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Structural and Functional Imaging Correlates for Age-Related Changes in the Brain

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In recent years, investigators have made significant progress in documenting brain structure and function as it relates to aging by using positron emission tomography, conventional magnetic resonance (MR) imaging, advanced MR techniques, and functional MR imaging. This review summarizes the latest advances in understanding physiologic maturation and aging as detected by these neuroimaging modalities. We also present our experience with MR volumetric and positron emission tomography analysis in separate cohorts of healthy subjects in the pediatric and adult age groups respectively. Our results are consistent with previous studies and include the following: total brain volume was found to increase with age (up to 20 years of age). Whole brain metabolism and frontal lobe metabolism both decrease significantly with age (38% and 42%, respectively), whereas cerebellar metabolism does not show a significant decline with age. Defining normal alterations in brain function and structure allows early detection of disorders such as Alzheimer's and Parkinson's diseases, which are commonly associated with normal aging.
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With life expectancy increasing during the past 100 years, it is projected that 30% of the population will be older than 65 years of age by 2010.[1-4] This triumph in public health has expectedly seen a parallel increase in the number of neurological degenerative disease states, such as Alzheimer's disease. With this in mind, research dedicated to understanding brain structure and function as it relates to the aging process in healthy adults, which we will term physiologic aging, will allow investigators to answer questions about its pathologic counterpart, the degenerative disorders.

Of notable significance is the number of in vivo imaging modalities that have been used in the last decade to understand age-related changes of the brain. Knowledge of the intricate relationships between the macrostructure, microstructure, and functional components of the brain as they relate to age has led to the development of normal indices of in vivo brain development and aging.[1,5-9] The utility of this cannot be overstated. Degenerative diseases are characterized by the lack of an inciting event, an insidious course, and earlier and accelerated cerebral atrophy.[10] Therefore, in vivo imaging has not only served as a benchmark for the evaluation of pathologic atrophy and differentiating physiologic from pathologic aging, but it will allow clinicians to detect degenerative disorders earlier, monitor treatment interventions, and assess outcome.

In recent years, investigators have made significant progress in documenting structure and function as it is related to aging by using conventional magnetic resonance imaging (MRI) (ie, macrostructural analysis),[5] magnetization transfer imaging (microstructural analysis),[9] diffusion tensor imaging (microstructural analysis),[11] functional MRI (functional analysis), and positron emission tomography (PET) (ie, functional analysis).[1,12] Neuroimaging parameters such as whole brain volume, segmented gray–white matter, regional volumes, apparent diffusion coefficient (ADC), mean diffusivity (MD), fractional anisotropy (FA), and cerebral glucose metabolism have collectively made significant contributions to understanding age-related changes of the brain. This article will describe the latest advances in understanding physiologic and metabolic maturation and aging of the brain as detected by in vivo neuroimaging. It is the hope of the authors that this review will serve as a platform for further investigations into brain aging and its pathologic counterpart.

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The Role of SPECT and PET Radioligands for Assessing Normal Aging in the Brain

Both single-photon emission computed tomography (SPECT) and PET have been used to examine the effects of normal aging in humans. The concept of and the first instruments designed for SPECT were developed in the 1960s by Kuhl and Edwards at The University of Pennsylvania.[13] This technique allowed for the acquisition and reconstruction of axial images of the brain. Initially, this technique was used primarily to study a number of neurological disorders that result in the breakdown of the blood–brain barrier (BBB).[14] SPECT was the first functional imaging modality used to study the central nervous system disorders with much success. Since the 1990s, the most commonly used radiotracers for SPECT are ^{99m}Tc-labeled HMPAO and ECD to measure cerebral blood flow (CBF). In addition, a number of SPECT radiopharmaceuticals have been developed to study various aspects of cerebral function, including metabolism and neurotransmitter activity.[15]

However, in the 1970s it was realized that positron-emitting radionuclides would allow for the optimal synthesis of radiopharmaceuticals that can be used for measuring important physiological and biochemical functions, such as blood flow and metabolism in the human brain. Therefore, radionuclides such as ^{11}C, ^{18}F, and ^{13}N have been used to synthesize a vast number of radiopharmaceuticals that can be used for studying body chemistry and function. PET provides a spatial resolution that is substantially superior to that of SPECT. High-resolution PET instruments provide images with detail and allow visualization of small structures of the brain.[16]

In 1976, the introduction of ^{18}F-fluorodeoxyglucose (FDG), a glucose analog that can be used for measuring regional cerebral glucose metabolism, added a major dimension to the assessment of brain function with PET.[17] The most commonly used radiopharmaceutical for imaging brain function is FDG, which measures cerebral metabolic activity. In addition, many other positron-labeled compounds have been introduced to determine the distribution, density, and activity of a multitude of neurotransmitter receptors (Table 1).

Table 1 A Partial List of PET Radioligands Used in Brain Imaging

Compound	Application
[^{15}O] H_2O	Blood flow
[^{18}F] fluorodeoxyglucose	Glucose metabolism
$^{15}O_2$	Oxygen metabolism
[^{11}C] l-methionine	Amino acid metabolism
[^{11}C] raclopride	Dopamine receptor activity
[^{11}C] methylspiperone	Dopamine receptor activity
6-[^{18}F] fluorodopamine	Dopamine receptor activity
[^{18}F] spiperone	Dopamine receptor activity
[^{11}C] carfentanil, [^{11}C] etorphine	Opiate receptor activity
[^{11}C] flunitrazepam	Benzodiazepine receptor activity
[^{11}C] quinuclidinyl benzilate	Muscarinic cholinergic receptors
6-[^{18}F] fluoro-L-DOPA	Presynaptic dopaminergic system
4-[^{18}F] fluoro-m-tyrosine	Presynaptic dopaminergic system
[^{11}C] ephedrine	Adrenergic terminals
[^{18}F] fluorometaraminol	Adrenergic terminals

Neuroimaging With PET in the Developing Brain

FDG-PET imaging has been used by researchers to assess the functional development of the pediatric brain. Chugani and coworkers[18] were able to demonstrate that, during the first year of normal development, the pattern of glucose metabolism generally corresponds to the anatomic phylogenetic order of development. Therefore, anatomic structures that develop first reveal high glucose metabolism earlier than those that develop later. Further, the pattern of glucose metabolism correlates well with the evolution of infantile behavior. The visuo-spatial and visuo-sensorimotor functions and primitive reflexes show a pattern of increasing glucose metabolism in the parietal, temporal, cerebellar, and primary visual cortices. High glucose metabolism also is observed in the basal ganglia as movement and sensorimotor function becomes more integrated. Metabolic activity in the frontal lobe remains relatively low during the first 4 months of life and increases as the infant begins to develop greater cortical and cognitive capabilities. As the infant develops complicated social interactions and improves its ability to perform various neuropsychological behaviors that specifically involve frontal lobes, associated increases are detected on FDG-PET images. By 1 year of age, the qualitative patterns of glucose metabolism in infants become similar to those of young adults.

Despite the similarity that is noted in qualitative glucose metabolism on FDG-PET images, infants typically have markedly decreased glucose metabolic rates compared with adults. Neonatal metabolic activity is approximately 30% that of adults. Metabolic rates increase until the third year when they surpass those of adults. Then, the metabolic rate for glucose reaches a plateau near the age of four and continues until approximately age nine. This may reach values as high as 1.3 times that of normal young adults.[19] Metabolic values then decline to adult rates by the end of the second decade.[18] It has also been hypothesized that increased metabolism reflects increased brain development and reorganization. Such increased activity may be the result of the overgrowth and elimination phases of neuronal development until appropriate neuronal connections are established. As an example, the decline of glucose metabolism in the visual cortex corresponds to the time when neuronal plasticity decreases.[20] This corresponds to the mature development of the visual system.

In addition to cerebral glucose metabolism, investigators have sought to describe the functional changes that take place in the developing pediatric brain with regard to regional cerebral blood flow (rCBF) and regional cerebral oxygen me-

tabolism with PET. Takahashi and coworkers[21] found that rCBF values are greater in adults than during the neonatal period; however, after this initial developmental stage, rCBF rates in children increase to levels greater than that of adults, peaking at age 7. During adolescence, these levels gradually decrease to adult levels, which continue to decrease throughout adulthood as part of a normal aging process. This group found no differences in rCBF values between the primary cerebral cortex and the basal ganglia, although differences were noted in the occipital lobe in all age categories. On the other hand, with the exceptions of the cerebellar hemisphere and the brainstem, regional cerebral oxygen metabolic activity peaks during adulthood, with the last region to demonstrate this increase being the frontal association cortex.

Functional Neuroimaging Findings in the Aging Adult Brain

Functional neuroimaging techniques have been used to study age-related functional and biochemical changes in the brain, including alterations in cerebral blood flow, cerebral metabolism, and neurotransmitter function.

Effect on CBF

CBF and metabolism are coupled under most physiological and pathological states. This coupling is governed by both chemical and neural mechanisms that signal an increased or decreased metabolic demand by the brain that automatically result in an appropriate response with regard to CBF.[22] Therefore, CBF studies have yielded results that are similar to those of metabolic test findings.

Most studies indicate that CBF tends to decrease in the frontal lobes bilaterally with increasing age.[23] A PET study by Martin and coworkers[24] described decreases in CBF in the cingulate, parahippocampal, superior temporal, medial frontal, and posterior parietal cortices bilaterally with increasing age. The areas with decreased CBF were the limbic system and the association areas. The authors suggested that these decreases might reflect the cognitive changes that are noted with age. Also with increasing age, there is a decrease in CBF to the gray matter whereas the CBF to the whiter matter is relatively preserved.[23,25] One study by Takada and colleagues[26] demonstrated that a significant age-related decrease in cerebral blood flow occurs in the left superior temporal area. However, it should be noted that neither Martin nor Takada and colleagues found any significant relationship between global blood flow and age, which may reflect a wide range of blood flow in the general population that also is affected by physiological, psychological, and environmental factors during such studies.

