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Differential aging of the brain: Patterns, cognitive correlates and modifiers

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Abstract

Deciphering the secret of successful aging depends on understanding the patterns and biological underpinnings of cognitive and behavioral changes throughout adulthood. That task is inseparable from comprehending the workings of the brain, the physical substrate of behavior. In this review, we summarize the extant literature on age-related differences and changes in brain structure, including postmortem and noninvasive magnetic resonance imaging (MRI) studies. Among the latter, we survey the evidence from volumetry, diffusion-tensor imaging, and evaluations of white matter hyperintensities (WMH). Further, we review the attempts to elucidate the mechanisms of age-related structural changes by measuring metabolic markers of aging through magnetic resonance spectroscopy (MRS). We discuss the putative links between the pattern of brain aging and the pattern of cognitive decline and stability. We then present examples of activities and conditions (hypertension, hormone deficiency, aerobic fitness) that may influence the course of normal aging in a positive or negative fashion. Lastly, we speculate on several proposed mechanisms of differential brain aging, including neurotransmitter systems, stress and corticosteroids, microvascular changes, calcium homeostasis, and demyelination.

Keywords

MRI; Brain; Cognitive aging; Longitudinal; Volumetric; White matter; Vascular risk; Hypertension

1. Inroduction

For the gods alone there comes no old age, nay nor even death;

but all other things are confounded by all-mastering time ... (Sophocles, Oedipus at Colonus, 607).

Aging—a biological companion of time—spares no organ or system, and in due course affects everything, from cell to thought. However, the pace of aging varies among individual organisms, organs and systems, and the very existence of such variability merits some measure of hope. If the positive extreme of healthy aging can be made more prevalent and if

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its worst and most negative expressions can be delayed if not completely eliminated, the viable and enjoyable segment of the lifespan can be prolonged into the later decades of lifespan. In other words, successful aging (Rowe and Kahn, 1987) enjoyed by relatively few may become the norm. To succeed in promoting such a shift, we ought to understand how successful aging is expressed in the structure, physiology and behavior of the organisms and their systems, among which arguably the brain is one of the (if not *the)* most important. In this review, we summarize the extant literature on age-related differences and changes in the brain as well as on their potential cellular underpinnings. We also discuss the putative links between the pattern of brain aging and the pattern of cognitive decline and stability. Finally, we discuss examples of activities and conditions that may influence the normal aging trajectory in a positive or negative fashion.

2. Postmortem studies

Postmortem (PM) studies of individuals within the adult age span reveal panoply of age-related differences in brain structure. The gross differences include reduced brain weight and volume, ventriculomegaly and sulcal expansion (Kemper, 1994; Skullerud, 1985). Microscopic studies documented myelin pallor (Kemper, 1994), loss of neuronal bodies in the neocortex (Pakkenberg and Gundersen, 1997), the hippocampus (Simic et al., 1997) and the cerebellum (Ellis, 1920; Nairn et al., 1989), loss of myelinated fibers across the subcortical cerebrum (Pakkenberg and Gundersen, 1997; Mamer et al., 2003; Meier-Ruge et al., 1992), shrinkage and dysmorphology of neurons (Haug, 1985), accumulation of lipofuscin (Terman and Brunk, 1998), rarefication of cerebral vasculature (Riddle et al., 2003), reduction in synaptic density (Morrison and Hof, 1997), deafferentation (Bertoni-Fred-dari et al., 2002), loss of dendritic spines (Jacobs et al.,1997), cumulative mitochondrial damage (Brunk and Terman, 2002), reduction in DNA repair ability, and failure to remove neurons with damaged nuclear DNA (Rutten et al., 2003). In nonhuman primates, no significant loss of neuronal bodies was found (Peters et al., 1998) but substantial loss and deformation of the myelin sheath was observed (Peters and Sethares, 2002). Some of the effects of aging on the brain are global and affect the central nervous system as a whole, but in many cases, age-related differences are highly circumscribed and confined to specific regions and laminae (Uylings and de Brabander,2002). The latter study is illustrative of the main strength of PM investigations: anatomic precision that permits interrogation of the brain at its most detailed level. By default, PM literature is limited to cross-sectional inquiries into the remains of persons whose medical and behavioral history is skimpy and whose concurrent assessment cannot be accomplished. Thus, considerably more global in vivo examinations of the living brain have added significant new information about structural and functional neuroanatomy of living people.

3. Cross-sectional volumetric studies in vivo

3.1. Regional brain volume, density and cortical thickness

In vivo volumetry of the healthy aging brain has been conducted since the advent of magnetic resonance imaging (MRI) almost 20 years ago. Summarizing the results of these two decades or research is a challenging task, for variability among the studies is significant

and not easily interpretable. Nonetheless, a general trend that emerges from this literature (for detailed reviews and tabulation of relevant studies see Raz (2000, 2004)) suggests that the prefrontal cortices are more significantly affected than the rest of the neocortical regions (median correlation of volume with age $r = -0.56$), whereas the correlations of temporal volumes with age suggest more moderate declines (median $r = -0.37$), with even smaller differences in parietal ($r = -0.20$), and occipital ($r = -0.19$) cortices (Raz, 2004). In addition, the hippocampal volume shows moderately negative association with age, as do the amygdala, the cerebellum and the neostriatum (median correlations ranging between −0.30 and −0.43). Little age-related differences have been observed in the globus pallidus ($r = -0.20$) and the thalamus ($r = -0.28$), although the reports on the latter are highly discrepant (from Raz (2004) with addition of Walhovd et al. (2005)). The ventral pons consistently appears insensitive to aging (median $r = 0.07$, Raz, 2004).

Recently, a semi-automated approach to study of structural integrity of the brain—voxel-based morphometry (VBM)—has been gaining popularity. In that method, signal intensity in every voxel of the acquired brain volume is used to gauge regional variations in structural properties of the imaged tissue. The index of integrity derived from this approach is local tissue “density”. Reduction in density estimated by this method is deemed to indicate atrophy. Although in general, VBM studies (e.g., Good et al., 2001; Tisserand et al., 2002) confirm the pattern of findings observed in volumetric studies, there are some noteworthy discrepancies. For example, prominent age effects on the anterior cingulate cortex (Good et al., 2001; Tisserand et al., 2002) and prominent striate cortex atrophy (Tisserand et al., 2002) reported in VBM investigations are not reported in the volumetric literature. A recent cross-sectional study of cortical thickness conducted with semiautomated voxel-based methods (Salat et al., 2004) confirmed some of the volumetric findings (age-related decline in the prefrontal regions) but produced contradicting results as well (significant thinning of the perical-carine and the primary motor cortices). A study of more than 600 healthy older adults has also revealed a less focused pattern of shrinkage than suggested by the volumetric literature, with association as well as some primary cortices affected by age (Lamaitre et al., 2005). However, measurements of sulcal morphology in 14 brain regions found that sulcal width increases and sulcal depth decreases with age, especially in cortical areas dedicated to multimodal processing (Kochunov et al., 2005). In light of accumulating evidence of the anterior posterior gradient of brain changes being associated with vascular disease rather than aging (Artero et al., 2004; Raz et al., Submitted), inclusion of participants with occult vascular disease may explain some of the discrepancies among the studies.

