8

Normal Aging

Brain Morphologic, Chemical and Physiologic Changes Detected with in vivo *MRI*

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Key Points

- MRI is sensitive to multiple dimensions of the aging process in the brain.
- Key dimensions which change in aging are regional atrophy, vascular differences, increased water diffusion, reduced perfusion, and metabolic and functional changes.
- MRI evidence has shown that brain changes related to healthy aging are distinct from specific brain changes due to neurological diseases of age.

Introduction

Magnetic resonance imaging (MRI) is a medical imaging technique that is widely used in the assessment of structural and functional brain changes in aging. MRI scanners use strong magnetic fields and radio waves to form images of the body. The popularity of MR methods in aging research can be attributed to their ability to probe the brain noninvasively using several different contrast mechanisms that are sensitive to different properties of brain tissue (e.g., water content, diffusion environment in the brain, concentration of different metabolites, perfusion, and oxygenation of blood). MR exams involve minimal risk and the hardware is now widely available, which makes MRI an ideal tool in aging research and clinical practice.

Imaging older individuals with MRI is associated with unique challenges. Claustrophobia related to the MRI environment was actually found to be lower in subjects over 65 years of age and higher in middle-age (40–65-year-old) individuals, particularly women.[1] Technical concerns of imaging older patients include motion artifacts[2] and limitations of subject positioning (for instance from exaggerated kyphosis) in the scanner. Subject sedation is frequently helpful to obtain a good quality study in these cases although sedatives may affect functional MRI data acquisition. Furthermore, ferromagnetic medical devices commonly prescribed to the elderly such as cardiac pacemakers, cochlear implants or neurostimulation devices constitute a contraindication for MRI. Other medical devices such as orthopedic instrumentation or vascular stents, albeit not a formal contraindication for MRI, are associated with image artifacts that may reduce the utility of MRI exam.

These challenges notwithstanding, this review focuses on age-related changes in the brains of healthy elderly subjects as measured with state-of-the-art MRI techniques. Specifically, the review

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covers changes in brain structure and volume (structural MRI), water diffusion (diffusion-weighted imaging: DWI and diffusion tensor imaging: DTI), biochemical composition of neural tissues (MR spectroscopy: MRS), neuronal activity (functional MRI: fMRI) and cerebral blood flow (perfusion MRI). Positron emission tomography (PET) imaging studies and findings in Alzheimer's disease are reviewed in chapters 9 and 21 of this book, respectively.

Structural MRI

Volumetric studies

Aging is associated with a number of brain structural changes that are amenable to noninvasive imaging evaluation. These changes include brain volume loss (brain atrophy), both global and regional (Figure 8.1), white matter T2 signal hyperintensities (also called leukoaraiosis), iron and calcium accumulation, functional rearrangements, and microstructural changes occurring in "normal appearing" brain that are only detected with functional imaging techniques. These changes seen in normal or physiologic aging typically present along the continuum leading to the morphologic features associated with cognitive impairment and dementia.

An important scientific question and a matter of debate has been whether brain atrophy as seen in normal aging can result from physiologic processes, or whether atrophy implies neurodegeneration as in Alzheimer's disease (AD).[3] This and other questions related to brain morphometric changes are best addressed by longitudinal imaging studies. Fjell et al.[4] presented a longitudinal study of brain atrophy comparing volume changes across the cerebral cortex in healthy elderly subjects and AD patients from the AD Neuroimaging Initiative (ADNI). Volumetric reductions of the cortex and subcortical brain structures with expansion of the ventricles were seen in normal aging after just one year of observation[4] with the hippocampus and amygdala being the two structures that showed the largest decline. Fjell et al. found that healthy elderly subjects had an atrophy rate of about 0.5% per year and that volume loss was widely distributed across the brain and included common regions for AD-associated pathology in addition to areas not typically associated with AD. Since it was not clear if these changes could have been affected by undetected early AD, a later study by this group measured one-year brain atrophy in 132 healthy elderly persons who had remained free of mild cognitive impairment (MCI) or AD for at least three years.[5] Volumetric reductions were found throughout the brain in all groups, regardless of the risk for developing AD. Volume reductions were especially pronounced in medial and lateral parts of the temporal lobe, medial and lateral orbitofrontal cortex, and precuneus/retrosplenial cortex, closely matching the previously described frontotemporal pattern of changes in healthy aging.[5] This suggests that

