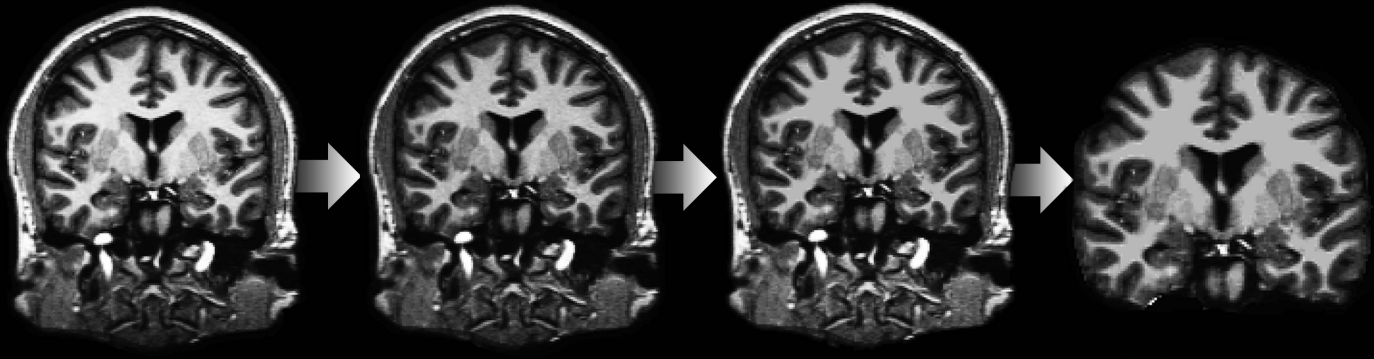


2 or more T1 weighted volumes are motioncorrected to increase the contrast-to-noise ratioa