3.2. Age-related differences in micro structure of the white matter

While the gross white matter volume remains relatively stable across most of adulthood, significant age-related differences in its microstructure have been observed (Kemper, 1994; Rees, 1976). On T2-weighted MRI scans, multiple hyperintense inclusions in the white matter (white matter hyperintensities, WMH) are evident even in asymptomatic older adults. Neuropathological underpinnings of WMH are diverse and include myelin pallor, gliosis, atrophy of the neuropil, and breakdown of the subependymal ventricular lining (De Leeuw et al., 2001). Other reasons for WMH formation include a reduction in cerebral perfusion coupled with greater vulnerability of the border zones (Brant-Zawadzki et al., 1987), and

subclinical ischemia (Pantoni et al., 1996). Age is the most robust predictor of WMH, but risk factors for cerebrovascular disease such as a hypertension, history of transient ischemic attacks, carotid atherosclerosis, collagenous thickening of cerebral veins, decreased cortical blood vessel density, and various blood circulating markers of small vessel disease are also associated with increased WMH burden (De Leeuw et al., 2001; Brown et al., 2002; Kidwell et al., 2001; Markus et al., 2005; Moody et al., 2004; Pico et al., 2002). Notably, anti-hypertensive treatment decreases but does not eliminate the risk for WMH (Dufouil et al., 2001; Raz et al., 2003a–c). There is a growing awareness that WMH burden is not distributed evenly across the cerebral white matter but shows predilection for the frontal regions (Raz et al., 2003a–c; Fazekas et al., 2005) and may progressively advance towards the posterior areas with increasing age and cardiovascular risk factors load (Artero et al., 2004). In sum, while WMH are present in ostensibly healthy older adults, they are not entirely benign.

Small connecting fibers of the anterior corpus callosum have been noted for their particular vulnerability to aging (Meier-Ruge et al., 1992; Aboitiz et al., 1996; Sullivan and Pfefferbaum, 2003). New approaches such as diffusion tensor imaging (DTI) and diffusion weighted imaging (DWI) (Sullivan and Pfefferbaum, 2003; Moseley, 2002), promise to open a window into age-related microstructural changes in the white matter (Sullivan and Pfefferbaum, this issue). Although diffusion-imaging studies are still scarce, some common findings have emerged. Advanced age is associated with an increase in average diffusion coefficient (ADC) of the whole brain, frontal white matter and lentiform nucleus but not in the parietal white matter, posterior limb of internal capsule, thalamus, and corpus callosum (Sullivan and Pfefferbaum, 2003; Abe et al., 2002; Nusbaum et al., 2001; Rovaris et al., 2003). Another marker of fiber integrity, fractional anisotropy (FA) decreases with age in centrum semiovale and parietal pericallosal regions, the genu of the corpus callosum and in some samples, in the splenium (Abe et al., 2002; Pfefferbaum et al., 2000; Zhang et al., 2005). Age-related decrease in anisotropy tend to be greater in the anterior vs. the posterior corpus callosum and in the frontal white vs. the temporal, parietal and occipital white matter (Head et al., 2004; Salat et al., 2005). Notably, in addition to a consistent age trend in FA decreases in the white matter, the gray matter (especially the lentiform nucleus) values increase with age (Furutani et al., 2005; Zhang et al., 2005). Although the biological basis of those trends is unclear, they are likely to reflect parallel processes of myelin loss and mineralization of the basal ganglia.

In general, the available studies of diffusion properties of the cerebral white matter converge on the notion of an anterior-posterior gradient of decline (Sullivan and Pfefferbaum, this issue), although such gradient may reflect pathological modification of aging rather than its normal course (Artero et al., 2004; Raz et al., submitted). At this time, it is still unclear whether global diffusion-based indices of white matter integrity add substantially to the information provided by traditional volumetry and semi-quantitative evaluation of WMH burden (Rovaris et al.,2003). It is possible however, that examination of local differences and longitudinal changes in ADC or FA will prove more useful than global measures of diffusivity (Mascalchi et al., 2003).

The cross-sectional studies of the normal aging brain support the notion of differential aging, in which association cortices emerge as more vulnerable to aging than sensory regions. Nonetheless, cross-sectional design is restricted to investigation of age-related *differences*, and is inherently unable to reveal real *change* due to possible cohort effects and secular trends as well as uncontrolled individual differences that may undermine true age effects. In addition, there are several major caveats to the interpretation of the cross-sectional findings. First, most of the surveyed samples are convenience samples that vary in their demographic and health-related characteristics. Whereas the sample size of an average in vivo study is substantially larger than in PM investigations, it still remains small by epidemiological standards and does not permit effective statistical control for multiple demographic and health variables. Second, age composition of the samples varies and because some regional differences in cortical volume may follow a nonlinear trajectory, tilting the sample age distribution upwards (50% above age 65 in (Salat et al., 2004; Lamaitre et al., 2005) may account for a pattern of results that differs from the one obtained in a sample with a rectangular age distribution (e.g., (Raz et al., 2004a–c)). Third, when "super-healthy" elderly are compared to average younger adults, age effects may be underestimated. On the other hand, older participants who are ostensibly healthy at the time of testing may harbor preclinical forms of age-related conditions that may inflate the estimates of age effects (Sliwinski and Buschke, 1999). Fourth, the measurement methods and demarcation of the regions of interest (ROIs) vary across the samples, even for the most frequently measured brain structures (e.g., the hippocampus, Jack et al., 1995), and inclusion of studies that use voxel-based methods increases methodological variability. However, when the method variance is controlled, the estimates of age differences (unlike sex differences and hemispheric asymmetry) in regional brain volumes are relatively stable across samples, at least when those are drawn from the same population and when similar methods are applied (Raz et al., 2004a–c). Longitudinal studies hold a promise of alleviating the deficiencies of the cross-sectional investigations.

4. Longitudinal volumetric studies

4.1. Ventricular system

Cerebral ventricles are not as stable a neuroanatomical structure as the brain parenchyma. The nuclei and white matter tracts that abut them define the volume of the cerebral ventricles, and thus it is a summary index of changes across the whole central nervous system. Global measures of the brain and ventricles can be accomplished with extremely high reliability and high degree of automation and are therefore a natural choice for first (and unfortunately, the only) measure in many neuroanatomical studies of aging. Across the studies, the measures of the cerebral ventricles revealed that the volume of the ventricular system increases at an average rate of 2.9% per annum (Raz, 2004). The rate of ventricular expansion may accelerate with age. For five studies of older subjects (Hu et al., 2001; Mueller et al., 1998; Resnick et al., 2003; Sullivan et al., 2002; Tang et al., 2001; mean age above 70 years), the median annual rate of expansion was 4.25% (2.90–5.56%), whereas in four samples composed of younger subjects (Cahn et al., 2002; DeLisi et al., 1997; Ho et al., 2003; Saijo et al., 2002; mean age below 40 years), the median value was only 0.43% per

annum. In addition, at least one study (Scahill et al., 2003) reported a significant age-related acceleration of ventricular expansion with age without providing the percent values.