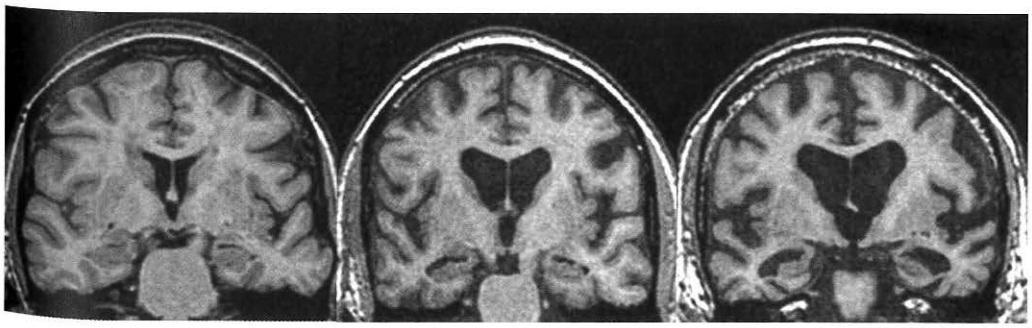

Figure 8.1 Coronal T1-weighted MRI at the level of the hippocampal head in a normal elderly subject (left), MCI patient (center) and AD patient (right). A continuum of cortical and hippocampal atrophy combined with loss of white matter volume is evident.

not all brain volume changes in aging necessarily reflect incipient AD, but rather that volume reductions are a general feature of normal aging.

Cross-sectional studies Cross-sectional MRI studies have demonstrated consistent age-effects,[6–13] particularly involving volume loss in the prefrontal cortex. Age-related atrophy suggests increased vulnerability of the lateral prefrontal cortex[6] and superior temporal lobe[12] versus other brain regions. Cerebral cortical thinning occurs by middle age encompassing widespread cortical regions including primary and association cortices.[7] Interestingly, sex does not appear to exert significant influence on the age-related trajectory of brain volumes among normal controls or AD patients.[11] In a meta-analysis of cross-sectional and longitudinal imaging studies[14] it was found that brain atrophy correlated with age even among subjects younger than 60, suggesting a linear trajectory of brain atrophy over time. In the same study, when two-year follow-up cognitive data of healthy elderly subjects from the ADNI cohort were used to exclude participants with cognitive decline, significant atrophy in all regions of interest (ROIs) was still found. This is consistent with the previously described account and suggests that brain atrophy is part of normal aging and not necessarily caused by underlying pathologic neurodegeneration.

Longitudinal studies Estimates of annual atrophy rates from longitudinal studies tend to be higher than estimates from cross-sectional studies.[15–17] For example, longitudinal studies have reported yearly whole-brain volume decreases on the order of 0.2–0.5%.[17–20] The hippocampus, the most frequently studied structure due to its association with AD pathology, shows annual atrophy rates from 0.79% to 2.0%.[15–17,19,21,22] Notably, age-related volumetric change in the hippocampus may be curvilinear rather than linear[23–26]. Entorhinal cortex longitudinal volume decline ranges between 0.3 and 2.4%. [16,19,27] Atrophy rates in other parts of the brain are less frequently assessed[16,28–30] but prominent volumetric decreases have been reported in prefrontal cortex, association cortices, caudate nucleus, cerebellum,[16] and parietal cortex[30]. The cumulative effect of cerebral atrophy—including gray and white matter—is expansion of the cerebral ventricles.[29] Longitudinal tracking of volume change in brain structures with advancing age has revealed several different trajectories related to anatomical region, tissue type, rate of change, and sex. The corpus callosum was the only structure which did not show a consistent volume change with age.[31] Longitudinal atrophy of the cholinergic basal forebrain (BF) was found to be significantly higher than rates of global brain shrinkage even in cognitively stable healthy elderly individuals.[32] Compared with healthy control subjects, very mild AD patients showed reduced BF volumes at baseline and increased volume loss over time.

Voxel-based morphometry studies There have been many voxel-based morphometry (VBM) investigations on gray matter volume changes with aging. Most cortical regions have been reported to show a linear, negative association between volume and age, most prominently in frontal and insular areas[33–40] with relative preservation of limbic and paralimbic structures.[34–36,39] Preservation of these limbic or paralimbic regions is consistent with the functional importance of the thalamolimbic circuits in sensory integration, arousal, emotion and memory.[35] Structural preservation in areas with earlier ontogenic maturation such as the limbic lobe supports the developmental hypothesis that the first structures to develop (like primary sensory and motor cortices) are the most resistant to aging effects, whereas later-maturing cortical regions (such as association cortices including the prefrontal cortex) are more vulnerable to age-related atrophy.[36] Before age 50, prefrontal areas showed linear volume reduction with advancing age, while medial temporal regions showed volume preservation.[39] Cortical gray matter volume showed age-related reduction even during adolescence, likely reflecting synaptic pruning.[41]

Regarding the functional consequences of brain atrophy: atrophy in hippocampus, entorhinal cortex, and prefrontal cortex is associated with impairment of declarative memory; reduced hippocampal volume in particular relates to memory declines in aging and dementia;[42] and decline

in entorhinal cortex volume predicts progression from MCI to dementia.[43,44] However, in healthy adults, the relationship between memory and regional volumes is unclear. The volumes of these three structures measured on MRI studies acquired five years apart showed that age was negatively correlated with the volume of hippocampus and prefrontal cortex,[45] although when memory performance was corrected for age, none of the regional volumes was significantly related to the age-corrected memory measures. However, greater annual rate of shrinkage in entorhinal cortex predicted poorer memory performance;[45] that is, absolute regional volume at a given age was not predictive, but the first derivative of volume versus age was predictive. Thus, in a healthy and educated population, even mild age-related shrinkage of the entorhinal cortex may be a sensitive predictor of declarative memory performance.