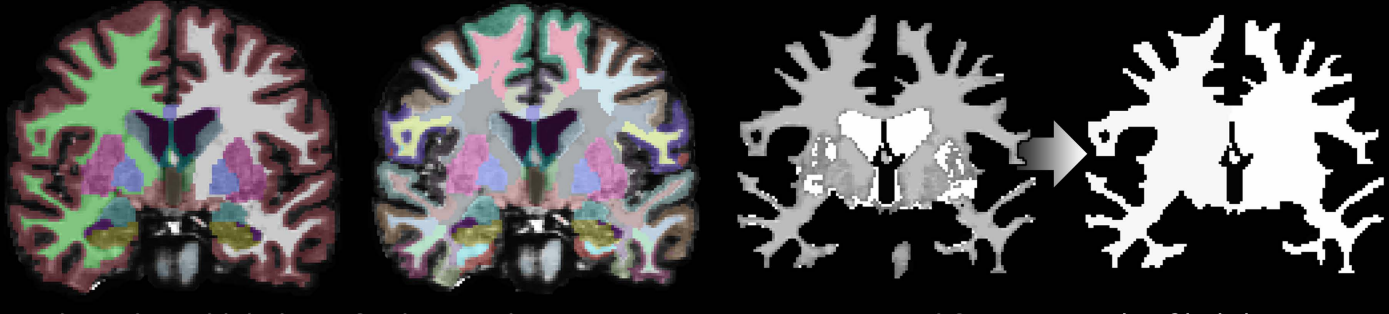
Motioncorrected volume



Converted to 1mm^3, 256^3

Talirach registration and intensity normalization

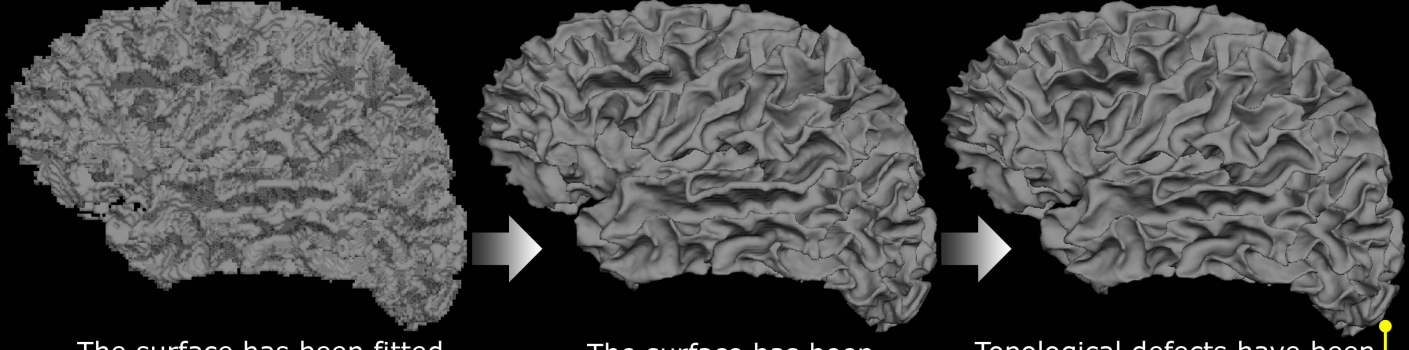
Skull and dura is stripped off



Volume based labeling of subcortical structures, grey matter and white matter.

WM separated from everything else

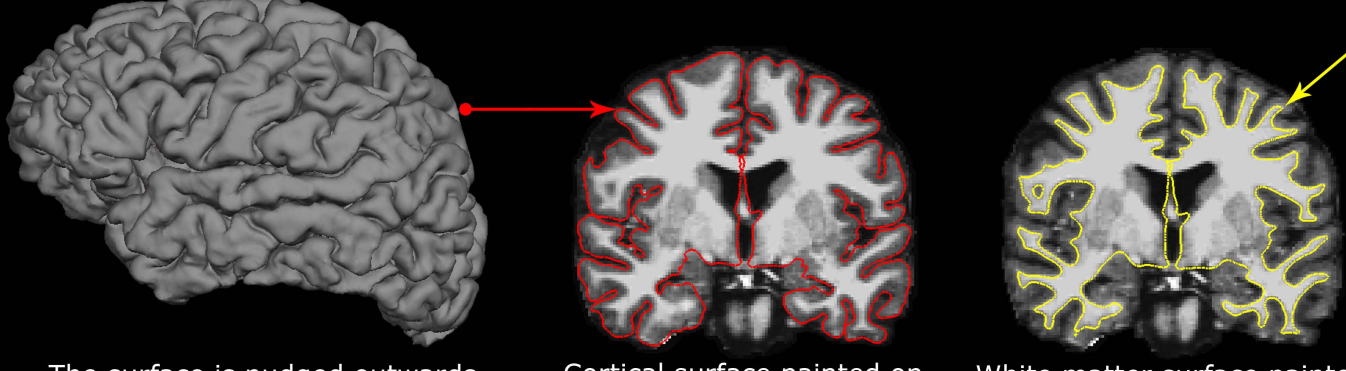
Holes filed, brainstem and islands removed



The surface has been fitted to the filled volume

The surface has been smoothed

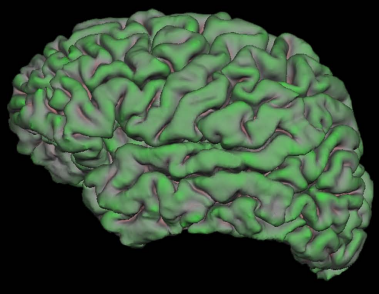
Topological defects have been fixed. This surface represents the wm/gm boundary



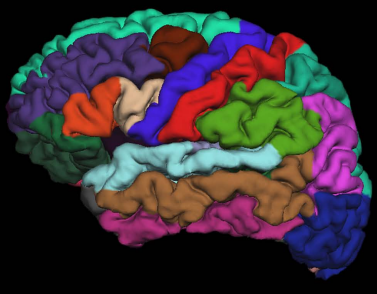
The surface is nudged outwards following T1 intensity gradients, creating the cortical surface