In general, on the basis of reports in the literature, CBF decreases with age. In addition, frontal lobes appear to be affected disproportionately compared with the rest of the brain. Possible mechanisms for decreased CBF in normal aging include a decline in regulatory mechanisms, diminished function in aging neurons, and age-related mild cerebrovascular disease.

Effects on Cerebral Metabolism

Results of FDG-PET studies of normally aging adults have been somewhat inconsistent. Although some groups have reported that no changes are seen on PET, others have noted significant decreases in whole brain cerebral glucose metabolic activity with advancing age. In addition, a number of investigators (including our group) have described diminished regional glucose metabolism in the temporal, parietal, somatosensory, and especially the frontal regions. Still others maintain that the most important changes associated with normal aging take place primarily in the prefrontal cortex. Mielke and coworkers[27] reported that although there is a trend to hyperfrontality during middle age, PET demonstrates a decline of regional cerebral glucose metabolism in frontal areas after this stage.

Kuhl and coworkers[28] showed that there was a decrease in mean glucose metabolic activity with normal aging. For example, at age 78, there was a decrease of 26% in the mean metabolic activity compared with subjects at age 18. Alavi and coworkers[29] also showed that there was a general decline in glucose metabolic rate in the frontal and somatosensory areas. Minor health problems did not appear to have a significant effect on regional or whole-brain glucose metabolic activity. In a more recent study, Loessner and coworkers examined high-resolution FDG-PET imaging in 120 healthy volunteers ages 19 to 79 years. These investigators noted that the most consistent finding associated with normal aging was a decline in cortical metabolism. In particular, the frontal lobe showed decreased metabolic activity with age. Other cortical areas, such as the parietal, occipital, and temporal areas, showed significant variation both within age groups and across age groups. There was also an increase in cerebellum-to-cortex ratio and an increased anterior–posterior metabolic gradient with increasing age.[30]

Another important finding of functional neuroimaging studies was that the metabolic activity in the frontal, parietal, and occipital lobes appeared to be symmetrical throughout the decades examined.[30] However, in general the left temporal lobe appeared to be hypometabolic compared with the right temporal lobe. Cerebral metabolic activity in structures such as the basal ganglia, thalami, hippocampi, cerebellum, visual cortices, and posterior cingulate gyrus was relatively preserved throughout the aging process and remained symmetric.[30] The visual cortices tended to be relatively hypermetabolic compared with the rest of the brain.[31,32] Although earlier studies have shown increased ratios of visual cortex to whole brain in elderly individuals compared with control patients, recent studies have yet to confirm these findings.[30]

Relative metabolic activity of the brainstem was found to increase significantly with advancing age.[30] Although the cause of this observation is unclear, it has been suggested that changes in neurotransmitter activity, such as in the dopaminergic system, may affect the metabolic activity of the brain stem.

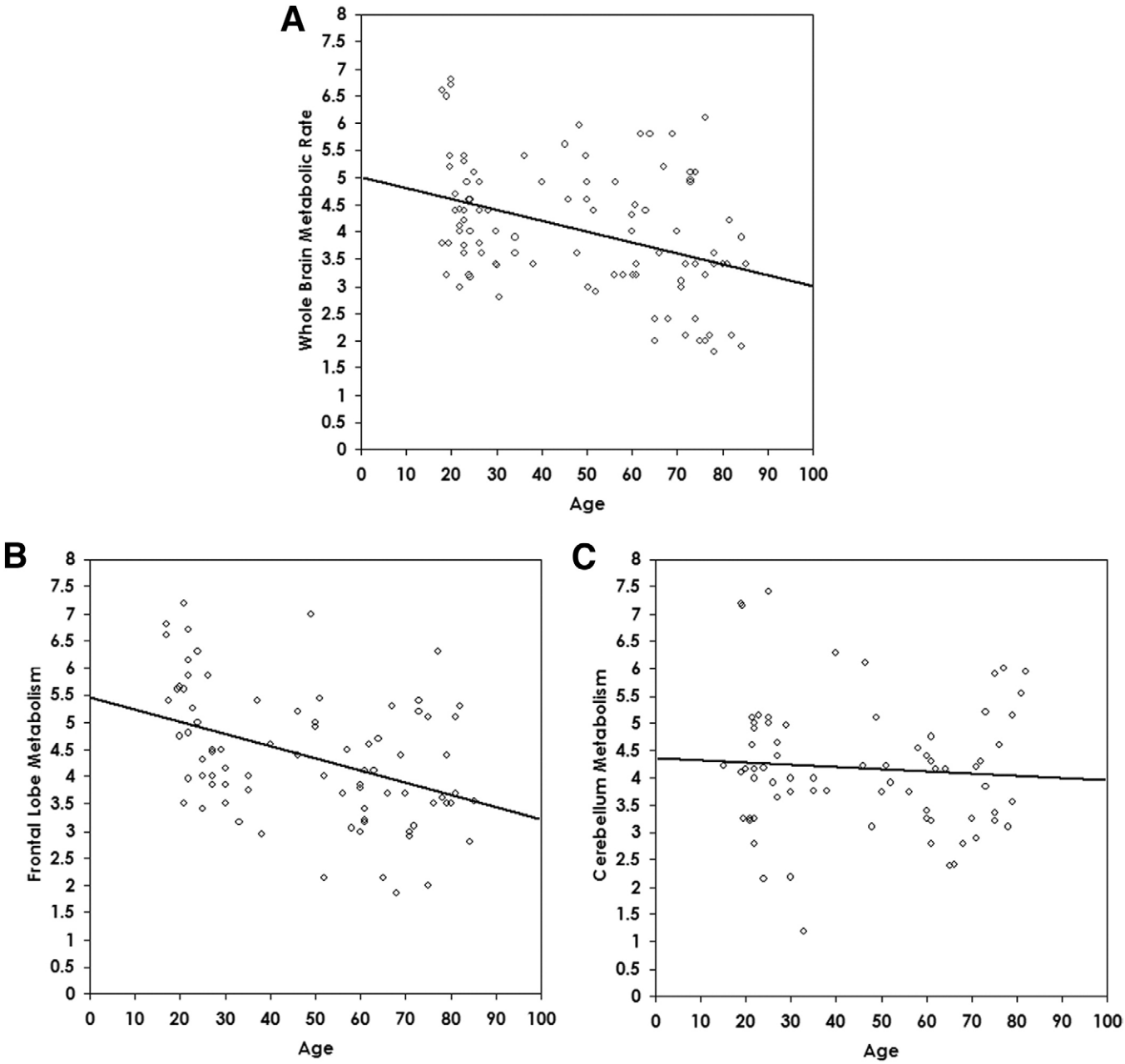

Figure 1 Correlations between age and whole-brain metabolic rate (A), frontal lobe metabolism (B), and cerebellum metabolism (C) show regression lines (age range, 17-85 years).

We examined 81 subjects (age range, 17-85 years) who underwent scanning on a PET V scanner after the administration of FDG using a scanning technique previously described by Chawluk and coworkers.[3] We found that whole-brain PET metabolism decreased with age (Fig. 1A). The Pearson correlation coefficient (r) between age and whole brain metabolism was -0.39 ($P < 0.05$, 95% confidence interval [CI] = -0.54 to -0.2, $r^2 = 0.15$). Analysis of the frontal lobe metabolism revealed decreased metabolism with age (Fig. 1B; $r = -0.42$, $P < 0.05$, 95% CI = -0.59 to -0.23, $r^2 = 0.18$) whereas cerebellar metabolism did not show a significant relationship with age (Fig. 1C; $r = -0.07$, $P > 0.05$, 95% CI = -0.3 to 0.16, $r^2 = 0.01$). Linear regression analysis showed a 38% decrease in the whole brain metabolism with aging whereas frontal lobe metabolism decreased by 42% and cerebellar metabolism decreased by 5%.

Reports in the literature indicate that, during senescence, in general there are no significant differences between men and women with regard to regional cerebral glucose metabolism.[30,33] This observation is interesting given that structural differences between men and women are noted with increasing age. A study by Gur and coworkers[34] indicated that there is significantly increased cerebrospinal fluid volumes in elderly men compared with age-matched women.

The observed decreases in cerebral glucose metabolism with increasing age are thought to be related to the rates of

FDG transport into the brain and/or phosphorylation once inside the neurons. However, 2 reports[35,36] have revealed that this observed decrease is not related to these rate constants.

By using nonimaging techniques, Dastur and coworkers[37] reported no differences in the global cerebral metabolic rate for oxygen with normal aging. However, PET studies using the ^{15}O inhalation method have shown decreases in oxygen metabolic rate in the gray matter with increasing age.[23,38] Similarly, a significant decrease in the mean oxygen metabolism has been observed in men and women older than the age of 51 compared with subjects younger than age 50.[26] Particular areas affected include the putamen bilaterally, the left supratemporal, left infrafrontal, and left parietal cortices. Other PET studies have found no significant decreases in CBF with normal aging[26] or have found that the decreases could not account for the extent of the decreased oxygen metabolism.[39] It has been hypothesized that oxygen extraction fraction increases with age, which may partly compensate for this decrease. This phenomenon may allow for maintaining the oxygen metabolic rate at a greater level than would be expected if oxygen extraction remained constant or decreased with aging.[39]

One concern with regard to the accuracy of PET imaging in this setting is related to the effects of age-related brain atrophy on the measurement of cerebral metabolism. The relatively low spatial resolution of PET instruments (even with today's standards) results in averaging signals from the brain tissue and inactive cerebrospinal fluid (CSF) spaces on reconstructed images. Therefore, mean cerebral metabolism as measured by PET appears lower than the actual rate of metabolism. Attempts have been made to manage this issue by using MRI. Most recently, Yanase and coworkers[40] reported having effectively corrected for partial volume effects in assessing cerebral glucose metabolism with advancing age using segmented gray matter volume from coregistered MRI. These investigators reported that the lower mean metabolic rates observed before correction for partial volume effect are accounted for by age-related atrophy in the medial frontal areas and bilateral perisylvian. A similar segmentation technique used by our group has allowed correcting for partial effects and accurately measuring the gray and white matter metabolic activities.[41] Previously, Tanna and coworkers[4] measured absolute ventricular and sulcal volumes in healthy elderly subjects and correlated these values with age. The best correlation was seen between age and either ventricular or total brain volume. Sulcal volumes appeared to correlate less with age.