Elderly compared to young controls showed a 10–30% reduction in cortical gray matter in widespread frontal, temporal, and parietal regions, 6–13% loss in the visual and sensorimotor cortices and up to 13% loss in the direct hippocampal network ROIs.[46] The pattern of cortical atrophy in moderate AD versus elderly controls was similar to that in prodromal AD, but was more severe in the direct hippocampal network ROIs and sensorimotor, visual, and temporal cortices (13–15% loss compared with elderly controls).[46] Although the brain shrinks with age, the trajectory of this atrophy and the degree to which it can be influenced by other factors is not clear. Atrophy in the lateral prefrontal cortex, the hippocampus, the cerebellum and the caudate nucleus can be detected over a six-month interval in young (age 20–31) and elderly (age 65–80) controls and is aggravated by hypertension.[47] Interestingly, cognitive interventions may interfere with this volume loss: intensive cognitive practice showed a protective effect for volume loss in the cerebellum, although not specifically related to improvement in the targeted cognitive skills.[47] Moreover, both younger and older normal adults in spatial navigation training displayed stable hippocampal volumes both within a four-month training phase and four months after termination of training, whereas non-trained participants that served as controls displayed declining hippocampal volumes consistent with normal age-related decline.[48]

In summary, age-related brain volume loss is a complex function of preferential cortical shrinkage with expansion of cerebrospinal fluid (CSF) spaces which is objectively measured using quantitative imaging and is different in quality and degree from changes associated with neurodegenerative diseases such as AD.

Brain iron and calcium deposition

MRI is very well suited for *in vivo* assessment of regional iron content in the brain. Paramagnetic materials such as iron have very high magnetic susceptibility and, thence, a short transverse relaxation time (T2). On T2-weighted images, iron-rich regions such as the basal ganglia, red nucleus, and substantia nigra appear hypointense (dark). A variety of MRI techniques are sensitive to detecting brain iron deposition such as gradient recalled echo (GRE), susceptibility-weighted imaging (SWI) and magnetic field correlation (MFC).[49]

Accumulation of nonheme iron in the brain has been proposed as a biomarker of the progressive neuroanatomical and cognitive declines in healthy aging. Cellular degradation related to iron accumulation might explain the cumulative structural declines that accompany aging and neurodegenerative disease.[50] Postmortem studies indicate that iron content is regionally specific, with a predilection for the basal ganglia, probably related to dopaminergic neurotransmission. A meta-analysis of MRI studies that estimated iron content in the caudate nucleus, globus pallidus, putamen, red nucleus, and substantia nigra supports a robust association between advanced age and high iron content in the substantia nigra and striatum, with a smaller effect noted in the globus pallidus.[50] The smaller age effect observed in the pallidus may reflect the earlier onset of free iron accumulation, resulting in a ceiling effect. Different brain structures accumulate iron at different rates throughout the adult lifespan. Typically, the striatum and brainstem structures are higher in

iron concentrations in older than younger adults, whereas cortical white matter and thalamus have lower concentrations in the elderly than young adults.[51] Finally, in healthy adults, age differences in memory can be explained in part by individual differences in hippocampal volume that in turn are associated with differences in hippocampal iron concentration.[52] Lower memory scores were linked to smaller hippocampi with higher iron concentration.

Symmetrical calcification in the basal ganglia is a frequent finding at computed tomography (CT) and MRI scans of the elderly general population.[53] Calcifications involving striatum and pallidum and eventually the dentate nuclei (strio-pallido-dentate calcification) reach an incidence of at least 0.7% of CT scans,[54] more frequently seen in the globi pallidi with symmetric distribution. Most of these are physiological and age related, without associated symptoms.[55]