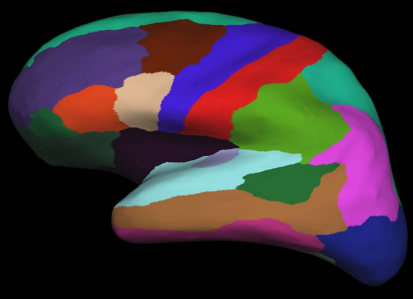
Cortical surface painted on the skullstripped volume

White matter surface painted on the skullstripped volume



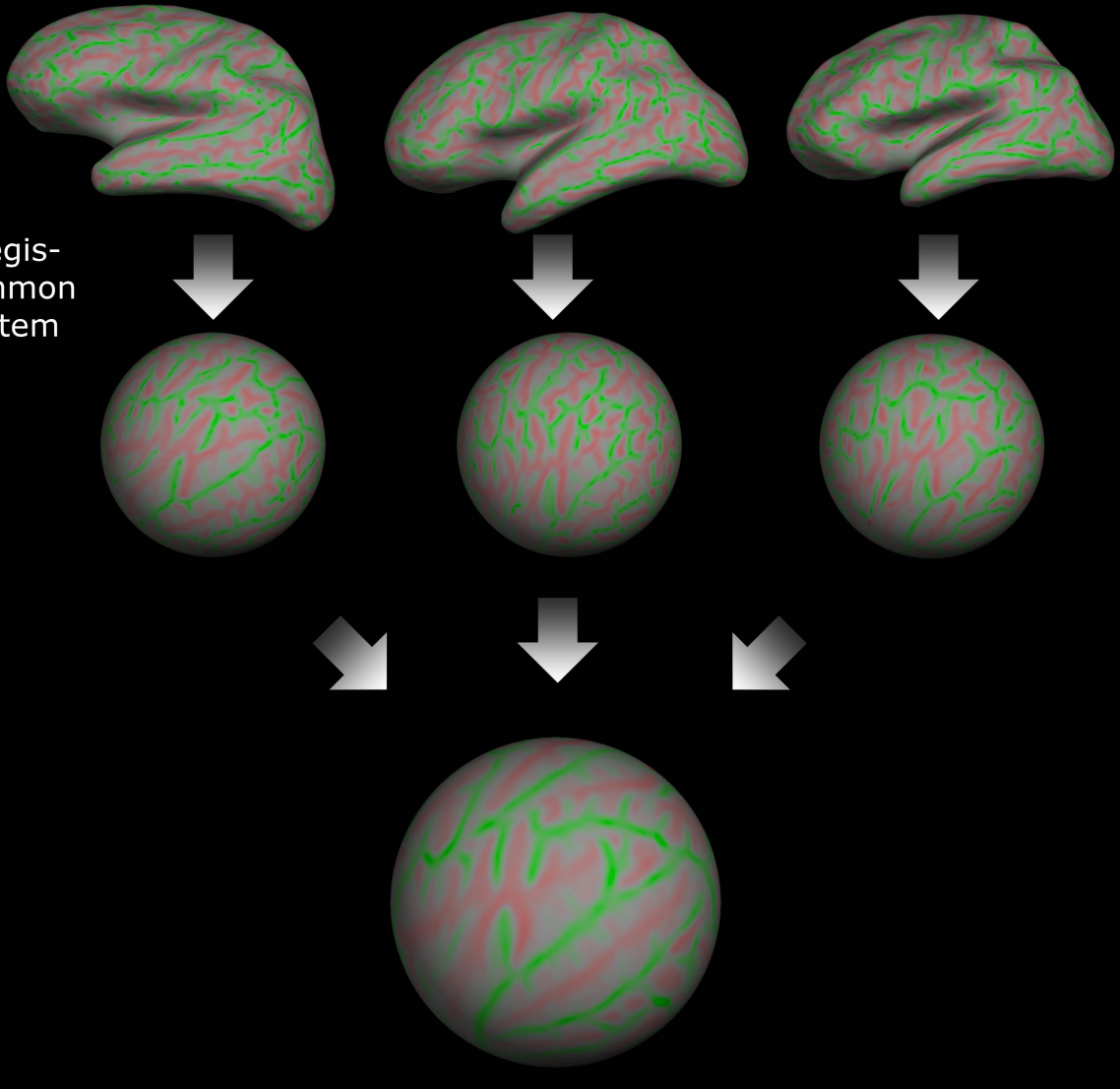
Curvature map. Gyri in green, sulci in red.