The total volume of the cerebral parenchyma, while presenting a global index similar to the ventricular volume behaves rather differently when age-related change is concerned. By comparison to age-related ventriculomegaly, shrinkage of the *total brain parenchyma* is small. Across 13 studies (see Raz (2004) for a complete list), the median value is only 0.18% per annum. Nonetheless, as in progressive ventriculomegaly, the rate of parenchymal shrinkage accelerates with age, although the magnitude of global shrinkage is quite modest even for the oldest participants (0.35% per annum). Notably, steeper volume declines were noted in two studies that considered gray and white matter separately. In one of those studies a substantial decline was found in gray and white matter of older individuals: 1.17% and 2.52% per annum, respectively (Thompson et al., 2003). In the other, the decline of gray matter volume was more than four times faster than the total parenchymal shrinkage: 0.90% vs. 0.20% (Cardenas et al., 2003). As it happens, the median annual decline of brain parenchyma volume is not much different from the rate of neuronal loss in the neocortex estimated at 0.18% per annum from a PM sample (Pakkenberg and Gundersen, 1997). It must be noted that the observed pattern of differential cortical shrinkage is not unique to aging; in younger individuals, frontal and parietal (but not occipital) gray matter volume decline after early teens into young adulthood (Giedd et al., 1999).

In contrast to the gray matter, several cross-sectional comparisons suggest that in samples with a broad age range, white matter aging follows a nonlinear course (Bartzokis et al., 2001; Bartzokis et al., 2003; Courchesne et al., 2000; Fjell et al., 2005; Jemigan et al., 2001; Raz et al., 2005) Significant age-related differences in white matter volume are usually found in the samples composed of very old participants (Salat et al., 1999). Moreover, a significant age × time interaction observed in the longitudinal study of healthy adults over 5 years (Raz et al., 2005), indicates that the magnitude of white matter shrinkage depended on age. Beginning at the fifth decade of life, healthy adults show significant shrinkage, whereas their younger counterparts displayed no change in the white matter volume. A pattern of steady increase in white matter volume between childhood and young adulthood was observed in a longitudinal study of normal development (Giedd et al., 1999). Thus, the volume of the white matter, especially in the prefrontal regions (Raz et al., 2005), follows a nonlinear longitudinal course, with linear increase from birth to young adulthood, plateau during the middle age and precipitous decline in the later years.

Medial temporal structures (the hippocampus, HC, and the entorhinal cortex, EC) attracted special attention of researchers for a variety of reasons but not the least because of their putative role as the earliest foci of Alzheimer's disease (AD) pathology (Braak and Braak, 1991). Furthermore, the EC is affected almost exclusively in those who showed significant ante-mortem cognitive decline (Kordower et al., 2001; Price et al., 2001). In contrast, the effects of normal aging on EC volume (Insausti et al., 1998) are negligible, although in some PM samples isolated but considerable age-related neuronal loss was observed in entorhinal islands of lamina II (Simic et al., 2005; but see Merrill et al., 2000). Whereas reduced hippocampal volume is a good predictor of a concurrent AD (Jack et al., 1992; Laakso et al., 2000; Tomlinson et al., 1970) and of AD-type pathology in non-demen ted individuals, the

volume of the EC may fare better as a prospective predictor of transition from normal aging to AD (Dickerson et al., 2001; Gosche et al., 2002; Killiany et al., 2000; Killiany et al., 2002).

The results of the longitudinal studies of HC indicate that it shrinks at a median rate of 1.23% per annum (Raz,2004). There is a trend for samples with younger and healthier subjects to show slower decline of the HC volume (under 1% per year or less), whereas in non-demented adults in the seventh decade of life and older the literature suggests a steeper decline of about 1.7% per annum. Within-sample comparisons reveal that even among very healthy adults, shrinkage rate among older subjects is more than twice that of their younger counterparts (Liu et al., 2003; Raz et al., 2004a–c). Such differences are in accord with expectations generated by findings of nonlinear relationship between age and HC volume in several cross-sectional samples (Raz et al., 2004a–c; Fjell et al., 2005; Jernigan et al., 2001). These shrinkage rates, however, are considerably slower than 3–4% annual declines observed in AD (Jack et al., 2000) and almost by an order of magnitude smaller than progressive reduction of HC volume in people with genetic variety of AD, for whom they reach 8% per annum (Fox et al., 1996). Although longitudinal shrinkage of the HC appears quite substantial, that observations must be qualified by the significant acceleration effect exerted by pathological factors such as hypertension and other cerebrovascular risk factors on the decline in HC volume (as discussed elsewhere in this review).

Only a handful of longitudinal studies examined changes in the EC of healthy adults. A significant reduction in the volumes of the parahippocampal gyrus (which includes EC) was observed in one of the first longitudinal studies of healthy brain aging (Kaye et al., 1997). In two small samples restricted to older adults, significant declines in EC volume (1.4% and 2.6% per year) were documented (Cardenas et al., 2003; Du et al., 2003). Two samples of broader age range revealed conflicting findings. In a small sample with a mean age of 46 years, no HC changes were found while a decline of 1.6% per annum was observed in the EC (Schott et al., 2003). In a larger sample of healthy adults whose HC and EC were measured with an interval of 5 years, we observed a different pattern (Raz et al., 2005). A significant decline in HC volume was accompanied by a minimal shrinkage of EC. Interestingly, the rate of decline in both structures accelerated with age and more so in the HC. Whereas for the younger participants (age below 50 years) no EC shrinkage and only mild HC shrinkage were observed, for their older counterparts the EC shrinkage was greater than zero and at about the magnitude of HC shrinkage observed for the younger adults (approximately 0.5% per year). These findings converge with metabolic imaging data. A study of hemodynamic properties of the medial temporal regions in healthy adults revealed a similar pattern of significant age-related decline in two hippocampal regions (the subiculum and the dentate gyrus) with no age-related differences in the EC (Small et al., 2000). Notably, in that study, a significant decline of basal metabolism in the EC was observed only in the oldest participants (70–88 years of age). It must be noted, however, that EC shrinkage appears independent of the vascular pathological factors that play a prominent role in HC atrophy (Du et al., 2006).

The *striatum*, despite its importance in motor control and learning (Alheid et al., 1990; Nakamura et al., 2001), received relatively little attention in longitudinal studies of aging.

Most of the available studies are limited to small samples of younger adults and short-term follow-ups, with one exception (Raz et al., 2003a–c). Among younger adults, the findings are mixed. Some, but not all, revealed significant shrinkage of the caudate nucleus even at a relatively young age, with annual percentage of change exceeding 1% per year. In a 5-year follow-up of 53 healthy adults whose ages ranged from 20 to 77 years at baseline, we found linear declines in all striatal nuclei. However, the rate of decline varied across the nuclei. The caudate nucleus evidenced the fastest decline (0.83% per annum), with the putamen and the globus pallidus showing lesser rates of decline (0.73% and 0.51%, respectively). The observed shrinkage was linear and unrelated to age, i.e., the striatal nuclei shrunk in young adults at roughly the same rate as in their older counterparts. These findings converge with the results of pharmacological neuroimaging, which revealed significant decline in dopaminergic (DA) activity in the striatum and prefrontal cortex ((Backman and Farde, 2004; Erixon-Lindroth et al., 2005; Kaasinen, and Rinne, 2002; Volkow et al., 1996); for review, see (Backman et al., this issue).