White matter T2 hyperintensities

White matter T2 hyperintensities, or leukoaraiosis (LA), are well established changes that occur in the aging brain (Figure 8.2). These are lesions which are known to increase in volume over time[56] and are also increased in AD compared to controls.[57] The pathologic substrate of LA is multifactorial, including demyelination, increased interstitial fluid, and gliosis. The intersection of these factors may contribute to the difficulty of correctly interpreting MRI evidence indicating potential demyelination. For example, T2-weighted or FLAIR scans overestimate periventricular and "perivascular" white matter lesions compared to histopathologically confirmed demyelination.[58] The relatively high concentration of interstitial water in the periventricular and perivascular regions due to increased blood-brain-barrier permeability and plasma leakage in brain aging may result in large LA volume despite relatively mild demyelination. Smooth periventricular hyperintensities such as caps around the frontal horns and parasagittal periventricular bands are likely to be of nonvascular origin.[59] They relate to disruption of the ependymal ventricular lining which in turn leads to widening of the extracellular space. These changes must be differentiated from true subcortical and deep white matter abnormalities. Among the latter, a distinction is made between punctate, early confluent, and confluent LA types. Although punctate white matter lesions often represent widened perivascular spaces without substantial ischemic tissue damage, early confluent and confluent lesions correspond to incomplete or complete ischemic infarction with gliosis.[59] In a meta-analysis on the association of LA location and cognitive function in the elderly, a greater number of studies

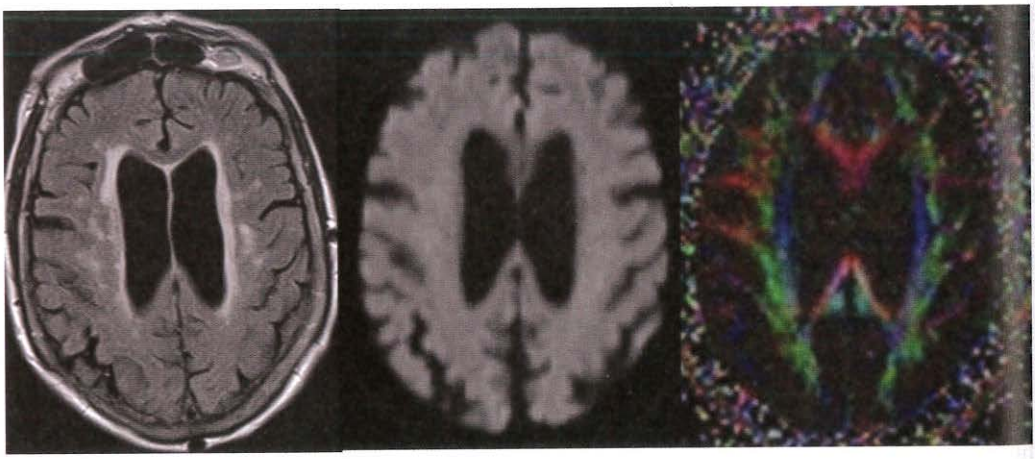

Figure 8.2 Axial FLAIR (left), average DWI (center), and DTI color map (right) coded for direction of diffusion (red: right–left; green: anterior–posterior; blue: craniocaudal). Healthy 92-year-old female showing paraventricular bands and patchy deep WM T2 hyperintensities typical of leukoaraiosis.

found an association between periventricular LA and executive function/processing speed, rather than for subcortical LA.[60]

Increasing age, vascular risk factors[61] and lower cognitive speed and flexibility (a component of executive function), were both significantly associated with LA throughout the brain.[57] Recently identified genetic factors correlate with load of LA, and these factors include a locus on chromosome 17q25 in addition to apolipoprotein E status.[59] LA is associated with motor, cognitive, mood, and urinary disturbances and disability as well as with gait and stance abnormalities, upper motor signs, and finger tap slowing. These effects are independent of age and sex, and from lacunar and nonlacunar cerebral infarcts.[62] LA volume predicts increased risk of transition from an autonomous to a dependent status after three years of follow-up.[63] Furthermore, executive function[64] and processing speed[57] are cognitive domains commonly affected by LA burden. The association between LA and cognition is imperfect, and the concept of reserve (both at the cognitive and brain levels) may account for a significant amount of variance.[65] For example, participants with higher estimated reserve had more pathology in the form of LA, suggesting that they are better able to cope with pathology than those with lower estimated reserve.[65] LA is an independent predictor of decline in physical function in the elderly and suggests that interventions to prevent the development or progression of LA may help preserve physical function in older people.[66]

Diffusion-Weighted MRI

Diffusion-weighted imaging

The motion of water molecules in biologic tissues, known as Brownian motion, is a physiologic parameter that is altered in disease states and can be captured by diffusion-weighted imaging (DWI).[67] DWI has become one of the routine MR imaging sequences of the brain. The clinical usefulness of DWI is the diagnosis of not only acute cerebral infarction but also neoplasm, infectious/inflammatory disease, toxic/metabolic disease, and degenerative disease.[68] DWI is usually obtained in three orthogonal orientations using spin-echo type single-shot DW echo-planar imaging with b-values between 0 and 1000 s/mm^2. These three planes are combined into isotropic DWI, and apparent diffusion coefficient (ADC) maps are calculated on a voxel-by-voxel basis. The distinction between these two measures is readily apparent as gray matter on DWI is generally hyperintense when compared with white matter, but typical ADC values of gray matter ($0.76 \pm 0.13 \times 10^{-3}$ mm^2/s) and white matter ($0.77 \pm 0.18 \times 10^{-3}$ mm^2/s) are identical in the adult brain.[69] ADC measurements are affected by the number and by the strength of b-values utilized.[70,71]