Because brain atrophy can result in partial volume effects and a perceived lowering of metabolic rates in the brain, attempts have been made to overcome such errors by using other novel approaches.[4,42,43] Partial volume correction for cerebral metabolism in the atrophied brain has been used successfully in patients with Alzheimer's disease and other types of dementia.[4] To our knowledge, this approach has not been used in calculating metabolic rates in normal aging. Although structural imaging techniques, including CT and MRI, have revealed significant atrophy in the frontal lobes as a part of normal aging processes,[44-46] at this time it is unclear whether this atrophy accounts for the observed hypometabolism in this region.[44] Therefore, the results obtained with atrophy correction in various types of dementia must also be considered with regard to normal aging. In several studies of Alzheimer dementia (AD), multiinfarct dementia (MID), and primary progressive aphasia (PPA), the actual changes in cerebral metabolism, when corrected for atrophy, yielded different information regarding the metabolic nature of the dementia. For example, in patients with AD, several studies have shown that although whole-brain metabolism is significantly reduced compared with age-matched control patients, this decrease is not significant when the metabolic rates are corrected for atrophy.[2,4] Thus, in patients with AD, it appears that the hypometabolism is related to the absence of brain tissue whereas the existing brain tissue has a metabolism comparable with that in control patitents. The same appears to be true in subjects with PPA. These subjects, who suffer from a slowly progressive aphasia without signs of a generalized dementia, have significant hypometabolism throughout the left hemisphere and particularly in the temporal lobe, where the language center exists. As in patients with AD, patients with PPA have cerebral metabolic rates in both hemispheres similar to those of control patients once corrected for atrophy.[47] Patients with MID have been found to have significant whole-brain hypometabolism compared with age-matched control patients, even after atrophy correction.[48] Thus, patients with MID have cerebral hypometabolism that is out of proportion to brain atrophy, suggesting that the process leading to dementia in patients with MID is metabolically different than from that in AD.

Yoshii and colleagues[49] used a larger number of healthy volunteers to determine the effects of gender, age, brain volume, and cerebrovascular risk factors on glucose metabolic activity values as determined by the FDG-PET method. When brain atrophy was not considered, mean glucose metabolic activity was lower in older patients, particularly in the frontal, parietal, and temporal regions. Also women had significantly higher mean glucose metabolic activity than men. When covariate analysis was used to account for brain atrophy, since brain volume was highly correlated with age, the effects of age and gender on glucose metabolic activity were no longer significant. Cerebrovascular risk factors in this population did not have any effect on glucose metabolic activity. Brain atrophy accounted for only 21% of the variance in glucose metabolic activity.

The following regions demonstrate significant loss of function with normal aging as determined by FDG-PET (regions of interest significant at $P = 0.001$):

- Frontal (anterior corpus callosum, cingulate gyrus, frontal pole, frontal eye fields, middle frontal gyrus)
- Temporal (middle temporal gyrus)
- Parietal (superior parietal gyrus)
- Sensorimotor (primary sensory cortex)

Effects of Normal Aging on Neurotransmitter Function Studied by PET and SPECT

In addition to measuring alterations that take place with normal aging in CBF and metabolism, both PET and SPECT can measure neurotransmitter activity, which also may change with age. As noted previously, a large number of neurotransmitter systems can be examined using either PET or SPECT. However, only a limited number of reports are noted in the literature using neurotransmitter analogues in the study of the aging brain.

Nigrostriatal dopaminergic activity has been studied using both PET and SPECT imaging. This pathway is important with regard to extrapyramidal symptoms that occur with normal aging. In particular, this system is significant to the study of Parkinson's disease. Changes in both D_2 and D_1 receptor levels with normal aging have been studied in vitro.[50-52] In general, D_2 receptor levels have been shown to decrease with age. However, studies with regard to D_1 receptor numbers have revealed inconsistent results, with some suggesting a decrease, some no change, and some as increasing with normal aging. The results from neuroimaging studies, with regard to the dopaminergic pathway in vivo, have also been inconsistent.

Aside from individually measuring changes that occur with regard to CBF and glucose metabolism, the use of PET also has helped determine the relationship between metabolic and neurotransmitter/receptor functional changes during senescence. In an investigation of the relationship between regional brain glucose metabolism and D_2 receptor levels, Volkow and coworkers[53] found that both frontal and cingulate glucose metabolism and D_2 receptor levels decrease with normal senescence. These investigators also noted significant correlations between D_2 receptor levels and glucose metabolism in the frontal cortex, temporal cortex, anterior cingulate gyrus, and caudate. After removing age effects (partial correlation) these correlations remained significant, suggesting that dopamine may influence frontal, cingulate, and temporal metabolism regardless of age.

As dopaminergic pathways relate to cognitive processes, their activity modulates a range of frontal cognitive processes such as memory, attention, and sequentially organized action. Cropley and coworkers[54] have reported that alterations of dopamine activity within the fronto–striato–thalamic circuits may correlate with the aforementioned deficiencies observed both in neurodegenerative disorders and in normal aging. These investigators conclude that striatal dopamine activity (involving D2 receptors) may enable mental processes as required for response inhibition, temporal awareness, and motor performance. Also, the involvement of dopaminergic pathways via D1 receptors may be important for maintaining ongoing behavior. Neuroimaging studies that further investigate and correlate these actions with specific findings may shed light on inconsistencies that are noted in the literature.

Several PET studies have shown decreasing uptake of ^{18}F-fluorodopa (F-DOPA) with aging. Cordes and coworkers[55] found a 21% decrease in F-DOPA uptake when uptake in grandparents (age range, 70-80 years) is compared with that of their grandchildren (age range, 18-29 years). This study corroborates earlier studies by the same group, who showed similar decreases in F-DOPA uptake with age.[56,57] Further, the authors suggested that this decrease is consistent with the decline in the number of nigral dopaminergic neurons with normal aging. In fact, the average decrease per year of 0.35% in F-DOPA uptake is similar to the mean decrease in nigral neurons of 0.6% per year.[58,59] Other studies have not found a decrease in F-DOPA uptake with normal aging.[60,61] This inconsistency may be related to the relatively small number of subjects included in each study and how regions of interest (ROIs) were drawn in acquired images. For example, in a related study, ROIs that included the entire striatum showed a relationship between F-DOPA uptake and age whereas small ROIs did not yield the same correlation.[62] PET studies using a different radiopharmaceutical, [^{11}C] raclopride, which binds to postsynaptic D_2 receptor sites, have found a decrease in receptor density.[63,64] Antonini and Leenders reported that, after age 30, there is a 0.6% decline per year in raclopride binding. Similarly, D_1 receptor density also has been shown to decrease with age using PET imaging.[65]

Radioligands that can measure the dopamine transporter system that transports dopamine from the neuronal synapse back into the terminal neurons for storage have also been examined. One such PET study by Tedroff and colleagues[66] showed a decline with aging of the dopamine transporter using [^{11}C] nomifensine.

SPECT studies also have been used to measure changes in the dopaminergic system with age. A study by Woda and coworkers[67] measured the age-related changes in IBZM uptake which measures D_2 receptor concentration. The results from this study indicated that, with increasing age, there was a significant decrease in the basal ganglia to cerebellum uptake ratio. However, these authors showed that there was no correlation between age and the uptake ratio between the basal ganglia and either the frontal, parietal, or occipital lobes. Another study, using the cocaine analog 2-BETA-carbomethoxy-3-BETA-(4-iodophenyl) tropane (BETA-CIT), indicated that with normal aging a decrease of uptake of this compound approximately 8% per decade from the age of 18 is noted.[68] This decrease likely reflects a decrease in the activity of the dopamine transporter and possibly in the number of presynaptic dopaminergic neurons with age. However, BETA-CIT also has been found to have a high affinity for the serotonin transporter system. Therefore, the decrease in uptake of this particular compound may reflect the dopamine and serotonin transporter systems. One should note that in the striatum the dopamine transporter has been found to be almost exclusively responsible for BETA-CIT uptake. Furthermore, in vitro studies have shown that the serotonin transporter density is relatively constant with increasing age.[69] The large number of radioligands available for both PET and SPECT imaging allows using these agents to test the effects of aging in a variety of neurotransmitter systems.

Alteration in Amino Acid Transport with Normal Aging

Neutral amino acids (NAAs) are transported across the BBB via a competitive carrier system into the brain. Using positron emitting-labeled NAA analogs, investigators have been able to measure transport of these compounds across the BBB using PET imaging.

PET imaging using [^{11}C] L-methionine in pediatric patients showed increased transfer of this amino acid across the BBB compared with adults.[70] This finding suggests the developing brain allows for a greater influx of amino acids in children. Thus, PET might be useful in the study of various inborn errors of metabolism in childhood. Preliminary studies of disorders such as adrenoleukodystrophy,[71] mitochondrial disorders,[72] and adenylosuccinase deficiency have yielded interesting results.[73]

Using [^{11}C] L-methionine to study amino acid transport, O'Tuama and colleagues[70] showed changes with normal aging in adults. They found a decrease in amino acid transport with increasing age. The frontal lobes appeared to be particularly affected. Unfortunately, the labeling process of natural amino acids with positron-emitting isotopes may affect the accuracy of the kinetics of these compounds. Koeppe and coworkers[74] found no significant decrease in uptake of the synthetic amino acid [^{11}C]-aminocyclohexanecarboxylate (ACHC) with aging. This may allow for accurately measuring amino acid transport since ACHC is not metabolized in the brain and may result in simplification of kinetic models. A PET study by Ito and coworkers[75] using L-(2-^{18}F)-fluorophenylalanine (^{18}F-Phe) corroborated the findings with ACHC indicating no observed decrease in amino acid uptake in the brain with increasing age. Interestingly, they noted an increase with normal aging in the rate constant for the transport of ^{18}F-Phe from the brain to the blood. This may suggest that decreased competition between ^{18}F-Phe and natural amino acids due to a decreased concentration of intracellular amino acids in the brain.