Four longitudinal studies (reviewed in Raz, 2004) examined changes in the *cerebellar volume* and one report focused on the longitudinal course of volume change in the cerebellar vermis and the ventral pons. All but one published longitudinal study of the cerebellum were conducted on samples with severely restricted age ranges, either young adults or the elderly. The results of the fourth longitudinal investigation demonstrate that all metence-phalic structures shrink with age. However, the rate of shrinkage differs among them. The annual shrinkage of the cerebellar hemispheres was somewhat greater than that of the vermis, whereas the ventral pons exhibits minimal volumetric change (Raz et al., 2003a–c).

Although longitudinal studies of WMH expansion in healthy adults are still scarce, they consistently show that WMH burden increases with age (Goldstein et al., 2005; Wahlund et al., 1996; Prins et al., 2004; Raz et al., submitted; Schmidt et al., 2003; Whitman et al., 2001). However, the progression of WMH is not uniform. The rate of increase in WMH burden may be slower for small punctate lesions than larger for confluent WMH (Schmidt et al., 2003), and periventricular and frontal WMH tend to increase with age more then lesions in the other regions (Prins et al., 2004; Raz et al., submitted). Although cross-sectional studies reveal age as the best predictor of WMH load, the place of WMH in healthy aging is unclear. A recent longitudinal study indicates that what seems to be age-related phenomenon may reflect increase in vascular risk and presence of vascular disease (Raz et al., submitted).

An interesting possibility was revealed by a recent study that used magnetization transfer (MT) imaging, an MRI technique highly sensitive to demyelination, to examine the predictors of WMH development (Fazekas et al., 2005). In that study, reduced myelination (as indicated by a lower MT ratio) was found in the WMH, and higher prevalence of WMH was associated with compromised MT characteristics of normally appearing white matter. Thus, it is possible that pre-clinical changes in the white matter precede the appearance of WMH and may become a sensitive predictor of cognitive changes.

In sum, cross-sectional and longitudinal studies of neuroanatomical aging indicate a substantial age-accelerated expansion of CSF-filled cavities, mild shrinkage of the cerebral parenchyma, and a pattern of differential regional changes. Age-related increase in white-

matter lesions is also consistently noted. Association cortices, the neostriatum, the hippocampus and the cerebellum, as well as the deep white matter tracts connecting those regions appear more sensitive to aging than are the primary sensory cortices, entorhinal cortex, the paleostriatum, the pons and the related white matter pathways. What are the cellular and metabolic correlates of these structural changes and can they be observed in vivo? To date, very few studies addressed that question with the help of magnetic resonance spectroscopy (MRS).

5. Age-related differences in metabolic markers of neural integrity

In contrast to structural MRI in which frequency information is used to encode location of the signal source in the brain, a direct use of frequency information in combination with the chemical shift phenomenon allows identification of specific chemical compounds within a circumscribed brain region. The latter approach, MRS comes in two basic varieties: proton-based ^{1}H-MRS) and phosphorus-based (^{31}P-MRS), although measurement of other elements, such as carbon and sodium are possible. Most frequently the technique of choice is proton MRS, which is sensitive to the resonance peaks of several basic brain metabolites: creatine (Cr), choline (Cho), *myoinositol* (MI) and *N*-acetylaspartate (NAA). In higher-field magnets, glutamate and GABA peaks can be reliably identified as well. The Cr resonance combines the signal from creatine and phosphocreatine and provides a measure of cellular energy activity. The Cho-containing compounds are critical for membrane construction and synthesis of membrane phospholipids; increased levels of Cho are taken as a sign of membrane breakdown, inflammation or demyelination (Schmidt et al., 2003). MI is considered a reliable glial marker. NAA is a neuronal marker as it is almost exclusively found in neurons (Pettegrew et al.,2000). Phosphorus-based ^{31}P-MRS can identify phosphoe-sters associated with membrane lipids, i.e., compounds such as inorganic phosphate (Pi), and phosphocreatine (PCr) that are related to cellular energy metabolism and phosphatidylcholine (PtdCho) levels that are usually interpreted as a factor in declining fluidity of cell membranes. In addition, intracellular pH can be calculated from PCr and Pi (Corbett et al., 1992).

The progress in study of metabolic markers of brain aging has been slow. Spectroscopy on clinical 1.5 T magnets is a time-consuming affair and selection of ROIs is limited to relatively large regions, especially in ^{31}P-MRS. However, MRS studies of normal aging have already produced several interesting findings. It has been found with a high degree of consistency that markers of neuronal viability (NA/NAA concentration or its ratio to Cr) declines with age in the prefrontal (Brooks et al., 2001; Chang et al., 1996; Driscoll et al., 2003; Urrila et al., 2004) and occipital (Christiansen et al., 1993) gray matter, the hippocampus (Driscoll et al., 2003; Schuff et al., 1999), midbrain tegmentum (Moreno-Torres et al., 2005) and the lentiform nucleus, (Chang et al., 2004; Harada et al., 2001) but not in the frontal (Chang et al., 2004; Harada et al.,2001) or parietal (Harada et al., 2001; Leary et al., 2000) white matter, or the pons (Moreno-Torres et al., 2005). Notably, in the latter study, NAA/water ratio exhibited a curvilinear relationship with age, similar to the one observed in the white matter and the hippocampus in some volumetric studies: flat in young adulthood and declining in the older participants. At the same time no Cho/Cr differences were observed (Schuff et al., 1999;Chang et al., 2004; Angelie et al., 2001), and a linear

decline of NA/Cho ratio in post-adolescent brains suggests a steeper age-related loss or shrinkage of neurons rather than the myelin (Kadota et al., 2001).

Previously, technical issues and difficulties in obtaining absolute metabolite levels have lead to other metabolites being normalized with respect to Cr. However, the use of ratio measures of metabolites in which Cr concentration features in the denominator is potentially misleading and should be avoided, as Cr itself may exhibit age-related differences. In some samples both Cho and Cr increase in parallel (Leary et al., 2000), whereas others noted increase only in Cr (Saunders et al., 1999) or Cho concentration (Chang et al., 1996). In some samples, there are no age differences in concentration of neuronal or myelin markers in healthy elderly despite observing significant cortical shrinkage (Urrila et al., 2004; Pfefferbaum et al., 1999). Thus, use of Cr-referenced indices in studies of aging brain should be avoided, and indeed the vast majority of the studies reviewed here were conducted with that caution in mind.

Two longitudinal ^{1}H-MRS studies of normal aging yielded contradicting results. One reported no age-related declines in concentration of NAA, Cho and Cr (Adal-steinsson et al., 2000), whereas the other revealed declines in Cho/CR and NA/CR ratios on average 3.8% per annum—steeper than most of the volumetric measures would suggest (Sijens et al., 2003). The findings from ^{31}P-MRS studies show negative correlations between intracel-luar pH and age (Murashita et al., 1999) and the link between aging and reduction in PtdCho (Babb et al., 2002) and Pi (Murashita et al., 1999) as well as an increase in PCr (Murashita et al., 1999; Longo et al., 1993).