ADC values of brain tissue have the potential to assess subtle structural changes that are not visible on conventional MRI.[72–77] Studies of ADC changes in normal brain due to aging, gender, laterality, and anatomical locations have been published.[78–82] DWI signals are higher in the cingulate gyrus and insula than in other cortices. However, there are no significant ADC differences among most areas of human cerebral isocortex.[78] The ADC values of the brain tissue gradually increase with aging.[69–71,79–84] Although this increase is mild and observed in all parts of the brain, it is usually more apparent in the white matter and lentiform nucleus than in the rest of the brain. Enlargement of extracellular space by the volume decrease of neurons and myelinated fibers, increasing heterogeneity of axonal organization, and change of capillary walls and loss of pericytes with aging contribute to increased ADC values.[75,83,85] To evaluate the effect of aging, it may be important to perform segmentation of gray and white matter. Whole-brain diffusion histogram analysis using the orientation independent DTI method is a good method to evaluate the age-related change of ADC.[84,86,87] Watanabe et al. measured mean diffusional age-related changes using whole-brain ADC histogram analysis and four different life stages were identified in ADC peak values: 1) exponential decrease of ADC at very fast (0–2 year) and 2) slower rate (2–20 years)

through infancy, childhood, and early adulthood, 3) stable peak ADC in adulthood (20–60 years), and 4) gradual, linear increases in ADC through the later adulthood (≥60 years).[84]

Hippocampal ADC is higher in MCI and AD patients.[75,77] ADC values in the hippocampal formation are elevated before conventional MRI reflects early ultrastructural changes in the progression of AD. ADC of the temporal stem and posterior cingulate, occipital, and parietal white matter is higher in AD compared to controls. Dementia with Lewy bodies is characterized by increased ADC in the precuneus.[88] Increased ADC is identified with different distribution patterns among different variants of frontotemporal dementia.[89]

Diffusion tensor imaging

Diffusion tensor imaging (DTI) can provide information on microstructural tissue integrity by measuring water diffusion in at least six directions to estimate a three-dimensional diffusion model (the tensor).[90] The directions of water diffusion can be color coded on the resulting images (Figure 8.2). There are two coefficients on DTI—mean diffusivity and fractional anisotropy, axial diffusivity and radial diffusivity. Mean diffusivity (MD) is synonymous with the apparent diffusion coefficient (ADC) described for diffusion weighted imaging. Fractional anisotropy (FA) is defined as a coefficient of variation of the eigenvalues and is an index of the degree of directionality of water diffusivity. The first eigenvalue is called axial diffusivity (AD; diffusion parallel to the axon fibers; not to be confused with the AD abbrevation of Alzheimer's disease), whereas the second and third eigenvalues can be averaged and expressed as radial diffusivity (RD; diffusivity perpendicular to the axonal fibers).[91] Axonal damage, as occurs in secondary degeneration, is likely to result in decreased AD values, while myelin breakdown is associated with an increased RD and a normal AD.[92–94] Scanner magnetic field strength has significant effects on diffusion tensor derived brain connectivity.[95] Normal regional reference data of DTI have been published on 1.5 and 3 Tesla MRI systems.[96,97] Intrasubject coefficient of variation was typically <1% for all scalars and regions. Intersite or intervendor coefficient of variation increased to 1%–3%.[98]

FA decreases by aging; however, there are no significant differences found due to gender and laterality.[86,87,91,99,100] There is a significant relationship between age and increased mean diffusivity/decreased FA.[101] This likely results from degradation of microstructure with age, including an increase of brain water content, demyelination, disruption of axon structure, and overall rarefaction of fibers. Increased RD is associated with increased MD and decreased FA with age.[102] It is usually assumed that RD is modulated by the extracellular distance between membranes, axon diameter, and degree of myelination.[91] Throughout adulthood, white matter volumes and microstructural changes as assessed with DTI show a linear negative association in the anterior thalamic radiation, internal capsule, cerebral peduncle, cerebellum, and external capsule,[103] and some reports suggest that white matter DTI changes precede volume changes. Nonlinear relationships between white matter volume and age have been found in the left superior longitudinal fascicle and bilateral superior corona radiate.[103]

Increased MD and decreased FA are consistently found in Alzheimer's disease, prodromal AD, and even in cognitively normal elderly who progress to MCI.[104,105] The patterns of DTI changes and areas of reduced FA differ among AD and dementia with Lewy bodies.[106–108]