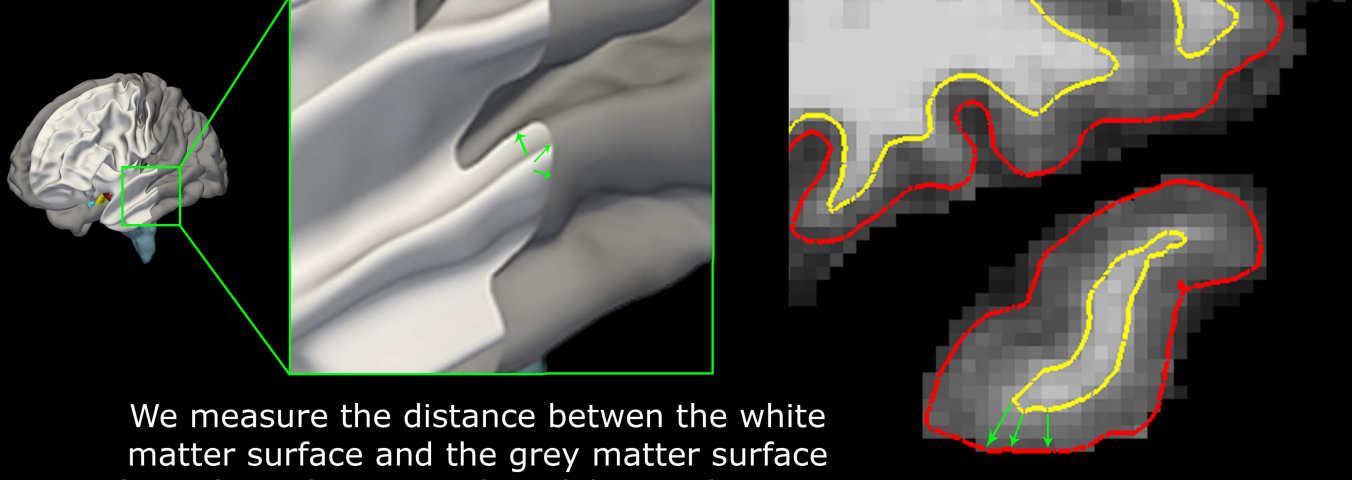




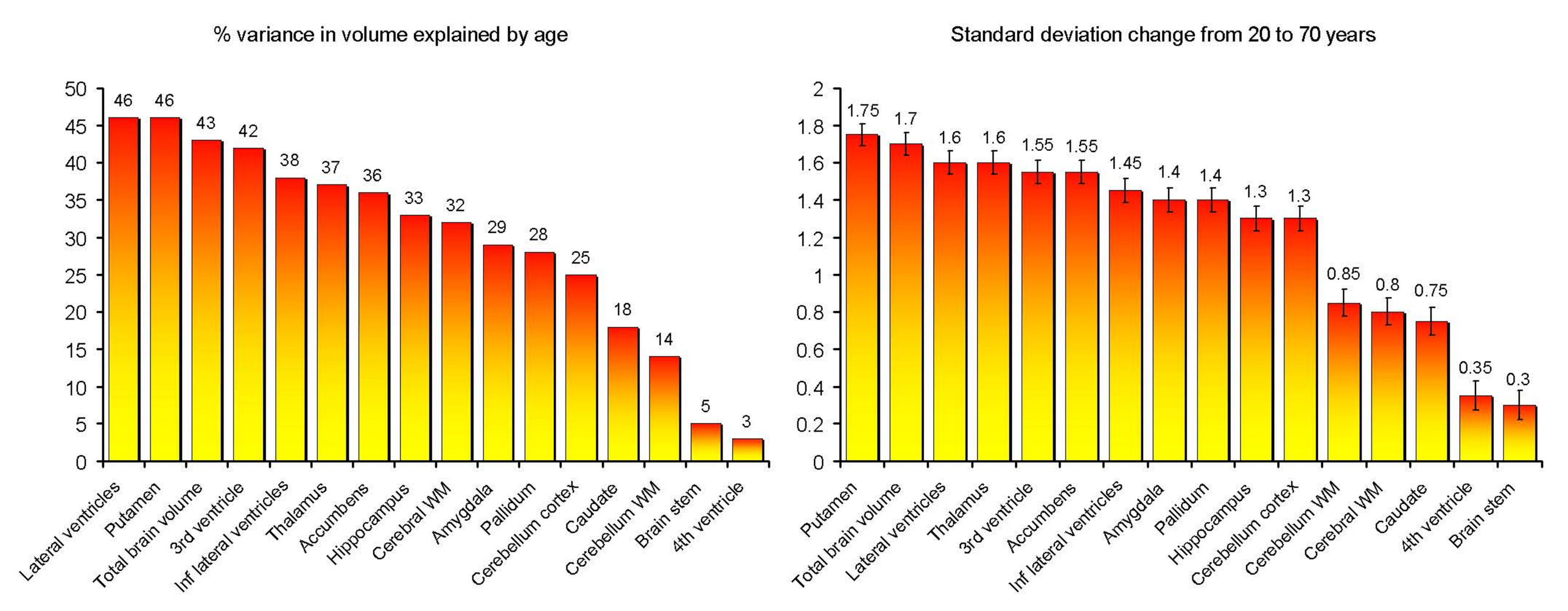
Cortical parcellations mapped to individual through spherical registration, shown on the pial surface, and on the inflated wm-surface