In sum, to date MRS has provided limited evidence of specific age-related differences in neural viability and integrity and their relation to structural declines. The most consistent finding is decline in metabolic markers of neuron viability in selected regions of the gray, but not white matter. In the absence of direct pathological evidence, this is an important indicator that age-related shrinkage of some cortical regions might indeed reflect reduction in size and/or number of the neurons. Future studies aided by stronger magnets which improve signal-to-noise ratio in combination with more sophisticated methods to analyze the spectra quantitatively will be able to examine the metabolic changes in multiple brain regions and in conjunction with differential age-related changes in regional volumes.

6. Cognitive aging and its brain correlates

6.1. Structural brain correlates of cognitive aging

Age-related differences in regional brain volumes and integrity of the white matter are associated with cognitive performance. However, reviews of the literature reveal that the magnitude of the observed associations is modest (Raz, 2000; Gunning-Dixon and Raz, 2000). When structure-cognition associations are found, they are not easily replicated and appear sensitive to the sample composition and choice of cognitive measures. To date, evidence of links between smaller volume of the hippocampus and memory performance turns out to be rather weak (Van Petten, 2004) and contradictory to the clearer results observed in pathological samples (Raz, 2000). It is possible that refinement of measurements of subdivisions of the hippocampus (Hackert et al., 2002) or assessment of memory at longer

delays (Walhovd et al., 2004) will yield more consistent links between regional volume and memory. It is also possible that the relationship will become clear when in vivo assessment of specific markers of brain aging such as neurofibrillary tangles vs. amyloid deposits becomes feasible (Guillozet et al., 2003).

Structure-function associations have been observed in other areas of cognitive aging. Better performance on some executive tasks (e.g., Wisconsin Card Sorting Test) is associated with larger prefrontal cortices—their putative substrates (Raz et al., 1998; Gunning-Dixon and Raz, 2003), and smaller burden of frontal WMH (Gunning-Dixon and Raz, 2003). Larger hippocampal volumes and higher levels of a neuronal metabolic marker (NAA) were observed in younger adults who showed better spatial memory performance than their older counterparts (Driscoll et al., 2003). In another MRS study, memorization of a word list was associated with increased prefrontal gray matter lactate (metabolic product of glucose utilization) in young but not older adults (Urrila et al., 2004).

Age differences in acquisition of perceptual-motor skills and speed and accuracy of performance may be mediated by differences in the volume of striatal structures (caudate and putamen) as well as the prefrontal cortex and cerebellum (Kennedy and Raz, 2005; Raz et al., 2000; Woodruff-Pak et al., 2001). Notably, the relationship between brain structure and performance may change in the process of skill acquisition. For example, at the advanced (asymptotic) stage of training in pursuit rotor task, only the volume of the cerebellum, but not the putamen, remained a significant predictor of performance (Raz et al., 2000). That study illustrates how fragile the relationship between cognitive function and supporting structure may be. The associations between regional cerebral volumes and performance may appear and disappear depending on what aspect and what stage of cognitive skill is measured.

It is possible that the relationship among the structures is affected by aging and age-related declines emerge from reduced connectivity that affects fronto-striatal and fronto-cerebellar synergism as discussed elsewhere in this issue (Sullivan and Pfefferbaum, this issue). Changes in cortico-subcortical connectivity may affect the use of resources that are needed for maintenance of cognitive performance, e.g., working memory. The role of working memory in mediating age-related differences in cognition is unclear. Working memory may affect cognitive and motor performance directly or via age-related differences in brain structures on which it relies. The problem is that even within the same sample, the indirect effect of working memory on performance may be mediated by age-related differences in diverse brain regions, such as the prefrontal cortex (in Tower of Hanoi task, Head et al., 2002) or the cerebellum (in pursuit rotor, Raz et al., 2000). There are, however, reports of isolated negative correlations between cortical volume in some prefrontal regions and performance on working memory tasks (Salat et al., 2002; Van Petten et al., 2004). Thus, in neurologically normal older adults, the connection between concurrently measured regional volumes and cognitive performance remains unclear, and a substantial proportion of the individual differences may be due to factors other than aging, e.g., vascular disease. For example, in one recent study, declines in working memory over time and their links to regional brain shrinkage were observed in persons with various vascular risk factors but not in healthy adults. Thus, even in a relatively healthy population, vascular risk may play a

significant role in explaining the link between performance and regional brain changes (Raz et al., submitted).

Increased burden of WMH predicts poorer performance on tasks that tax speed of processing and executive control and the contribution of this index of white matter integrity may be independent from that of the prefrontal volume (Gunning-Dixon and Raz, 2000; Gunning-Dixon and Raz, 2003). Recent studies using DTI to assess white matter integrity reported specific associations between functions that may be mediated by the prefrontal circuits (such as verbal fluency) and anisotropy of the anterior white matter (O'Sullivan et al., 2001). However, age-related increases in WMH may share age-related variance in executive functions (Gunning-Dixon and Raz, 2003; Prins et al., 2005).

In sum, the true magnitude and even direction of association between regional volumes and cognitive functions in normal aging cannot be assessed at this stage. More comprehensive investigations with diverse executive and mnemonic tasks are needed to clarify the issue. It is plausible, however, that the associations between structural features taken as a cross-sectional snapshot and concurrent cognitive performance will prove too difficult to discern among the substantial individual differences in both domains of measurement. Longitudinal studies, in which individual differences in level are controlled and individual differences in change can be measured independently of the individual differences in level, indicate more significant association between brain structure and cognition. For example, EC shrinkage is associated with reduced memory performance even in healthy adults (Du et al., 2003; Rodrigue and Raz, 2004) and metabolically compromised EC predicts later declines of memory (de Leon et al., 2001). Longitudinal increase in WMH was associated with declines in performance on some executive tasks (Cook et al., 2004) and a specific association between increase in frontal WMH and decline in motor dexterity was reported as well (Fazekas et al., 2005). Thus, longitudinal studies show potential for clarifying the neuroanatomical underpinnings of cognitive aging but at the time of this writing such studies are still too scarce to allow drawing firm conclusions.

7. Modifiers of brain aging: the good news and the bad news

Whereas aging is associated with the passage of time, it should not be confused with it. Multiple factors affect brain development and aging and alter the trajectories of individuals and whole species. Some of those modifying factors act as accelerators of age-related declines, while others may slow age-related deterioration and delay attainment of pathological levels. Identifying such factors and gauging their contribution to emergence of the observed pattern of brain aging is crucial to understanding the neural foundations of cognitive aging.