Magnetic Resonance Spectroscopy (MRS)

Proton magnetic resonance spectroscopy (^{1}HMRS) detects signals from relevant brain metabolites such as N-acetyl aspartate (NAA; a putative neuronal marker[109]), lactate (Lac; by-product of anaerobic metabolism), creatine (Cr; energy intermediary), choline (Cho; membrane turnover marker), myo-Inositol (mI; glial marker), and the neurotransmitters glutamate (Glu) and GABA. Since

MRS detects signals from metabolites with a concentration four orders of magnitude lower than water, it has an intrinsic low signal-to-noise ratio compared to MRI techniques, which is the most important limitation of the method.

Meta-analyses of MRS studies comparing younger with older healthy volunteers suggest that the neuronal integrity marker NAA decreases[110,111] and Cho and Cr increase with age.[111] On the other hand, a constant concentration of brain NAA between young and elderly healthy controls was reported[112,113] suggesting that neuronal integrity is maintained across the lifespan. MRS metabolites showed substantial heritability, which was greatest for NAA (72%).[114] Furthermore, no age-dependent NAA decreases were observed in the posterior cingulate cortex or in the left hippocampus in 90 healthy volunteers.[115] This is in contradistinction to the well-established NAA deficits in these locations in AD[116] (Figure 8.3). However, NAA as measured in arbitrary units correlates inversely with age,[117] while white matter choline increases with aging.[118] mI increased slightly and total NAA decreased slightly with increasing age in the supraventricular white matter.[119] Metabolic differences related to aging could result from relaxation changes: elderly NAA, Cr, and Cho T2s were 12%, 6%, and 10% shorter than for adolescents, a change of under 1 ms/year assuming a linear decline with age.[120] This change in relaxation would result in a concomitant reduction in signal for the corresponding metabolite when absolute concentrations are not reported. Older age was associated with lower Glu levels in the striatum, but not in the cerebellum or pons,[121] as well as in the parietal gray matter and basal ganglia, and to a lesser degree in the frontal white matter.[122] Frontal and parietal GABA was negatively correlated with age in healthy controls between 20 and 76 years of age.[123]

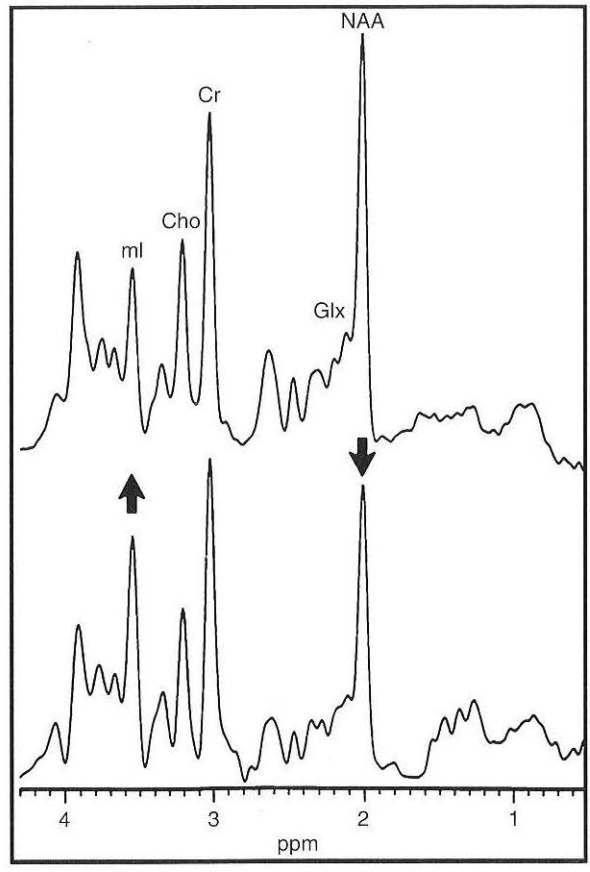

Figure 8.3 Proton spectrum in normal control (above) and AD patient (below) displaying reduced NAA and increased mI in AD.