Intersubject registration to a common coordinate system

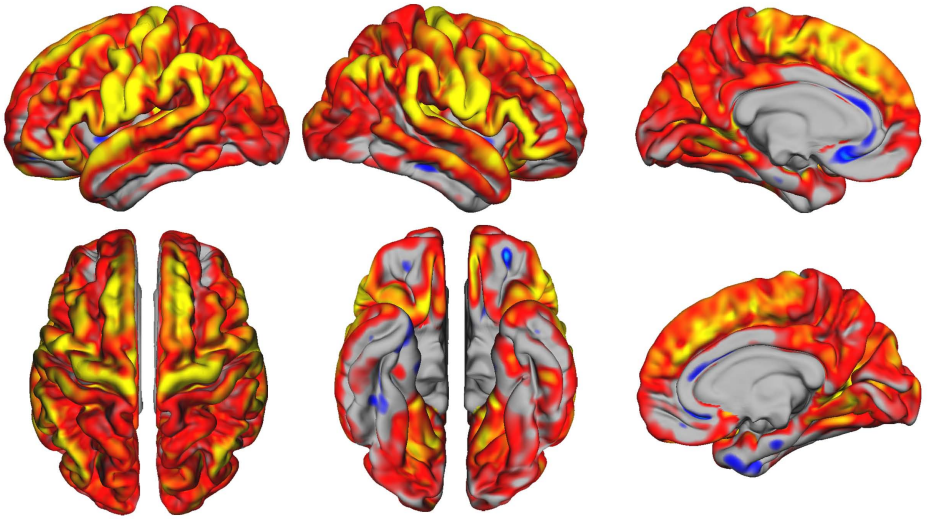




We measure the distance betwen the white matter surface and the grey matter surface from the 3 dimensional model at each vertex