7.1. Hypertension and other cardiovascular risk factors

Essential hypertension is a chronic age-related condition associated with multiple changes in the vascular system (Marin and Rodriguez-Martinez, 1999). Even when defined very conservatively by systolic blood pressure in excess of 160mmHg or diastolic pressure greater than 90mmHg, hypertension affects over 55% of Americans (Burt et al., 1995). Chronic elevation of blood pressure augments the effects of aging on brain structure (De

Leeuw et al., 2001; Raz et al., 2003a–c; Carmelli et al., 1999; Goldstein et al., 2002; Salerno et al., 1992; Schmidt et al., 1996; Strassburger et al., 1997; den Heijer et al., 2005), and persons with medically controlled hypertension are at lesser risk for cognitive declines than those who are undiagnosed or untreated (Dufouil et al., 2001; Fukuda and Kitani, 1995; Tzourio et al., 1999). Notably, exclusion of medically treated hypertensive participants from a sample can bring a significant reduction in age effects on brain and cognition (Raz et al., 2005; Head et al., 2002). However, even treated hypertension may be associated with higher prevalence of white matter abnormalities than observed in matched normotensive controls (Raz et al., 2003a–c; van Swieten et al., 1991), as well as reduced volumes of the prefrontal gray and white matter (Raz et al., 2003a–c). Moreover, hypertension appears to accelerate age-related shrinkage of the hippocampus and may account for its highly nonlinear age trajectory (Raz et al., 2005; Du et al., 2006). Hypertension-related HC shrinkage is exacerbated by presence of lacunar infarcts, whereas no such influence on EC atrophy rates was found (Du et al., 2006). Persons with hypertension and other vascular disease factors show longitudinal declines in the regions that are usually stable in normal aging, such as the primary visual cortex (Raz et al., submitted). The latter may be an expression of a proposed model in which general trend of aging (anterior atrophy) is modified by vascular disease that induces posterior changes (Artero et al., 2004). Indeed, in contrast to healthy adults, persons with vascular risk factors and vascular disease show the fastest WMH expansion in the parietal areas, and increase in the pace of expansion is associated with higher systolic blood pressure (Raz et al., submitted). Unfortunately, little is known about neuroa-natomical correlates of hypertension in standard animal models. However, selective vulnerability of the prefrontal regions to hypertension was observed in spontaneously hypertensive rats, and treatment with antihypertensive agents seemed to show the greatest neuroprotective effect in the prefrontal cortex (Sabbatini et al., 2001).

In addition to and in conjunction with hypertension, metabolic markers of cardiovascular risk may be associated with structural brain differences usually attributed to aging. One such marker is homocysteine (Hey), an amino acid that is synthesized with participation of the vitamins of the B-group as co-factors. In healthy adults, Hey increase is associated with atrophy of the hippocampal (but not amygdala) (den Heijer et al., 2003; Williams et al., 2002), reduced total gray matter volume (Whalley et al.,2003) and ventriculomegaly (Sachdev et al., 2002). Increased plasma total Hey levels predict cognitive declines (especially cognitive slowing) in nondemented elderly, and are linked to poorer performances on a wide range of neuropsychological tests (Teunissen et al., 2003) especially those measuring delayed recall and executive control (Dufouil et al., 2003). Thus, it is possible that Hey is an important contributor to brain changes that are frequently identified with normal aging. However, the extant studies do not provide information on the pattern of brain effects of elevated Hey (as no attempts were made to assess regional volume differences) and leave open the question of the interaction between age and Hey levels (as all samples were restricted to old age). Moreover, because of the cross-sectional nature of the studies, it is impossible to conclude whether Hey elevation precedes brain decline, is concurrent with it, or results from it. Notably, some known promoters of brain shrinkage, such as chronic alcoholism are also linked to elevated Hey, which predicts atrophy of the hippocampus beyond the age-expected levels (Bleich et al.,2003).

7.2. Aerobic fitness

To offset the bad news about brain aging surveyed in the previous section, we can cautiously offer some good news, or at least some hopeful findings that suggest that the pathological influence of cardiovascular risk factors on the aging brain can be alleviated and even prevented. A growing body of studies indicates that aerobic fitness positively affects a wide variety of variables that have been linked to brain health (Cotman and Berchtold, 2002). Until recently, studies on brain aging and exercise were based on indirect measurements of brain structure and function such as global electrical activity (EEG) and cognitive performance on tasks with known sensitivity to brain lesions (Churchill et al., 2002). Nonetheless, the general direction of findings supports the assertion that executive functions and by inference brain structures that support them, are especially sensitive to beneficial effects of aerobic fitness (Colcombe and Kramer, 2003; Colcombe et al., 2003; Lesniak and Dubbert, 2001).

7.3. Hormone-replacement therapy

Age-related alterations in the endocrine system affect the majority of older adults. Thus, hormone-replacement therapy (HRT) as the way of combating brain-aging generated a significant debate and controversy among researchers. While testosterone therapy for men is still in the phase of extensive preliminary investigations, estrogen-replacement therapy has been prescribed to millions of women. A significant body of animal research suggests that estrogen may have multiple beneficial effects on the CNS and cognition (McEwen, 2002a; Packard, 1998; Van Amelsvoort et al., 2001). Although the results of cross-sectional comparisons of HRT recipients with controls have been mixed (Eberling et al., 2003; Erickson et al., 2005; Raz et al., 2004a–c), longitudinal studies have yielded more encouraging results. In comparison to the controls, HRT recipients evidenced fewer silent strokes and lesser burden of WMH (Schmidt et al., 1996), slower progression of gross brain changes (Cook et al., 2002), larger hippocampi (Eberling et al., 2003), increased rCBF in limbic and association cortices (Maki and Resnick, 2000) and slower rate of longitudinal shrinkage of the age-sensitive neocortical regions (Raz et al., 2004a–c).

While animal investigations and small-sample human studies of HRT-generated significant enthusiasm, the positive expectations have been tempered by negative findings from large scale clinical trials, in which HRT was linked to higher prevalence of cerebral infarcts (Luoto et al., 2000), excessive risk for strokes (Wassertheil-Smoller et al., 2003) and increased risk for developing dementia (Shumaker et al., 2003). Not only have the neuroprotective benefits of HRT been called into question, the notion that high levels of estrogen are good for the aging brain and cognition has been doubted as well, when higher total estradiol levels were reportedly associated with smaller hippocampal volumes and poorer memory (den Heijer et al., 2003). Moreover, recent animal studies also revealed a potentially harmful side of HRT. In a rodent model, a harmful interaction between HRT and induced neuroinflammation was observed (Marriott et al., 2002). Pathological age-related changes and AD pathology have been attributed to neuroinflammation (McGeer and McGeer,2001). Thus, interactions between HRT and pre-existing inflammatory processes may act to offset the potential benefits of HRT or even amount to harmful outcome.

8. Mechanisms of differential brain aging

There is no dearth of theories of aging, and some sources put their number at more than 300 (Polla et al., 2003). It is unlikely that one or two basic mechanisms would account for the observed complex pattern of differential aging. However, it is equally unlikely for the changes replicated across multiple studies to reflect a set of random events. Several possible explanations of differential aging can be proposed, with no assumption of their mutual independence or exclusion.

Not all neurons are equally ready to cope with hypoxia, ischemia, hypoglycemia, and toxins, even when they reside in the same nucleus (Calabresi et al., 2000). Age-related declines in specific brain neurotransmitter systems (cholinergic and DA) may account for some features of the regional distribution of age-sensitive and age-invariant areas (Bartus et al., 1985; McGeer, 1981). Age-related changes in DA system and their role in brain aging are especially well documented. Effects of DA on brain shrinkage may be indirect, via its influence on cerebral vasculature responsivity (Palmer, 1986).

A number of life-course factors—prenatal, perinatal and early postnatal history, stress, recurrent inflammation and subclinical cerebrovascular events—have been identified as potential contributors to brain aging. Because virtually all parameters of the brain are influenced by events at gestation, birth and early childhood, it is plausible that teratogenic events at that time may set an organism on a path of increased age-related vulnerability (Terry and Katzman, 2001). After all, starting with a smaller complement of information processing elements that undergo constant attrition may bring an organism to a threshold of critically low redundancy earlier than expected.