Tissue levels of the membrane-associated phospholipids phosphocholine (PC), phosphoethanolamine (PE), glycerophosphocholine (GPC), and glycerophosphoethanolamine (GPE) can be studied by *in vivo* ^{31}P MRS, which has even lower sensitivity than proton MRS due to the lower concentration of phosphorus vs. proton (hydrogen) nuclei in cells. Strong inverse relationships of the PE/GPE and PC/GPC ratios with age were found.[124] A significant age associated decrease in brain pH (-0.53% per decade), increase in phosphocreatine (PCr) (1.1% per decade) and decrease in phosphomonoesthers (PME) (1.7% per decade) were found in total tissue.[125] Compared with young subjects, neuronal mitochondrial metabolism and glutamate-glutamine cycle flux was approximately 30% lower in elderly subjects as assessed with combined ^{1}H and ^{13}C MRS. The reduction in individual subjects correlated strongly with reductions in NAA and Glu concentrations consistent with chronic reductions in brain mitochondrial function with aging.[126]

Functional MRI

Task-related fMRI

Paramagnetic deoxyhemoglobin in venous blood is a naturally occurring contrast agent for MRI which produces what has been referred to as the blood oxygen level dependency (BOLD) effect.[127] Changes in the BOLD effect signal are induced by neurovascular coupling in response to neuronal activation, and this observable correlate of brain activation has been extensively used to noninvasively assess brain function with functional MRI (fMRI). Task-based fMRI relies on comparative measurement in which contrasts are created between the BOLD signal observed in one condition (e.g., performing a naming task) to BOLD signal observed during another condition (e.g., passive fixation, simple arithmetic, or perceptual judgment). The contrast between BOLD signals obtained during different conditions is then analyzed to create a map reflecting condition-specific patterns of BOLD signal and—by extension—neural activity. This technique has been frequently applied to aging populations with goals including distinguishing healthy aging from pathological aging, characterizing regional differences between brain activation in young and older adults, and monitoring longitudinal changes in individual patterns of brain activity with age.

One well-known theory of cognitive aging has suggested that changes in the functional organization of the aging brain are the result of progressive cortical disconnection due to an increasing burden of white matter damage.[128] Specifically, some researchers have suggested that brain networks are adaptively reorganized in response to age-related decline in neuronal, structural, and functional integrity leading to an increase in prefrontal activation in the brains of older adults.[129] On the other hand, reduced activation has been observed in posterior cortical areas subserving cognitive domains including visual attention, episodic retrieval, and working memory.[130] In addition to the posterior-to-anterior shift in brain activity, increased activation has been observed contralateral to brain regions most active in young subjects and particularly in the frontal lobes. This pattern has been dubbed Hemispheric Asymmetry Reduction in OLder ADults (HAROLD), and HAROLD has been observed in a variety of cognitive tasks, including perception, episodic memory, semantic memory, working memory, language, and inhibition tests.[131]

Age-related asymmetry reductions in functional activation may reflect compensation in response to structural brain damage or other age-related changes in brain function.[131] Relevant evidence consistent with this perspective has emerged from studies of several cognitive domains including memory. As noted earlier in this chapter, the volume of hippocampus is reduced in older adults and is associated with declines in memory function. A corresponding reduction in medial temporal lobe activation has been observed in fMRI studies of memory processes in older adults.[132] However, successful memory in older adults was uniquely related to bilateral activation in the prefrontal cortex,[132,133] which is suggestive of compensation-related recruitment of PFC to offset declining hippocampal function.

This broad pattern of functional decline in one brain region being offset by functional recruitment of another is cited in support of the Scaffolding Theory of Cognitive aging (STAC) proposed by Park and Reuter-Lorenz.[134] Those authors describe scaffolding as "the recruitment of additional circuitry that shores up declining structures whose functioning has become noisy, inefficient, or both" (p. 183). This and other theoretical accounts have frequently incorporated primarily task-related fMRI data, but resting-state fMRI (rs-fMRI) has also contributed significantly to the literature of functional changes related to aging.

Resting state fMRI

In contradistinction with task-related functional studies, resting-state functional connectivity (RSFC) targets the coordinated nature of brain function between brain regions, and is often measured using estimates of temporal correlation in the BOLD signal between different brain areas while participants rest passively in the MRI scanner.[135] Supporting the notion of age-related changes in network organization, alterations have been observed in the patterns of temporal coherence of spontaneous activity in the brain at rest in older versus younger adults. These changes encompass multiple brain networks in addition to the organization of whole-brain networks.[136]

The most widely studied resting state network (RSN) is the so-called "default mode network" (DMN).[137] The DMN is composed of the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and portions of the inferior, medial and lateral parietal cortices[138] (Figure 8.4). Age-related reductions in RSFC have been reported in the DMN as well as in the dorsal attention and the frontoparietal control networks.[139] In comparison to young individuals, older adults show an interesting dissociation: weaker RSFC is observed within brain networks subserving high-level cognitive functions; but stronger connections are observed between networks.[140] Furthermore, network boundaries are less distinct (i.e., reduced "system modularity") in older compared to young adults.[140]