The Role of Structural Imaging Techniques for Assessing Normal Aging in the Brain

Neuroimaging With MRI in the Developing Brain

Cortical and white matter maturational changes are first documented on fetal MRI starting after 17 weeks of gestation, when organogenesis is completed. The specific MR sequence used is based on the desired parameter to image. For example, T2-weighted contrast sequences are used to demarcate gyri, sulci, and other surface structures, whereas T1-weighted sequences are used to quantify cell density changes such as in the developing thalamus. Various sequences are used to image myelinating processes and other maturational processes such as the different layers of brain parenchyma.[76]

In brief, neuroepithelial cells located in the germinal ventricular zone divide and give rise to cortical neurons and the future cerebral hemispheres.[77,78] On T1-weighted and diffusion-weighted images (DWIs), the germinal zone appears hyperintense, whereas on T2-weighted images it appears hypointense.[79,80] On DWI, the hyperintense periventricular band represents the germinal, intermediate, subventricular, and periventricular zones. The high density of cells in this area most likely explains this hyperintense signal. On T1-weighted images and DWI, the subplate is hypointense, perhaps secondary to the extracellular matrix deposition by cells and from the seemingly unsystematic synapse alignment leading to decreased anisotropy. At 18 weeks of gestation, gyration patterns first start to be appreciated in the temporal regions of the fetal brain. The central sulcus begins to be noticed at 24 weeks and by the 35th gestational week, all primary and the majority of secondary sulci can be appreciated.

The intermediate zone lies between the ventricular zone and the marginal zone and is the primary location of white matter development.[76,81,82] Although a delay occurs before MR images are able to detect myelination signaling, using DWI, researchers are able to recognize premyelination stages because anisotropy is detectable before the onset of myelination.[81-84]

In a landmark study, Barkovich and coworkers[85] investigated the pattern of white matter maturation in normal infants (4 days to 2 years old) in T1-weighted and T2-weighted images. This study demonstrated that brain maturation occurs in a stepwise fashion, beginning in the brain stem and progressing to the cerebellum and the cerebrum (Table 2). Also noted was that in the first 6 months of life, T1-weighted images were optimal in subjects, whereas after 6 months of age, T2-weighted images were more effective in discerning maturational changes (Fig. 2). By 18 months, the majority of the brain would have an appearance to that of adult brain. Diffusion tensor imaging also has been used extensively to study white matter tract formation[80,83,86] whereas PET has been used to study maturational changes in cerebral function (Fig. 3).[18,87,88]

Structural Neuroimaging Findings in the Aging Adult Brain

Both the use of postmortem studies and conventional MRI have shown that advancing age is associated with a decrease in whole-brain volume and an increase in CSF volume.[45,89] Quantitative analysis of a number of brain structures and neuroimaging parameters has been the subject of many investigations in the past decade and only recently has the entire brain life span development and aging been imaged in vivo and documented.[7]

We examined 122 subjects (72 male, 50 females, age range: 4 months to 20 years) who underwent MRI with a 1.5-T unit with a head coil (Signa; GE Medical Systems, Milwaukee, WI). Axial proton-density weighted (repetition time (ms)/echo time (ms) = 2,500 to 3,000/20 to 30) and T2-weighted (2,500-3,000/80) images were obtained in each

Table 2 Specific Ages When Myelination Pattern Changes Appear

Anatomic Region	Age When Changes of Myelination Appear	
	T1-Weighted Images	T2-Weighted Images
Middle cerebellar peduncle	Birth	Birth to 2 months
Cerebral white matter	Birth to 4 months	3-5 months
Posterior limb internal capsule		
Anterior portion	Birth	4-7 months
Posterior portion	Birth	Birth to 2 months
Anterior limb internal capsule	2-3 months	7-11 months
Genu corpus callosum	4-6 months	5-8 months
Splenium corpus callosum	3-4 months	4-6 months
Occipital white matter		
Central	3-5 months	9-14 months
Peripheral	4-7 months	11-15 months
Frontal white matter		
Central	3-6 months	11-16 months
Peripheral	7-11 months	14-18 months
Centrum semiovale	2-6 months	7-11 months

Reprinted with permission from Barkovich.[156]

patient. Images were acquired with a matrix of 256 × 128, field of view of 20 cm, pixel size of 0.781 mm, and section thickness of 5.0 mm. A 2.5-mm gap was used between sections. No compensation was made for pulsatile CSF flow. The images were transferred to a workstation (Sun Microsystems, Mountain View, CA) and formatted to 8-bit size. An automatic 2-feature segmentation of brain and CSF was performed with the techniques developed in our laboratories.[90] The segmentation was verified visually and applied to all serial MRI that together best encompassed the supratentorial space. To automatically process the data, 5 regions of interests (ROI) were defined. Gradient-based automatic edge detection and boundary tracing were used to develop a subdural (intracranial) ROI. An ROI that included ventricular CSF but excluded sulcal CSF was drawn with a mouse. The segmentation was automatically applied to each of these ROIs and to the third ventricular ROI; and pixels representing total, ventricular, and third ventricular CSF and total brain were summated. The accumulated pixels were converted to volumes in milliliters by multiplying their number by unit voxel. These segmented images served as input files for another program developed at our institution to generate 3-dimensional display of brain, ventricles, and extraventricular CSF.[91] The measurements include volumes of each of the following structures alone and in combinations: brain hemispheres, lateral ventricles and the extracerebral CSF space. Measurements were normalized to the total intracranial volume (TICV) and were used in the analysis of the data generated.

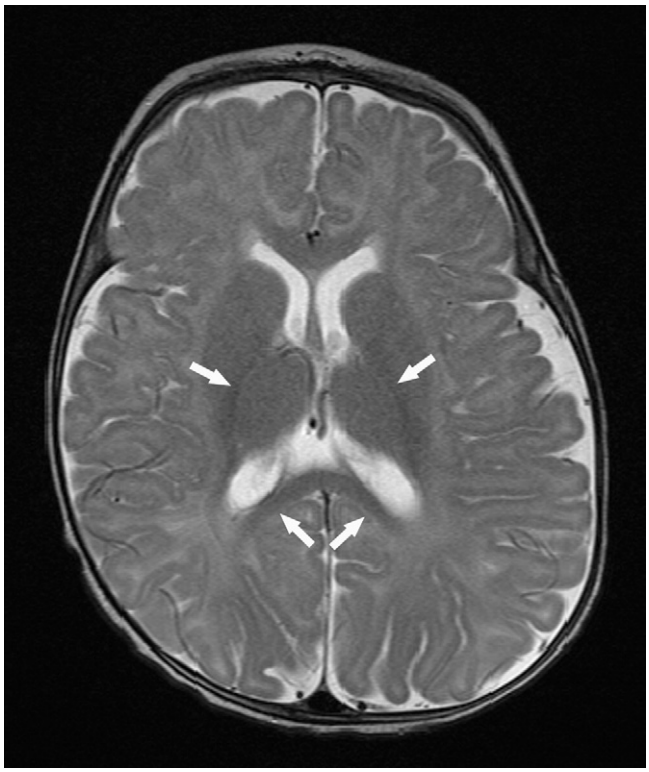

Figure 2 Axial T2-weighted image of brain at 8 months of age demonstrates myelination of the splenium of corpus callosum and posterior limbs of internal capsules (arrows). (Image courtesy of Deborah Zarnow, MD.)

Total brain volume increased with age in subjects from 1 month to 20 years of age (Fig. 4). The Pearson correlation coefficient (r) between age and brain volume was 0.59 ($P < 0.05$, 95% CI = 0.45–0.69, $r^2 = 0.34$).

Fundamental neuroimaging parameters of the brain that have been measured as they correlate with aging include the following: whole brain volume, CSF volume, gray matter, white matter, and regional volumes of the brain, including the hippocampus, cerebellum, thalamus, and brainstem. Several methods of measuring these volumes have surfaced in the past 2 decades: manual, semiautomated, and automated. These methods quantify MR image volumes in the brain using different techniques and have yielded specific patterns of physiologic aging. The following section will de-

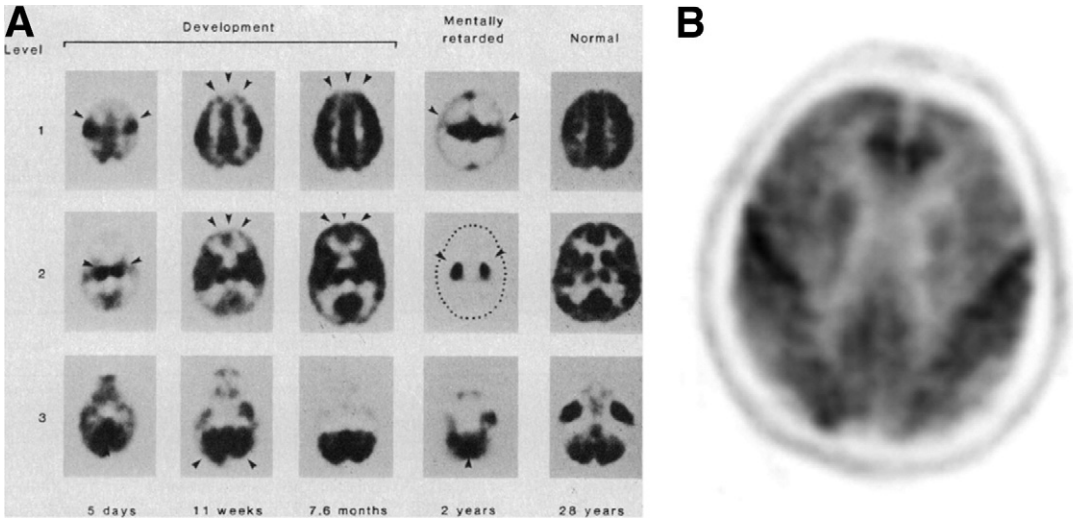

Figure 3 Glucose utilization in infants with increasing age using FDG-PET imaging (A). In infants at age 5 days, highest glucose metabolism is seen in sensorimotor cortex, thalamus, midbrain, and vermis (arrows). By 3 months, activity increases in parietal, temporal, and occipital cortices (arrows) and basal ganglia with subsequent increase in frontal cortices and association cortices by 8 months (arrows). (Reprinted with permission from Chugani and Phelps.[87]) Note preservation of glucose metabolism in sensory-motor cortex in patient with Alzheimer's disease (B) which mimics metabolic activity in infants up to 5 weeks of age.

scribe what age related associated findings have been documented with their relative segmentation technique.