Age-related brain shrinkage may be associated with the cumulative effects of stress mediated by release of corticosteroids. High levels of glucocorticoids are associated with synaptic loss in the hippocampus, hippocampal atrophy, and cognitive decline during aging (Sapolsky et al., 1987; McEwen, 2002b), and stress hormones released on acute or chronic schedule are detrimental to memory performance at all ages (Lupien et al., 2005). However, the contribution of glucocorticoids to brain aging depends on the physiological and cellular context and some of these effects are reversible (Lee et al., 2000; Nicolle et al., 2001). Nonetheless, some preliminary evidence ties corticosteroid release and hypothalamic-pituitary-adrenal (HPA) axis reactivity with age-related shrinkage in some regions (Sapolsky et al., 1987; Lupien et al., 1998; Magri et al., 2000; Wolf et al., 2002). Moreover, decrease in cortisol levels may result in reversal of apparent hippocampal atrophy (Starkman et al., 1999). However, the exclusive focus on the hippocampus may be unwarranted as there are some reports that point to the effects of stress on the prefrontal cortex, a region with elevated vulnerability to aging. Chronic back pain, a known stressor, was associated with reduced prefrontal and thalamic density, “an equivalent of 10–20 years of normal aging” (Apkarian et al.,2004). In a rodent model, even relatively mild stress induced profound changes in prefrontal cortical plasticity and inflicted significant structural damage (Brown et al.,2005).

Age-related vascular change can contribute to the observed pattern of gross neuroanatomical transformations. Brain regions located upstream of the major cerebral arteries, especially at

the watershed areas, are more vulnerable to subclinical ischemia and reperfusion. Age-related rarefication of microvasculature may contribute to impaired cerebral blood flow and increase risk of such injury (Marin and Rodriguez-Martinez, 1999; Dewar et al.,2003). Brain tissue may be destroyed by inflammation, chronic or acute. Enzymes involved in the inflammatory response are more abundant in the association and limbic structures than in primary sensory cortices (Uz et al.,1998), thus exposing them to increased risk of cumulative damage from subclinical inflammation. Notably, some antihypertensive agents (e.g., Ca^{2+}-channel blockers) may be neuroprotective by stimulating increases in capillary density and creating more favorable conditions for recovery of neural activity (Amenta et al., 1985).

Calcium plays an important role in mitochondrial fission that was proposed as an important mechanism of brain aging (Bossy-Wetzel et al., 2003; Lenaz et al., 2002), and there is a possibility that direct modulation of Ca^{2+} channels by free radicals may occur in aging organisms (Annunziato et al., 2002). Such modulation is consistent with a view of brain aging that can be described as the dark side of plasticity. Although this view was first articulated in the context of Alzheimer disease (Khachaturian, 1984), it can be applied to non-pathological aging as well.

The regions that exhibit the greatest vulnerability to aging are also the most plastic structures of the adult mammalian brain. Primate adult neurogenesis, if and when it occurs, is limited to association (prefrontal, inferior temporal and posterior parietal) cortices and the hippocampus while excluding the primary sensory areas (Gould et al., 1999). Plasticity-promoting factors such as growth-associated protein (GAP-43) are rare in the brainstem, tectum and tegmentum but frequent in the associative areas of the neocortex, the dentate gyrus (molecular layer), the neostriatum, and the amygdala (Neve et al., 1988; Benowitz et al., 1989).

Recently, a theory emphasizing the role of myelin rather than neurons in aging and age-related diseases was proposed (Bartzokis, 2004a, b). That account of brain aging draws attention to the nonlinearities in the aging trajectories of the white matter (Bartzokis, 2004a, b) discussed in this article. A link between neural plasticity and the extent of regional myelination has been demonstrated in several studies (Kapfhammer and Schwab, 1994). We noted a significant association between the rank order of regional myelination developed more than 100 years ago by Flechsig (1901) and the magnitude of age-related differences observed in vivo (Raz, 2000). Myelination is a relatively recent evolutionary development and unlike many types of neurons and synapses, it is present only in vertebrates (Zalc and Colman, 2000). Although it requires substantial metabolic investment and consumes precious energy resources, myelination pays off handsomely in metabolic savings and information-processing dividends. Thus, as long as the organism can afford its maintenance, myelination goes on and attrition of oligodendroglia through apoptosis is successfully counteracted or even overcompensated. When the rate of myelogenesis slows down because of scarcity of metabolic resources (as physiological aging) or due to intervention of powerful pathogenic factors (as in MS or AIDS, e.g., Bell, 1998), the dynamic equilibrium tilts towards ever decreasing levels.

9. Limitations of neuroanatomical techniques

This survey would be incomplete without at least a summary of the limitations that measures of brain structure impose on the investigation of the aging brain. All research approaches have their windows of sensitivity and their limitations that must be explicated if a balanced interpretation of the data is sought. Below, we dwell on some of the major constraints that PM and in vivo neuroanatomy impose on the interpretation of the results.

9.1. Limitations of PM neuroanatomy and histology

As powerful and productive as it is, the PM approach suffers from several intrinsic limitations. First, by its very nature, the PM methodology is confined to a cross-sectional design. Second, the difficulty of specimen procurement creates a significant pressure on researchers to limit the sample size. Thus, a typical PM sample is restricted to tens of subjects, with 10–20 cases per study being the rule. Because of that limitation, modern multivariate statistical techniques cannot be applied to the analyses of PM data. Because of the small sample size and meager statistical power, little can be said about estimated age trajectories of change, including an important question of linearity or lack thereof. Whereas in vivo research on aging is frequently based on samples of convenience and not on a random or stratified population sampling procedures, in the case of PM approaches, the problem is more acute. Post mortem research depends on the ill fortune of the individuals who succumb under suitable circumstances and on the availability of the clinical personnel who can handle research specimen without jeopardizing the integrity of the collected data. Third limitation stems from the fact that immediately after death the mammalian brain undergoes a series of very rapid transformations. If not stopped properly, those transformations would render the specimen so vastly changed that serious doubts would be cast on attribution of the findings to the factors unrelated to PM state itself. To add complications, the post mortem changes related to degradation, fixation and storage are differential and do not affect various components of the brain to the same extent. Fourth, and related, limitation is the ante-mortem changes that occur due to the agonal state. In the short run before death, variability in duration of hypoxia, ischemia, exposure to toxins and bacteria adds an uncontrollable dimension to every post mortem sample. In the long run ante-mortem, variability in life history may add, unbeknown to the researcher, differential variability to the size and integrity of brain regions.

9.2. Limitations of in vivo neuroimaging methodology

The MRI methods discussed in this review inspired considerable enthusiasm of the students of brain-behavior relations. Indeed, what can be more exciting than an opportunity to peek inside the living, working brain? However, MR imaging as applied to the aging brain, has its own limitations both in acquisition and in post-processing. The constraints on validity of MRI-based studies have two main sources: the machine and the human operator as well as the interaction between the two. On the machine side, one needs to keep in mind that MRI is just a gray-scale reconstruction of numeric information about the behavior of brain protons and small alterations of local magnetic properties. To the extent that the phenomenon in question is sensitive to those factors, the MRI is a valid tool. Unfortunately, the very same

phenomena that are employed in the service of studying age-related change are also a source of several problems.