% variance in volume explained by age
50
45
40
35
30
25
20
15
10
5
0
46
46
43
42
38
37
36
33
32
29
28
25
18
14
5
3
Lateral ventricles
Putamen
Total brain volume
3rd ventricle
Inf lateral ventricles
Thalamus
Accumbens
Hippocampus
Cerebral WM
Amygdala
Pallidum
Cerebellum cortex
Caudate
Cerebellum WM
Brain stem
4th ventricle
Standard deviation change from 20 to 70 years
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.75
1.7
1.6
1.6
1.55
1.55
1.45
1.4
1.4
1.3
1.3
0.85
0.8
0.75
0.35
0.3
Putamen
Total brain volume
Lateral ventricles
Thalamus
3rd ventricle
Accumbens
Inf lateral ventricles
Amygdala
Pallidum
Hippocampus
Cerebellum cortex
Cerebellum WM
Cerebral WM
Caudate
4th ventricle
Brain stem

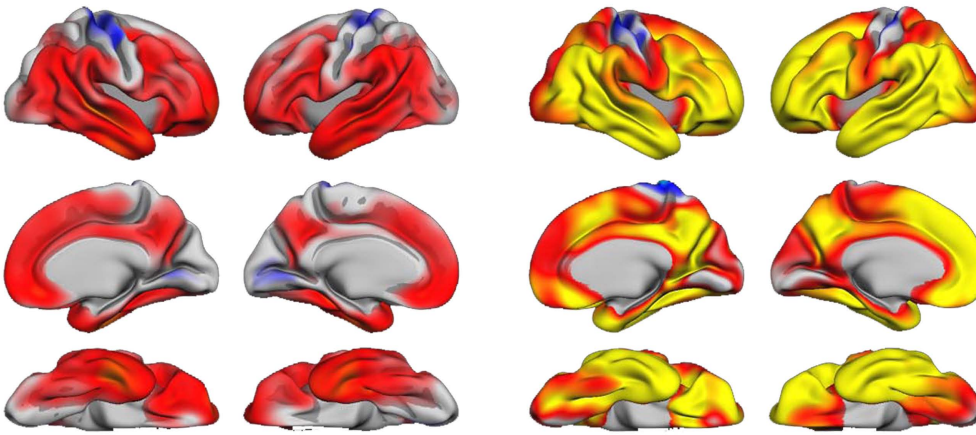
Changes in cortical thickness per decade estimated cross-sectionally



Longitudinal changes in cortical thickness

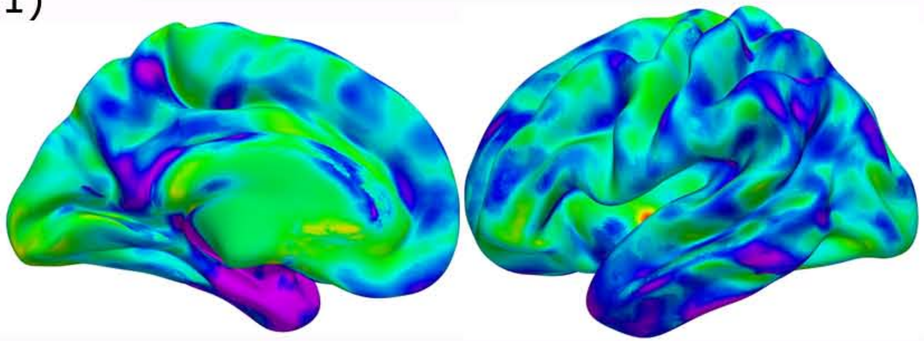
One year

Two years



Cortical thickness in Alzheimer's patients vs. healthy elderly

(1)



Unique cortical predictors of Alzheimer's and normal aging

(2)