One important caveat for rs-fMRI in older adults is that motion can be a serious confound[2] which has affected some previously published work. Resting-state studies are even more vulnerable to motion-related confounds than task-related fMRI because rs-fMRI inherently lacks any time-based model for patterns of coordinated activation, relying instead on sophisticated post-processing of data.[141] Recent rs-fMRI studies that have addressed these concerns have shown that the effects of age on the various RSNs are independent of decreases in gray matter volume, sex, and subject motion.[142] This supports the notion of network-specific effects in aging which manifest as increased tonic activation of task-positive networks (e.g., those supporting higher-order cognitive functions and cognitive control), along with reduced task-negative DMN and posterior sensory visual networks activations during rest.[142] It has also been suggested that age reduces the brain's ability to disengage the so-called "task-negative" DMN in favor of task-relevant brain networks,

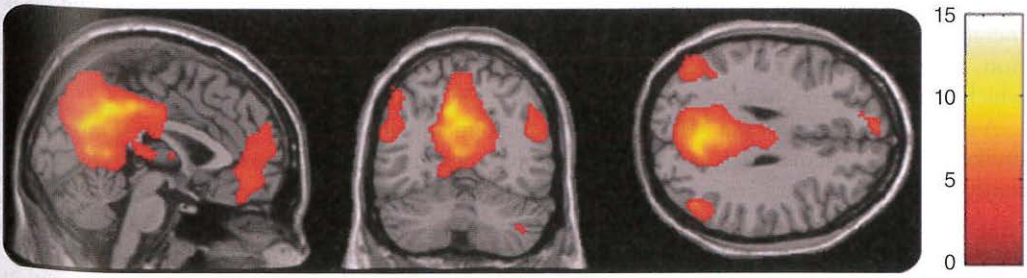

Figure 8.4 DMN activation areas in normal subjects.

and that this pattern may contribute to some cognitive aging effects.[143] Intriguingly, this pattern may extend to pathology as recent studies of RSFC in AD and MCI have reported decreased connectivity in the DMN along with increases in other RSNs.[144]

Perfusion-Weighted MRI

Oxygen metabolism and cerebral blood flow (CBF) were traditionally studied *in vivo* with invasive nuclear medicine methods requiring contrast agent administration and radiation exposure such as positron emission tomography (PET). Noninvasive quantitative MRI can also be used to measure CBF and O_2 metabolism. Different MRI techniques are available for this purpose such as dynamic susceptibility contrast (gadolinium based) or arterial spin labeling (ASL) perfusion MRI[145] that assess CBF and other blood flow related parameters. Furthermore, BOLD based T2* mapping MRI informs on the degree of tissue oxygenation and local concentration of deoxyhemoglobin.[146] Changes in CBF therefore have implications for the use of fMRI techniques in older adults, especially when estimated changes in brain activity are compared to those of younger adults with potentially different patterns or values of CBF.[147]

CBF of the cerebral gray matter decreases with increasing age,[148] which might be explained by impaired cerebral autoregulation or, alternatively, by a decrease in oxygen demand. Furthermore, degenerative microvascular changes associated with the normal aging brain may also reduce the level of CBF. Using pulsed ASL, a CBF decrease of approximately 30% in the elderly compared to young controls was detected in the cerebral cortex together with reduced T2′ (T2 corrected T2*) consistent with higher deoxyhemoglobin content.[149] The CBF decrease in the elderly is thought most likely to result from physiologic age-related changes leading to neuronal shrinkage and/or degenerative change of the microvasculature. A correlation was found between hippocampal perfusion and memory performance in the absence of atrophy in cognitively normal elderly, suggesting that perfusion correlates more strongly than tissue volume with memory performance.[150] Brain hypoperfusion in AD as detected with continuous ASL perfusion MRI reliably identifies AD patients from elderly controls.[151]

Outlook and Future

The utility of MRI in aging research and clinical practice is steadily improving with the introduction of novel contrast mechanisms to probe the brain tissue. Most of the above imaging methods will benefit with the emergence of high field (e.g., 7 T) MRI scanners, compared to the widely available 1.5 T and 3 T scanners. The increased field strength will provide a significant increase in MRI signal, which can be capitalized upon to improve spatial resolution.[152,153] The improved spatial resolution translates to improved volume estimates and the imaging of brain substructures, which was not often possible at lower field strength.[152] The improved signal strength as well as the increased spectral range at higher field strength can translate to much higher sensitivity in detecting weak metabolites in applications such as MRS, which were not possible at lower field strengths. In addition, many of the contrast mechanisms (e.g., BOLD) are further strengthened at higher fields, which again translates to higher spatial resolution and sensitivity.[154,155]

A drawback of most of the MRI methods is the difficulty in obtaining quantitative information, unlike imaging schemes such as computed tomography and positron emission tomography. Currently several researchers are investigating quantitative MRI methods, where accurate maps of tissue properties such as T1, T2, T2* relaxation maps are generated. A challenge associated with these quantitative methods is the increased scan time required to estimate the parameters. These problems may be mitigated by advances in parallel MRI, which significantly accelerates the acquisition time of MRI.[156]

Key Readings

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