

19

IMAGING AGING

Present and Future

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Traditionally, cognitive aging research has been based on behavioral measures of cognitive performance such as response time and accuracy. Data have indicated that age-related decline occurs in multiple cognitive functions (e.g., speed of processing, attention, episodic memory), whereas others remain relatively well preserved (e.g., semantic knowledge). Given that cognitive processes depend on brain anatomy and physiology, previously observed behavioral changes in aging are likely intimately linked to changes in the integrity of cerebral architecture and function. As novel imaging techniques have been developed, application to age-related issues typically occurs shortly thereafter. For instance, over 60 years ago, cerebral blood flow in humans was assessed by having research participants inhale nitrous oxide and measuring the difference in nitrous oxide concentration in blood samples simultaneously collected with needles inserted in the femoral artery and in the jugular vein (Kety & Schmidt, 1945, 1948). The application

of this technique to address age-related issues followed shortly thereafter (Freyhan, Woodford, & Kety, 1951; Kety, 1956), with authors suggesting that observed reductions in cerebral blood flow in older adults reflected neuronal loss. Despite these early attempts to link cerebral changes to aging, neuroimaging of aging studies have only recently proliferated, with the development of less invasive imaging techniques, leading to significant advances in cognitive aging research.

Within the last 25 years, neuroimaging of age-related changes has typically correlated behavioral with structural neuroimaging measures, such as magnetic resonance imaging (MRI) or resting functional neuroimaging measures, such as positron emission tomography (PET), which measures blood flow and metabolism. For example, cross-sectional structural MRI studies have revealed a negative relationship between age and hippocampal volume (for a review, see Raz, 2000), and age-related hippocampal atrophy has been typically associated

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with reductions in episodic memory performance (Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998), although these results are not always consistent across studies (for a review, see Van Petten, 2004).

Within the last 15 years, activation neuroimaging techniques, such as functional MRI (fMRI), which measure brain activity during cognitive task performance, have continued to elucidate the relationship between cognitive aging and cerebral aging. Activation neuroimaging studies have associated aging not only with *decreases* but also with *increases* in brain activity. Whereas age-related decreases in activation are usually attributed to neurocognitive decline, age-related increases in activation are typically attributed to functional compensation. Activation imaging studies have yielded two consistent aging effects across different cognitive domains. The first effect is known as *Hemispheric Asymmetry Reduction in Older Adults* (HAROLD; Cabeza, 2002) and refers to an age-related increase in the hemisphere less activated by young adults (YA), leading to a more bilateral activation pattern in older adults (OA) than YA. The second effect is known as *Posterior–Anterior Shift in Aging* (PASA; Dennis, Daselaar, & Cabeza, 2006) and refers to an age-related reduction in occipital activity coupled with an age-related increase in prefrontal cortex (PFC) activity. Both the contralateral recruitment in HAROLD and the PFC recruitment in PASA have been attributed to compensatory mechanisms in the aging brain, an idea that has received substantial support (e.g., Cabeza, Anderson, Locantore, & McIntosh, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, in press).

The goal of this chapter is to briefly review recent advances in neuroimaging methods and analysis that will continue to shed light on cognitive and cerebral aging. Topics were selected on the basis of novelty and potential to elucidate age-related changes in cognition and cerebral function. We first consider advances in structural and functional neuroimaging, followed by novel imaging domains. Finally, we conclude with suggestions for methodological integration to further our understanding of the relationship between age-related cognitive and cerebral changes.

DEVELOPMENTS IN STRUCTURAL NEUROIMAGING

Longitudinal Neuroimaging

The majority of age-related structural neuroimaging studies have used a cross-sectional approach (for a review, see Raz, 2000), which is insensitive to individual differences and susceptible to cohort effects. A handful of longitudinal structural MRI studies have recently begun to address these limitations (Persson et al., 2006; Pfefferbaum, Sullivan, Rosenbloom, & Mathalon, 1998; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Scallin et al., 2003). For example, in a series of studies by Raz and colleagues, healthy adults (age range at baseline: 20–77 years) were scanned 5 years apart. Differential reductions in volume of basal ganglia structures were observed (Raz et al., 2003). Although decreases in volume of the caudate nucleus and putamen were predicted, the reductions in volume were larger than expected based on previous cross-sectional estimates. Furthermore, although previous cross-sectional studies suggested that the volume of the globus pallidus was stable, significant reductions in pallidum volume were observed. Finally, the results indicated that shrinkage in the basal ganglia was not restricted to OA: Shrinkage was linear across the life span.

In contrast to the basal ganglia, medial temporal regions show differential rates of shrinkage across the life span (Raz, Rodrigue, Head, Kennedy, & Acker, 2004). In adults over age 50, clear annualized reductions in volume were observed in the hippocampus and entorhinal cortex. In adults less than 50 years old, less severe annualized volume reductions were observed in the hippocampus, and there was essentially no loss of entorhinal cortex volume. Furthermore, the results indicated strikingly greater atrophy in the hippocampus relative to the entorhinal cortex. Finally, Rodrigue and Raz (2004) reported that although greater annualized volume reductions were observed in the hippocampus and PFC relative to entorhinal cortex, only change in entorhinal cortex volume predicted episodic memory performance, results that are relatively consistent with a previous resting PET study (de Leon et al., 2001).