White Matter Hyperintensities

Normal brain aging often is accompanied by periventricular and subcortical white matter lesions that are defined by the following characteristics: (1) hyperintensity on T2-weighted MRI without contrast enhancement, (2) a lack of mass effect, and (3) a lack of relation to any infection, inflammation, or neoplasm.[92] It has been termed by investigators as white matter hyperintensities,[93] nonspecific leukoencephalopathy,[92] and leukoaraiosis.[70,94] We will use the term white matter hyperintensity (WMH) in this article while keeping in mind that it serves as an umbrella term. Thirty percent of subjects older than 60 years of age have WMHs that increases in frequency with age.[95] The etiology, although not completely understood, is believed to be secondary to vascular insufficiency on a sublethal level, resulting in atrophic perivascular demyelination.[11,96,97] It should be noted that WMH burden runs a spectrum that is correlated with signs of cognitive decline such as attention and speed,[98,99] memory and motor function,[45,100] and gait dysfunction and balance.[101] MRI findings may be early markers for these subjects and identification of risk factors could be instrumental to altering the progression of these symptoms.[102] However, because the prevalence of WMHs increases with age, age plays a confounding role when attempting to determine risk factors.[93,102,103] A number of investigators have identified risk factors for WMHs, including hypertension and decreased respiratory function,[104-106] glycated hemoglobin level, cholesterol, low-density lipoprotein,[93] and the female gender.[107] In the Cardiovascular Health Study, Longstreth and coworkers[102] also showed that WMHs correlated with age, silent stroke, hypertension, FEV_1, and income. Importantly, they have recently been shown to be a predictor of stroke.[108]

The influence of various vascular risk factors in the 2 locations of WMHs (perivascular versus subcortical) is still unclear. Murray and coworkers[93] found that an elevated glycated hemoglobin was the strongest predictor of both subcortical and periventricular WMHs. When type 2 diabetics were removed from the analysis, hypertension and normalized peak expiratory flow rate were the main predictors of subcortical WMHs, whereas normalized peak expiratory flow rate was the main predictor of periventricular WMHs.

In regards to pathologic origin, a number of previous MRI pathologic correlation studies[78,79,92-101] have supported the

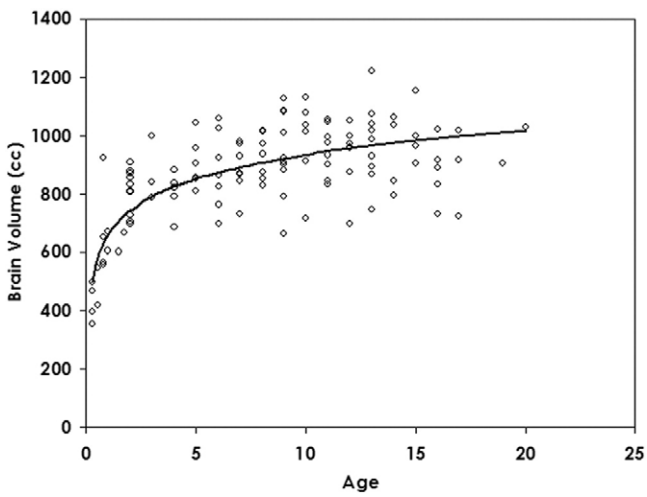

Figure 4 Correlation between age and total brain volume shows logarithmic regression line (age range, 1 month to 20 years).

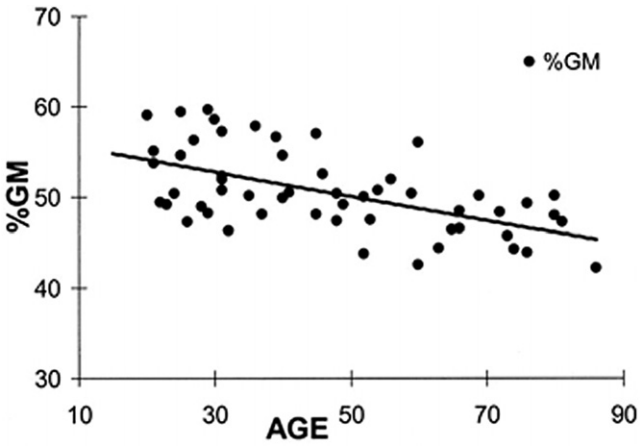

Figure 5 Regression analysis of gray matter (GM) fractional brain tissue volume on age in healthy adult subjects. (Reprinted with permission from Ge et al.[5])

notion that subcortical and periventricular WMHs have different etiologies. However, both areas have been shown to exhibit similar pathologic characteristics on biopsy, specifically, vascular fibrosis, and lipohyalinosis.[97,109,110] This supports the notion that, irrespective of etiology, there is a common unifying ischemic process that leads to tissue change. Using new MRI segmentation and 3D anatomical mapping techniques, DeCarli and coworkers[111] showed that no distinctions existed between the WMHs in the 2 locations, leading them to conclude that a common pathophysiological mechanism exists.

Novel Imaging Methods for Assessing Structural Changes

Manual Segmentation

Manual segmentation is one of the earliest methods of segmenting regions of interest. Coffey and coworkers[112] studied gender differences in an elderly population (66-96 years of age) who had participated in the Cardiovascular Health Study, using MRI morphometry. They found that the effects of aging on the peripheral CSF, the lateral fissure CSF, and the parieto-occipital region area were more pronounced in men than in women. Cerebral hemisphere volume, frontal region area, lateral ventricular volume, and third ventricle volume showed significant correlation with age but not with gender. This work raised the need for further investigation to functional correlation. However, manual segmentation is time consuming, labor intensive, and suffers from the lack of reproducibility consequently creating the need for semiautomated and automated segmentation techniques.

Semiautomated MR Segmentation

Gray matter is mostly composed of cell bodies in the cerebral cortex and also in clusters located deep inside the hemispheres and cerebellum. White matter consists mainly of axons and supporting glial cells.[113] The subject of gray and white matter in aging has been an area of interest to many investigators in the past 2 decades. White and gray matter have been noted to have very different age-related changes.[8]

Semiautomated MR segmentation is one method that has been used to measure these volumes. Ge[5] and coworkers found that gray matter loss begins early (age 20 years) and is constant and linear in fashion thereafter (Fig. 5). The rate of decline was not significant between younger and older subjects, although there was a 4.9% difference in gray matter between the groups. White matter, on the other hand, increased until the age of 40 then decreased in a quadratic fashion (Fig. 6). The rate of change of white matter was significant between subjects older than 50 years and those younger than 50 years. White matter also showed a significantly less amount of age-related loss than gray matter. Although absolute values of intracranial volume and gray matter were significantly different between the sexes, white matter interestingly was not. Also, sex differences were not significant in percentages of gray or white matter. Percent decrease of gray matter and white matter with age was not significant between the sexes. This study supported the idea that gray and white matter changes contribute to brain aging, that they have different roles in age related change, and that their pattern of change may explain why whole brain volume remains constant until the ages of 40 to 50 years and then subsequently declines. Similar studies using semiautomated techniques supported the notion that gray matter peaks early, with subsequent decline during late childhood or early adulthood.[7,45] Whether this is part of a normal process secondary to neuronal pruning or purging of redundant neurons, or represents an actual degenerative process is not entirely clear.

In a longitudinal study, the effect of age on the rate of whole brain volume atrophy and ventricular volume was examined. Scahill and coworkers[6] found that the mean rate of atrophy across each age range (31-84 years of age) was 0.32% per year with the rate of atrophy not accelerating or significantly changing with increasing age. However, ventricular volume was noted to have an accelerated change in rate, with an accelerated rate after 70 years. Interestingly, this demonstrates that cerebral atrophy may not solely explain ventricular expansion with aging. No significant effect of gender on rates of atrophy or ventricular volume was noted.