First, the image acquisition parameters may be sensitive to age-related changes. For example, age is associated with changes in relaxation times (Cho et al., 1997) that to a substantial extent determine image contrast. If differential changes are observed, the assumption is that the age-related differences in T1 and T2 are uniform and do not vary across the regions. Thus, the method-related variability becomes a less likely confound, unless a region-specific bias can be demonstrated. Second, the subject of an MRI study enters the magnet in a physiological state that usually poorly controlled. Transient variables such as dehydration through insufficient consumption of fluids, disease, or medication may affect the observed size of brain regions (e.g., Duning et al., 2005). While it is unlikely that water homeostasis is severely impaired in normal volunteers who have not undergone a process of deliberate dehydration, it is always possible in patient populations. Third, manual tracing of the brain ROIs is performed by human operators, and therein a potential for significant increase in error variance. While most studies maintained high standards of operator training, some failed to report the duration of such training and the criteria to which the operators were trained.

Manual volumetry is a straightforward approach to measuring volumes of brain structures as they appear on the MRI scans. In that sense, volumetry treats an acquired image as just that: an image. Manual measurements require careful and well-reasoned selection of a limited set of target regions on the basis of previous human lesion studies and animal models. Manual volumetry has substantial face validity and is considered a “gold standard” against which other methods are judged. Moreover, trained operators are capable of easily distinguishing between “true” anatomy and an image artifact and can perceptually compensate for a wide range of contrast-to-noise situations. However, it is a method that demands from its practitioners both substantial knowledge of neuroanatomy and excellent eye-hand coordination. The process of training operators to a reliable level of performance may take weeks, and for some structures months, of practice, and while the rule-based definition of regions can be shared, the procedural aspects of tracing are likely to be lab-specific. Semiautomated voxel-based methods of digital morphometry (VBM, Ashburner et al., 2003) were recently introduced to overcome the limitations of manual volumetry and to standardize the methods of regional volume estimation. Although neither fully automated nor truly assumption-free as often stated, voxel-based measures are perfectly repeatable and are well suited for hypotheses-free exploration of the voluminous MRI data sets by operators with very limited anatomical acumen. By contrast, even in the hands of highly trained operators manual methods do not attain perfect reliability of the computerized approaches, although in reputable labs, reliability estimates for the reported regions top intraclass correlations of 0.90. Unfortunately, what VBM gains in reliability, it may sacrifice in validity. Trained human observers have several advantages over digital approaches that are guided almost exclusively by local data and have no access to the “top-down” knowledge of anatomy available to a human operator, although recently attempts were made to incorporate “training-like” information in computer decision making (Fischl et al., 2002). While dependence on local data is not a problem in measurement of large and relatively smooth structures and regions that exhibit relatively minor individual differences, in evaluation of

smaller and more irregular structures that vary substantially across individual brains, local differences in signal intensity increase the likelihood of misrepresentation. Finally, although both manual and VBM analyses start with the same high-resolution volume images, in the latter, subsequent segmentation, filtering and warping designed to fit diverse brains into a standard template may reduce the resolution 100-fold (from 1 × 1 mm acquired pixel to 10 × 10 mm filtered pixel) and make the measures more vulnerable to partial voluming errors, especially in small structures (Scahill et al., 2003). A direct comparison of VBM methods with manual volumetry in an investigation of age-related differences reveals some notable discrepancies (along with some significant areas of agreement) between the two approaches (Tisserand et al., 2002). Thus, although the VBM approach is not likely to replace manual volumetry, it may prove to be a valuable source of hypotheses generated with relative ease and in a reasonably short time.

10. Conclusions

Drawing on the extant literature reviewed above, we can suggest several tentative conclusions. First, the postmortem and structural neuroimaging literature indicates that the human brain shrinks with age, and brain shrinkage is selective and differential, not uniform or randomly distributed. Through most of the adult lifespan, the tertiary association cortices, the neostriatum, and the cerebellum are more profoundly affected by aging than sensory cortices and the pons. The subcortical white matter and the hippocampus show substantial shrinkage in the older old and the rate of shrinkage may be accelerated by hypertension.

Second, the study of age-related differences in metabolic markers of neural integrity in vivo has begun to yield important contributions to our understanding of neural viability and their relation to more molar measures of the human brain. Studies consistently find a decline in brain metabolites in selected regions of the gray but not the white matter. These apparent differences on the cellular level parallel the structural findings suggesting that age-related shrinkage of regional cortical gray matter may indeed reflect reduction in the size or the density of neurons that make up these cortical regions.

Third, these structural changes in the human brain may impact cognition across the older age span. Lesser volumes of the brain regions that are thought to underlie and support varying aspects of cognition have been linked to poorer performance in those domains. For example, poorer performance on executive function tasks has been associated with smaller volume of the prefrontal cortex and increased white matter hyperintensity burden. Skill acquisition performance is enhanced in those individuals who show larger volume of the striatum, prefrontal cortex and cerebellum. Spatial memory performance has been linked to hippocampal volume and NAA level. Entorhinal cortex shrinkage has been found to predict memory decline, even in healthy individuals. Results across studies (particularly cross-sectional) are not unequivocal, however, and the relationship between cognition and brain changes with aging may be most clearly elucidated with longitudinal designs.

Fourth, both positive and negative modifiers alter normal aging trajectory. Hypertension is a salient and significant negative modifier of brain aging, even when diagnosed and treated. Presence of vascular risk factors and even mild vascular disease augurs a significant

acceleration in regional brain aging, especially in the hippocampus and posterior regions of the brain. The evidence suggesting that a large share of age-related changes is accounted by vascular pathology continues to accumulate. The hippocampus appears especially vulnerable to multiple negative modifiers of aging. Other putative negative modifiers are stress and hormonal depletion. Aerobic fitness may be a protective factor (a positive modifier) for the aging brain. Whereas reduction in the level of sex steroids has a negative affect on the brain and consequently cognition, the role of hormone-replacement therapy remains unclear vis-à-vis the apparent discrepancy between the positive results of laboratory and small-sample human studies and the negative findings from large-scale epidemiological studies and clinical trials. Understanding the modifying mechanisms of brain and cognitive aging will serve to both better understand the normal aging process and to identify potential points of intervention to the aging process.

Lastly, numerous mechanisms that potentially initiate and promote brain aging have been proposed but as far as human aging is concerned, those theories remain untested. As it is unlikely that a single mechanism causes the diversity of phenomena that constitute biological and cognitive aging, the future challenge to research in this area is to interpret the findings in the context of multiple and at least partially synergistic biological mechanisms. Such mechanisms that may combine to converge on the end state of brain shrinkage and cognitive decline include wear and tear of the neural infrastructure (demyelination, altered microvasculature, loss of dendritic arbor, apoptosis and impaired synaptogenesis) as well as function (underperformance of selected neurotransmitter systems, dysre-gulation of glycemic control and stress response, impaired hemodynamic shift in cellular calcium flow patterns). More systematic studies of combined structural and metabolic imaging in humans and longitudinal studies combining noninvasive imaging and histology in a suitable animal model are needed to determine the neural basis of the observed differential brain shrinkage.

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