The aforementioned longitudinal studies highlight age-related changes, as opposed to age differences (cross-sectional comparisons of YA vs. OA). It should be noted that longitudinal studies have weaknesses as well. Data collected in longitudinal aging studies are typically derived from the healthiest portion of the population, because follow-up data collection is negatively impacted by mortality in OA, morbidity in middle-aged adults, and mobility in YA (the “three M’s”; see Raz, 2005, or additional discussion). Differential rates of volume reduction among brain regions and across the life span were identified. These results raise interesting questions about the aging brain, such as whether functional compensation can occur in the face of structural degradation. It will be important for future studies to continue to address the relationship between longitudinal changes in cognitive function and neural structure.

Diffusion Tensor Imaging

The development of diffusion tensor imaging (DTI) represents a significant advance in neuroimaging white matter in the brain (Basser, Mattiello, & LeBihan, 1994). White matter was previously presented on MRI as a relatively homogeneous structure. With DTI, direction (e.g., anterior–posterior, superior–inferior, right–left) of white matter structures can be determined and, furthermore, specific white matter tracts (e.g., cingulum bundle) can be identified. DTI reflects water diffusion, which in the brain is restricted by axons, cell bodies, and myelin (for technical review of diffusion properties and MRI, see Beaulieu, 2002, and LeBihan, 2003). In regard to white matter, less diffusion reflects greater white matter integrity. Two measures of diffusion, fractional anisotropy (FA) and the apparent diffusion coefficient, are commonly reported. FA measures the directionality of movement of water molecules, with values ranging between 0 and 1. Higher FA (closer to 1) is assumed to reflect greater white matter integrity. The apparent diffusion coefficient measures the diffusion of water, and in this case, lower values are assumed to reflect greater white matter integrity.

In healthy OA, reductions in FA appear to follow an anterior-to-posterior gradient in the brain (Head et al., 2004; Madden et al., 2006;

Pfefferbaum et al., 2000; Salat et al., 2005). This trend fits with the idea of “last in, first out”: Frontal lobe white matter is the latest to mature, increasing in volume into the early 40s, and it is the first one to show the deleterious effects of aging (Bartzokis et al., 2003). Decreases in indicators of frontal lobe white matter (e.g., FA values) have been associated with measures of processing speed and reasoning (Stebbins, Carillo, et al., 2001; Stebbins, Poldrack, et al., 2001). Madden, Whiting, et al. (2004) found that decreased reaction time was predicted by FA in the splenium of YA, but in the anterior limb of the internal capsule in OA, suggesting that performance in OA is more dependent on the integrity of fronto-striatal circuitry rather than the frontal circuitry alone.

To date, most DTI studies of aging have used a regions-of-interest approach whereby FA or apparent diffusion coefficient are measured within a white matter volume that is crossed by several different tracts (for a review, see Moseley, 2002). Whereas the regions-of-interest approach does not provide independent measures for the various fiber tracts passing through a region-of-interest, these measures can be provided by the technique of quantitative fiber tracking (Corouge, Gouttard, & Gerig, 2004; Mori & van Zijl, 2002; Xu, Mori, Solaiyappan, van Zijl, & Davatzikos, 2002). Using this method, FA or apparent diffusion coefficient values for different groups of individuals (YA vs. OA) can be compared across the entire fiber or for sections of the fiber and can be correlated with cognitive performance. For example, the effects of aging on cross-hemispheric genu fibers, which connect left and right anterior PFC regions, are obvious even in individual participants (see Figure 19.1 inset). Mean FA can be separately extracted for segments of the fiber, and the effects of aging can be assessed (see Figure 19.1). The effects of aging on each segment of each fiber can be linked to the effects of aging on behavior by means of correlations and regression analyses. Of course, these analyses can be performed on multiple fibers, such as the cingulum bundle, uncinat fasciculus, and so on.

There are several limitations to DTI. First, the spatial resolution of DTI (millimeters) is poor compared with postmortem tract tracers (μm), which can identify single axons. Indeed,