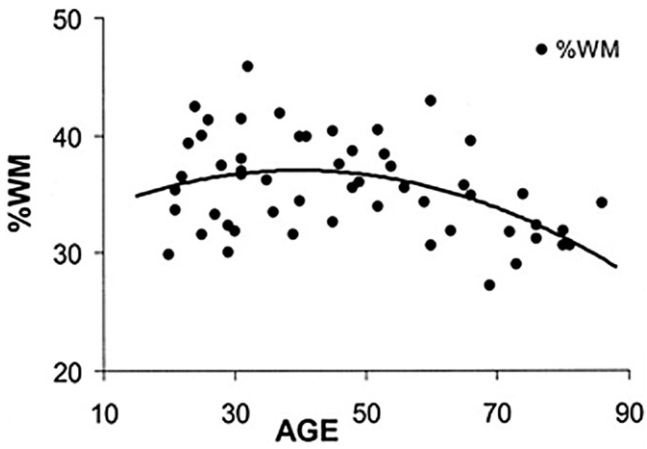

Figure 6 Regression analysis of white matter (WM) fractional brain tissue volume on age in healthy adult subjects. (Reprinted with permission from Ge et al.[5])

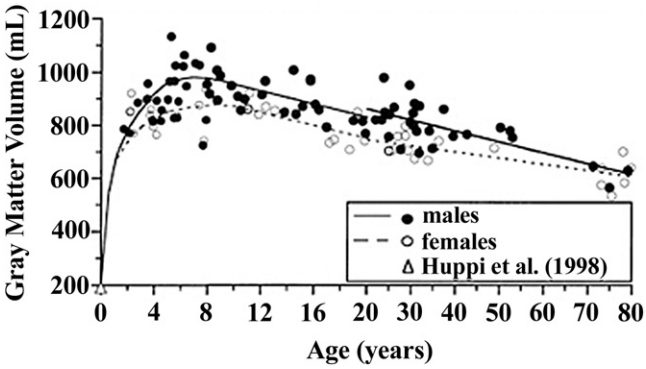

Figure 7 Growth and aging changes in gray matter via automated segmentation. Gray matter volume reached a maximum by 6 to 9 years of age and declined linearly thereafter by 5%. (Reprinted with permission from Courchesne et al.[7])

Automated MR Segmentation

Our results in pediatric subjects provide objective evidence for increase in total brain volume with age (up to age 20; Fig. 4). In a study done by Courchesne and coworkers,[7] healthy volunteers ranging in age from 19 months to 80 years were imaged. The study found that whole-brain volume grew exponentially by 25% between early childhood (19-33 months) and adolescence (12-15 years). From ages 16 to 80 years, whole-brain volume gradually decreased, and those in the age bracket of 71 to 80 years had brain volumes smaller than healthy 3-year-old children. Gray matter increased by 13% from 6 to 9 years of age and declined linearly by 5% every decade thereafter (Fig. 7). Although whole-brain volumes across all ages of females were approximately 12% smaller than males, there was no difference in the percentage of gray matter volume to total intracranial volume between the sexes. White matter volume had a different pattern of age-related change, with an increase of 74% from 19 months to 15 years of age and a plateau by the fourth decade of life (Fig. 8). For ages 71 to 80, white matter volume decreased by 13% age group of 71 to 80, indicating that white matter loss was not as significant as gray matter loss. There was no difference among the sexes in regards to percentage contribution of white matter volume.

Instead of actual cell loss in the gray matter, the decreasing cortical volume is currently believed to be secondary to neuronal shrinkage.[114] White matter decline, although not shown to be as affected by age, nonetheless exists and is believed to be secondary to demyelination and decreased length of myelinated fibers. A significant difference was found between the elderly (total length in myelinated fibers averaging 86,000 km) and young subjects (118,000 km).[115,116]

Voxel-Based Morphometry

Voxel-based morphometry, a form of automated segmentation, is more accurate in MRI volume quantification. An innate bias exists with manual tracings and semiautomated measured ROI that do not apply to automated techniques. The different morphometric methods of quantifying volume may partly explain why investigators have reported different linear and/or quadratic pattern changes on the same tissue compartments with age.

Gray matter volume involving cortical and deep structures has been shown to decline with age with voxel-based morphometry. In a study done by Good and coworkers,[8] the rate of total gray matter volume in males was greater than in females and this trend approached, but did not show significance ($P < 0.06$). They also found that there was no significant decline in white matter volume. There was a global increase in CSF volume with age as shown in other studies. Between the sexes, there was no significance in mean CSF volumes or rate of increase with age.

In a similar study, Kruggel[117] found that gray matter accounted for approximately 70% of whole brain volume atrophy, whereas the rest was secondary to white matter decline. The patterns of loss were also notable. Although males experienced white matter decline in a linear fashion, females had a pattern of loss that was best described in a quadratic fashion and both were not statistically significant. These findings supported previous studies that gray matter decline plays a more significant role in whole brain volume atrophy than its white matter counterpart.

Interestingly, another study showed that age did not show to correlate as strongly with CSF volume as previous studies have claimed.[118] They argued that secondary to proper selection of healthy subjects, even individuals in their 60s and 70s had CSF volume that was relatively constant. The authors' findings did support similar studies[5,7,119] that gray matter declined starting in early adulthood in a steady, progressive manner. White matter was shown to increase with age and did not decrease as stated in previous studies. Of significance, this study questions the mainstream view that CSF volume increases significantly with a decrease in the gray and white matter.

Regional Volumes

Frontal Lobes

The effects of aging on the frontal lobes have been well documented.[26,36-45,120] The frontal lobes are among the most

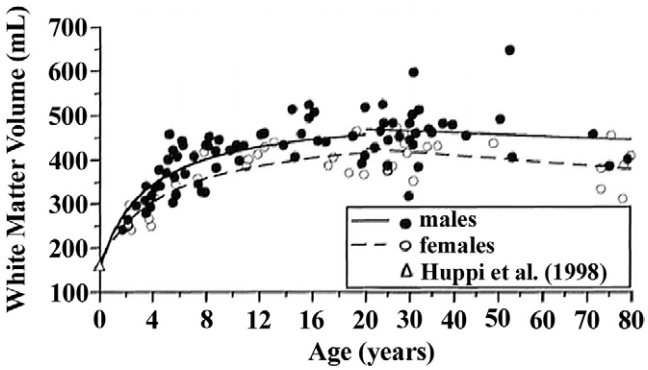

Figure 8 Growth and aging changes in white matter via automated segmentation. White matter volume increased most rapidly until 12 to 15 years of age and thereafter continued to increase at slower rate to plateau at about fourth decade. (Reprinted with permission from Courchesne et al.[7])

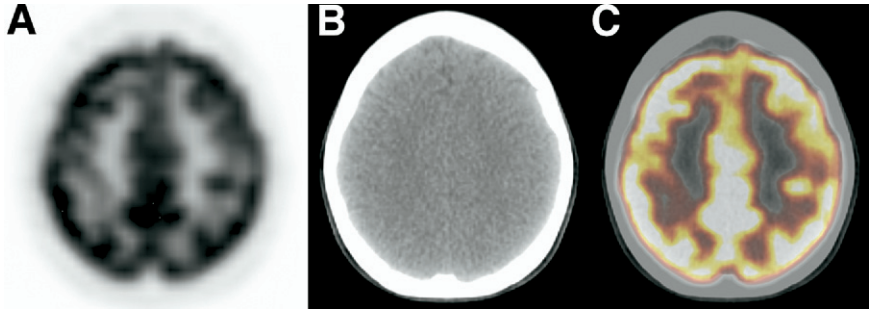

Figure 9 Axial PET (A), CT (B), and fused PET/CT (C) images through frontal lobe of adult brain.

greatly affected regions by age as determined by volumetric and functional analysis (Figs. 9 and 10). Consequently, this region has become one of the most investigated with regards to structure–function correlations in the brain. In a study by Tisserand and coworkers,[121] 57 healthy subjects (ages 21 to 81 years old) were used to measure regional frontal lobe volume via 3 methods: manual tracing, semiautomatic volumetric segmentation, and voxel-based morphometry. The authors found that the specific effects of age on regional volumes within the frontal lobes were dependent on the segmentation method used. Age-related volume decreases were most significant in the lateral and orbital frontal gray matter when manual tracing was used. The semiautomatic and voxel-based analyses found that age effects were most prominent within the lateral frontal and cingulate regions. Along with showing that different segmentation methods show different age-related affects, this study also served to show that regional volumes within the frontal lobes may be affected differently by age, showing structural heterogeneity as a function of age. Frontal lobe structure and function will be further discussed in the functional imaging section since major contributions of frontal lobe structure and function correlations have been shown via functional MRI and positron emission tomography.

Hippocampus

The hippocampal formation is located within the medial temporal lobe, is part of the limbic system, and plays a critical role in memory function.[113] The effect of aging on hippocampal volume has been found to be variable at best in studies. Several studies[8,45,122,123] did not show a significant age-related loss of hippocampal volume in healthy volunteers. However, other studies[120,124-126] have found that hippocampal volume decreases significantly with age. These contradictory findings can most likely be explained by the difference in population samples, techniques of data acquisition, segmentation techniques, and scanning protocols.[127,128] Szentkuti and coworkers[129] used 22 healthy old adults (ages 60-75 years) and 13 healthy younger adults (ages 22-27 years) and reported age-related changes of the hippocampus using MR-volumetry, ^{1}H MR spectroscopy, and DWI. They reported that hippocampal volume and apparent diffusion coefficients did not significantly decrease with age, although the N-acetylaspartate (NAA)/(Creatine [Cr] + mobile Choline moieties [Cho]) ratio did. This decrease was not specific to the hippocampus and was found in extrahippocampal brain tissue also. They concluded that age-related changes in the hippocampus are mainly metabolic rather than volumetric in nature. Because NAA is mainly found in neural tissue and Cr and Cho are found in glial tissue, their finding of a decreased ratio raises interesting points. Because both neuronal loss and gliosis would be accompanied by a change in ADC and volumetry, they concluded that the abnormal spectroscopic findings intra- and extrahippocampally most likely point to a decrease in intracellular metabolite content across all tissue.

Cerebellum

The cerebellum is responsible for coordinating in a smooth fashion the sensory and motor input from the brain and spinal cord. It is similar to the basal ganglia in that it has no direct connections to lower motor neurons. Instead, it directly influences the motor neurons of the brainstem and

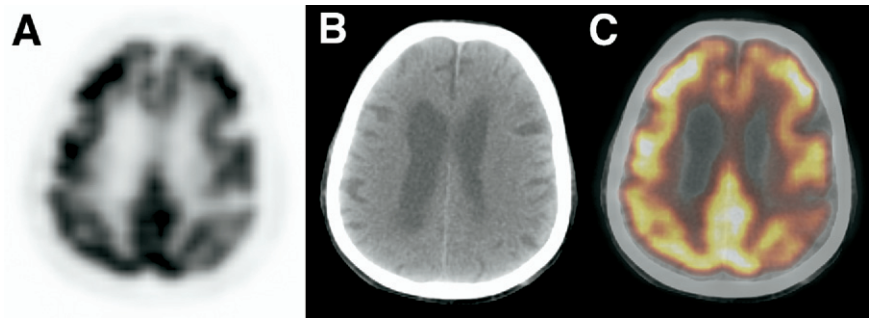

Figure 10 Axial PET (A), CT (B), and fused PET/CT (C) images through frontal lobe of elderly adult brain. Both brain volume and metabolic activity are decreased compared with younger adult brain.

cortex. Cerebellar lesions have clinical consequences that include ataxia, eye movement disorders, and vertigo.[113] Many studies have examined the effect of age on the cerebellum.[45,60,124,128,130-134] The general consensus has been that cerebellar volume decreases with age, although findings otherwise have been reported in earlier studies.[130] Walhovd and coworkers[128] recently investigated the effect of age across 16 automatic segmented brain volumes, including the cerebellum in 73 healthy volunteers aging from 20 to 88 years. Both cerebellar gray and white matter were segmented and were found to decrease in volume with age, best described as a curvilinear relationship. This curvilinear relationship was not seen in other structures analyzed such as the thalamus, cortex, and amygdala, where linear relationships with age were noted. Consequently, regional volumes that have curvilinear trends such as the cerebellum may show accelerated decreases in volume that are normal. This makes it more difficult to differentiate pathologic versus normal accelerated atrophy in those regional volumes that have a curvilinear relationship with age.

Thalamus

The thalamus is a subcortical gray matter structure that serves as a link between the motor inputs of the cerebellum and basal ganglia to the cortex, as well as almost all sensory pathways that synapse in the cortex.[113] Because it serves as the major relay station for most of the sensory circuitry, as well as the cerebellar and basal ganglia motor circuitry, characterization of potential volume loss with age is a significant one among subcortical regional volumes. Of interest is how this subcortical gray matter structure changes with time when compared with cortical gray matter and additionally, other subcortical gray matter areas, such as the cerebellum. Sullivan and coworkers[45] studied the effect of aging on thalamic volume in a healthy cohort of volunteers ranging from 23 to 85 years of age and found that thalamic volume significantly correlated with age in both sexes. The investigators reported that thalamic volume and cortical gray matter were similarly affected by age with respect to volume attrition. However, they differed in that cortical gray matter volume showed a faster decline with age in men than in women; rate of decline between the sexes with respect to the thalamus was equivocal. Other studies have supported the notion that thalamic volume decreases with age.[135,136] However, Jernigan and coworkers[124] did not show a significant relationship in thalamic gray matter reduction.

Brainstem

The brainstem includes the midbrain, pons, and medulla and is located in the posterior fossa. It is the main interface between the brain and the rest of the body and houses the cranial nerve nuclei. Using 3D MRI volumetry, Luft and coworkers[133] found that brainstem volume did not decline significantly with age. However, more recently, with newer segmentation techniques, Walhovd and coworkers[128] found that the brainstem significantly decreases with age in a quadratic fashion, similar to cerebral white matter. Considering the fact that the brainstem is mostly composed of white matter, this finding is consistent with other white matter in vivo imaging findings. Pontine volume also has been separately correlated with age and has not been shown to be significantly affected.[45,131,132] Further investigation is needed to be address whether certain areas of the brainstem are more prone than others to age, considering that total brainstem volume may decrease while the pontine volume does not.

Magnetization Transfer Imaging and Diffusion Tensor Imaging

Brain tissue undergoes complex aging processes that, as mentioned previously, can be detected by conventional MRI on a macroscopic level. These macrostructural parameters provide one view of the aging process, albeit they most likely represent end-stage morphological changes.[137] Newer MRI methods have been developed that analyze microscopic structure before conventional MRI has detected a change. These microstructural analyses play a vital role in that they provide a bridge to the functional assessment of the aging process as well as describe normative data for assessing pathologic conditions such as multiple sclerosis.[9]

Magnetization Transfer Imaging

Magnetization transfer imaging is a form of MRI that is sensitive to microstructural changes in the brain that are beyond the spatial resolution of conventional MRI. In brief, this imaging technique is based on the idea that protons that are bound to macromolecules in tissue (immobile protons) exchange magnetization with protons that are in free water (mobile protons). By this interchange, the protons bound to macromolecules influence the signal obtained from the free protons. The normal relationship between the free and bound protons is disrupted with the resultant difference being magnetization transfer.[138] The magnetic transfer ratio (MTR) is an index measurement of the efficiency exchange between bound and free protons and it is believed that this transfer efficiency is compromised with tissue disorganization secondary to aging, demyelination or axonal shrinkage.[11]

Ge and coworkers,[119] in another study, assessed age related MTR histogram measurements in healthy subjects younger than and older than 50 years of age (54 healthy volunteers aged 20-86 years of age) and further subdivided those subjects by gray and white matter. They found that the two age groups were significantly different in their MTR histograms with respect to the mean, median, first quartile, and peak heights (Figs. 11 and 12). One can conclude that microstructural change occurs with age and influences either the protons of macromolecules in tissues or in free water. Processes that may be responsible for this include gliosis, axonal degeneration, and demyelination.

Also of note in this study was that both gray and white matter MTR histograms followed quadratic curves (Figs. 13 and 14). They both increased up until middle adulthood and then both declined significantly. This indicates that myelination may still be continuing until middle adulthood. Recall that gray matter volume loss as detected by conventional MRI

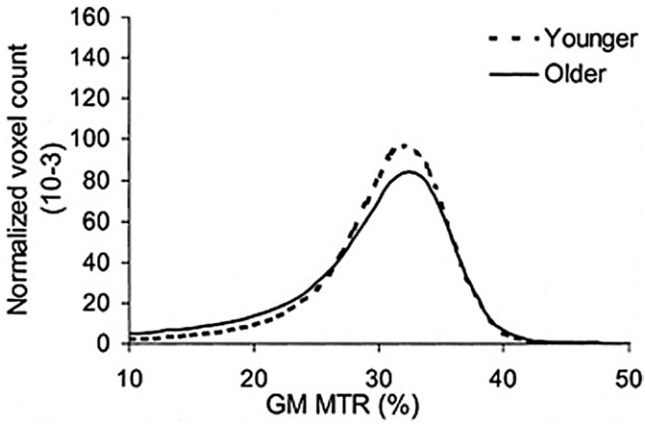

Figure 11 Gray matter MTR histograms in younger (<50 years) and older (50 years) healthy adult subjects. The normalized peak height was significantly lower in older group in both tissues. Compared with WM, GM has smaller MTR values. (Reprinted with permission from Ge et al.[119])

showed a linear relationship and was significant, while white matter loss was insignificant or variable. The interesting point here is that MTR histograms may be similar between gray and white matter because changes in gray matter MTR may caused by to the loss of the small amount of white matter in the gray matter compartment. This could explain why conventional MRI shows significant loss in gray but not white matter, although both gray and white matter have significantly decreased MTR ratios. The conclusion may be that age-related processes of the brain may be strongly influenced by myelin changes.

A similar study by Hofman and coworkers[139] of 51 healthy subjects ranging from 21 to 77 years of age also showed a significant correlation between segmented white matter mean MTR and age. However, in 2 studies of 89 healthy subjects ranging from 11 to 76 years of age, Rovaris and coworkers[11] first looked at whole-brain age-related changes

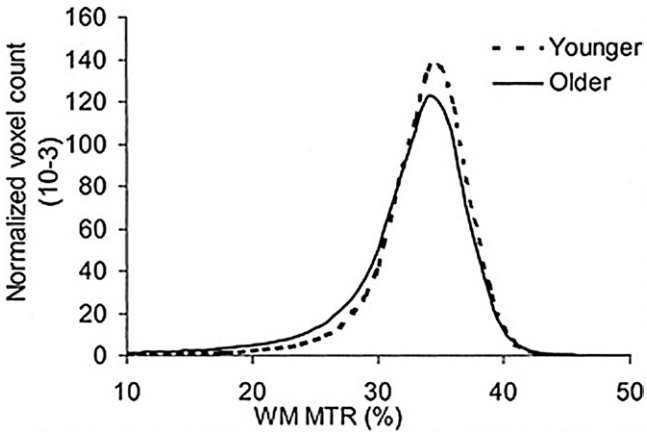

Figure 12 White matter MTR histograms in younger (<50 years) and older (50 years) healthy adult subjects. Normalized peak height was significantly lower in older group in both tissues. Compared with WM, GM has smaller MTR values. (Reprinted with permission from Ge et al.[119])

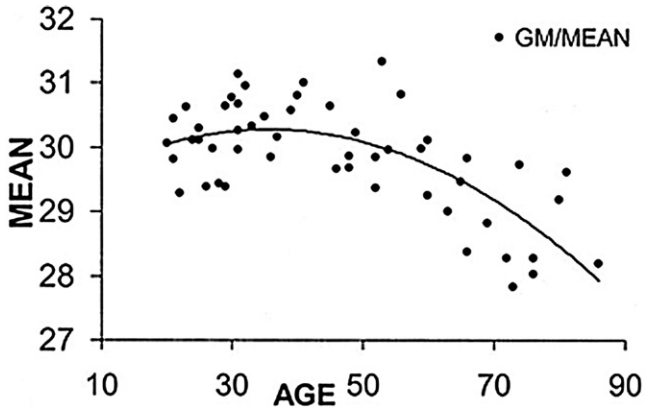

Figure 13 Regression analysis of MTR means in healthy adult subjects. GM MTR means show quadratic pattern with age. (Reprinted with permission from Ge et al.[119])

with MTR histogram measures and did not find a significant correlation. In the second study,[137] segmented gray and white matter MTR with age was examined and found that only gray matter MTR histogram measures correlated with age. After correcting for T2 hyperintensities, normal appearing white matter MTR histogram measures did not correlate with age. They concluded that because they used normal appearing white matter and did not correlate MTR with total white matter, this could explain the discrepancy in findings.

Diffusion Tensor Imaging

Diffusion tensor imaging is another technique that has been used to analyze microstructural changes in the brain. Although magnetization transfer depends on the magnetization transfer properties of protons, diffusion tensor imaging is used to characterize the 3-dimensional behaviors of water diffusion, elucidating tissue microstructure that is beyond conventional MRI resolution. It provides a quantitative assessment of highly organized tissue as it relates to normal and pathologic brain processes.[140] Several units of measurements have used diffusion tensor imaging. They are the following: ADC, MD, and FA. In brief, water in simple liquids has a

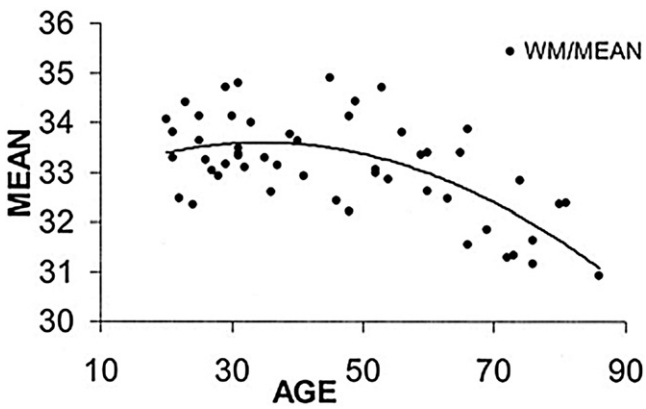

Figure 14 Regression analysis of MTR means in healthy adult subjects. WM MTR means shows quadratic pattern with age. (Reprinted with permission from Ge et al.[119])

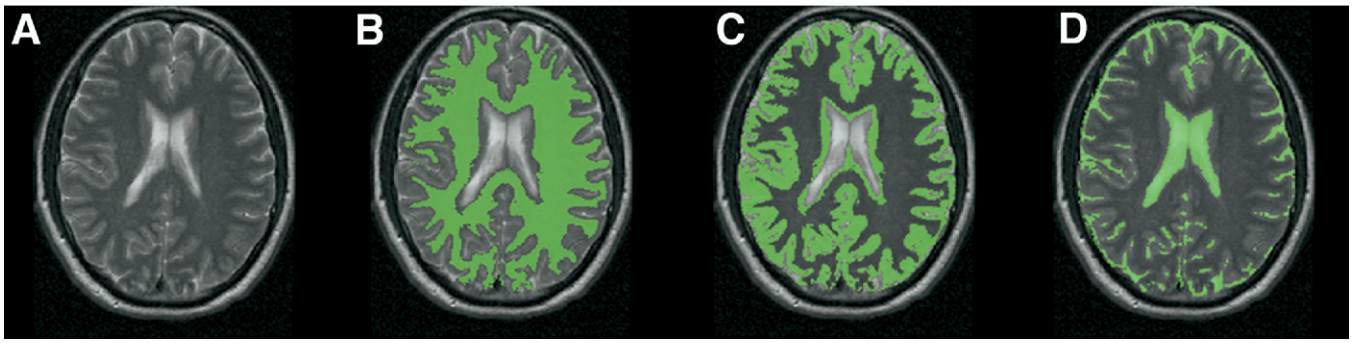

Figure 15 Segmentation technique used to calculate standardized uptake values in gray matter, white matter, and CSF fluid. One slice of intensity inhomogeneity corrected and intensity standardized T2-weighted image is shown in (A). (B-D) Overlap between slice in (A) and corresponding slice of segmented WM, GM, and CSF, respectively. (Image courtesy of Jay Udupa, PhD.)

higher diffusion coefficient than water in tissues with organizational barriers such as myelin. With this in mind, spin within a single imaging voxel influences diffusion coefficients, thus appropriately, it is the apparent coefficient of diffusion that the MRI is measuring. Mean diffusivity is as it name implies, is a measure of average molecular motion as influenced by tissue organization or disorganization. Fractional anisotropy is the degree of directional organization of brain tissue. As one can imagine, all 3 measure different specific variables of microstructural organization of the brain.[9]

Rovaris and coworkers[11] studied diffusion tensor images in 89 healthy subjects. Significant correlations were found between subject age ADC peak height and FA peak height. Normalized whole brain volume also correlated with mean ADC, ADC peak height, and FA peak height. Interestingly, no significant correlation was noted between MTR and ADC histogram measures. Because the amount and degree of direction of water diffusion was shown to correlate significantly with age, the conclusion drawn was that tissue disorganization increases with age but that MTR and ADC, while both measures of tissue disorganization, are independent of each other. It is also important to recognize that without these normal references, fewer conclusions could be drawn from utilizing these methods in diseases states such as multiple sclerosis. Using the same volunteers, but this time using normalized gray and white matter volumes, Benedetti and coworkers[137] found that age and gray matter average MD, MD peak height, and normal appearing white matter had significant correlation. With different patterns of aging, they concluded that microstructural tissue experienced different susceptibilities to their organization.

Nusbaum and coworkers[141] applied diffusion MRI in 20 healthy subjects, ages 20 to 91 years, and found statistically significant decreases in regional anisotropy with increasing age in the periventricular and frontal white matter as well as in the genu and splenium of the corpus callosum. Note that they did not detect any signal abnormalities (ie, hyperintensities) in the white matter under conventional MR. ADC histograms showed higher mean ADC values and reduced peak heights in the older age group.

The Role of Functional Imaging With MRI for Assessing Normal Aging in the Brain

Although a great number of imaging studies have investigated structural age-related changes, an impressive effort of equal magnitude has been dedicated to its functional imaging counterpart. PET imaging has become one of the most accurate and widely used methods of measuring energy metabolism and function. Early studies of brain function using PET[9,23,39-41,103-113] have laid the groundwork for significant advances in functional imaging, including assessment of cerebral metabolic rates for glucose, regional oxygen consumption, neuroreceptors, and regional CBF. Alavi and coworkers[2,4,90] coupled PET and MRI in patients as early as 1991 to assess atrophy-weighted total brain metabolism and absolute whole brain metabolism showing the broad applications of PET with structural imaging that could further elucidate structure-function relationships. Bural and coworkers[41] recently coupled MRI automated segmentation with PET providing an unconventional technique to calculating standard uptake values in the gray matter, white matter, and CSF (Fig. 15). Functional MRI from its earlier days[142] has equally taken off, with advances such as blood oxygen level-dependent functional MRI providing insight into tissue oxygen use.

Three main cognitive areas have been repetitively examined using functional MRI and PET as they relate to aging: memory, perception, and attention. Discussion of these 3 areas of cognition, the types of behavioral tasks used, and the regional areas involved with each parameter is beyond the scope of this article. Consequently, the authors have chosen to discuss memory (episodic and working) as it relates to prefrontal cortex functional imaging and aging because this topic has experienced the most investigatory efforts and because memory is significantly influenced by aging.

Briefly, working memory (WM) is a category of memory used to temporarily store and manipulate information. WM tasks examine subjects on their ability to store, maintain, and retrieve information that was recently asked on them. Episodic memory (EM) is another category of memory that has

been defined as a multistage process that involves the recollection of personal events that have occurred for an individual person and is believed to be different from other types of memory that include for example, facts about the world.[143] Both forms of memory have been investigated by using MRI and PET[117-131] and involve at least 2 stages; encoding, which analyzes stimuli and relates it to processed information from the past, and retrieval, which is responsible for bringing up information that has been stored and subsequently brought to consciousness.[33] Interestingly, functional imaging studies have found contradictory findings with WM and EM tasks as they relate to aging, confounding the exact relationship between brain function and memory. Although some investigators have found a decrease in prefrontal cortex function with age when subjects are asked to perform memory tasks,[33,53,144] other studies have shown that prefrontal cortex function increases with age.[45,145-148] Grady and coworkers[33] recently examined brain function via MRI during memory tasks in subjects ranging from 20 to 85 years of age. They found that areas that normally were not task-oriented, such as medial prefrontal cortex and parietal region, increased in activity with age, whereas areas traditionally activated with memory tasks, such as the bilateral prefrontal cortex and caudate nuclei, decreased in activity with age. They concluded that with age, more functional activity was seen in medial brain structures than with frontal regions. This is of importance because the medial regions traditionally are not activated with specific tasks but with monitoring one's external and internal environments.[149] Therefore, this makes older subjects more prone to distracting events when attempting to perform a specific memory task.

Rajah and coworkers[150] recently performed a meta-analytic review on the effects of aging on prefrontal cortex (PFC) function when subjects performed memory tasks as determined by functional MRI and PET. Because previous structural studies of frontal cortex have shown region-specific changes with age, there has been a growing interest in whether these structural region specific changes have specific functional correlations or not. They found that, contrary to traditional views, prefrontal cortex regions did show specific patterns of functional change, supporting the notion that PFC is structurally and functionally heterogeneous. Traditional views have held that PFC changes with aging are homogeneous and nonspecific.[151-155]

Conclusion

Modern structural and functional imaging techniques have permitted the visualization of changes that are associated with normal maturation of the brain and its senescence in later years of life. In particular, exquisite details provided by MRI and the PET as well as the novel methodologies that are related to these modalities have revealed unprecedented observations about such processes in the brain structures in children and in adults. Using FDG-PET during the past 30 years and several other radiolabeled positron-emitting biologically important compounds also have contributed substantially to the understanding of cerebral function in the maturing brain during normal aging. Overall, these developments have been of great value for detecting disease processes either related to normal aging or pathology in early stages, translating into optimization of therapeutic intervention.

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