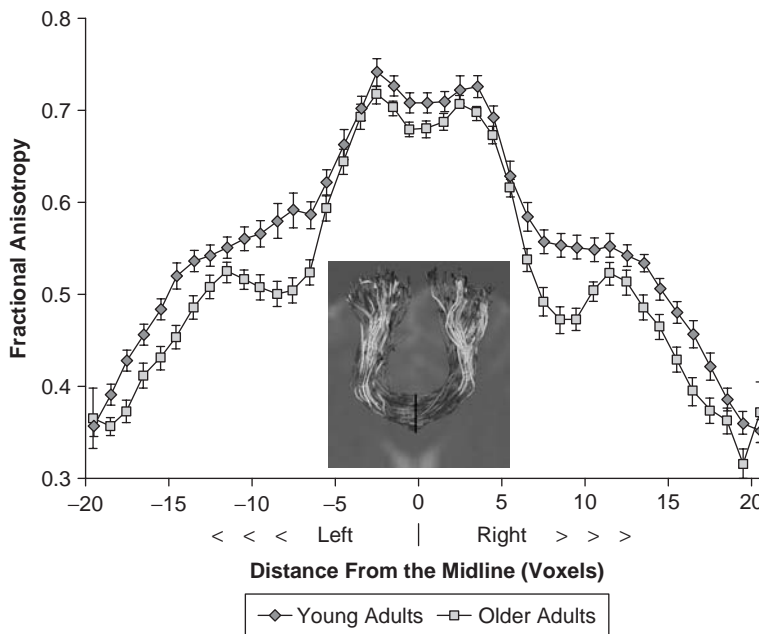


Figure 19.1 Results of Cross-Genu Fiber Tracking in Young and Older Adults

The image inset displays multiple fibers identified by quantitative fiber tracking in a single individual, with the black bar in the center of the fibers representing the midline. The graph represents fractional anisotropy values in a group of young and older adults. X-axis units correspond to voxel distance to the left (negative values) and to the right (positive values) of the midline ($x = 0$) of cross-genu fibers. Voxel size was 2 mm^3 .

the spatial resolution of voxels using DTI consists of a large number of axons. Furthermore, DTI cannot distinguish between efferent and afferent projections. Nevertheless, the potential of DTI to inform cognitive aging has yet to be fully tapped, because few studies have applied quantitative fiber tracking to age-related issues.

DEVELOPMENTS IN FUNCTIONAL NEUROIMAGING

Hybrid Designs

The first generation of functional neuroimaging studies used *blocked designs*, in which trials belonging to different experimental conditions had to be presented in different blocks or scans. About a decade ago, functional neuroimaging studies started using *event-related designs*, in which trials from different conditions could be randomly intermixed. Blocked and event-related designs sometimes yield different results, not only

because of differences in cognitive strategies but also because of differences in sustained versus transient activity. *Sustained activations* persist across several trials of the same kind and tend to reflect mental states associated with the task, whereas *transient activations* decay between trials and tend to reflect cognitive operations specific to each trial. Given that blocked designs emphasize sustained activations and event-related designs, transient activations, the results of these two kinds of designs do not need to be identical.

A few years ago, researchers developed a new kind of design known as *hybrid designs* (e.g., Donaldson, 2004; Otten, Henson, & Rugg, 2002; Visscher et al., 2003), which essentially combine the features of blocked and event-related designs and allow simultaneous measures of sustained and transient activations (see Figure 19.2). Similar to blocked designs, hybrid designs consist of blocks separated by interblock intervals (represented in Figure 19.2 by the large + symbols) and, similar to event-related designs, the trials within the blocks are

separated by jittered intertrial intervals (represented in Figure 19.2 by small + symbols). In a hybrid design, sustained activity is identified by comparing block activity to interblock activity, and transient activity is identified by comparing trial activity to intertrial activity.

The use of a hybrid design provides a within-subject method for reconciling conflicting results between blocked and event-related studies of cognitive aging. For example, whereas most of the blocked PET and fMRI studies of episodic encoding have found age-related *decreases* in PFC (Anderson, Idaka et al., 2000; Cabeza, Grady, et al., 1997; Grady, Bernstein, Beig, & Siegenthaler, 2002; Grady et al., 1995; Logan, Sanders, Snyder, Morris, & Buckner, 2002; Schiavetto, Kohler, Grady, Winocur, & Moscovitch, 2002), the few event-related fMRI studies in this domain have found age-related *increases* in PFC activity (Gutchess et al., 2005; Morcom, Good, Frackowiak, & Rugg, 2003). Although this inconsistency may reflect differences between general encoding activity and successful encoding activity, an intriguing possibility is that it reflects differences between the effects of aging on sustained versus transient activity.

This possibility was investigated in a recent study from our laboratory that used a

quasi-hybrid design that included rests between trials but not between blocks (Dennis et al., 2006). This study yielded a dissociation between the effects of aging on sustained versus transient activity: Aging reduced sustained encoding activity in right PFC but increased transient encoding activity in left PFC. One possible explanation of these effects is that OA have a deficit in sustained attention, for which they attempt to compensate by recruiting additional transient activity. More generally, this finding suggests a possible solution for observed inconsistencies between blocked and event-related functional neuroimaging studies of encoding and aging.

Hybrid designs may also clarify age-related changes in the default network. Functional neuroimaging studies have revealed a network of brain regions, including anterior and posterior midline cortices and lateral parietal cortex, that are consistently deactivated during attentionally demanding cognitive tasks compared with resting baseline (Greicius, Krasnow, Reiss, & Menon, 2003; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). Raichle and colleagues have suggested these regions comprise a *default network*, which is normally active during conscious rest but must be able to temporarily shut down or

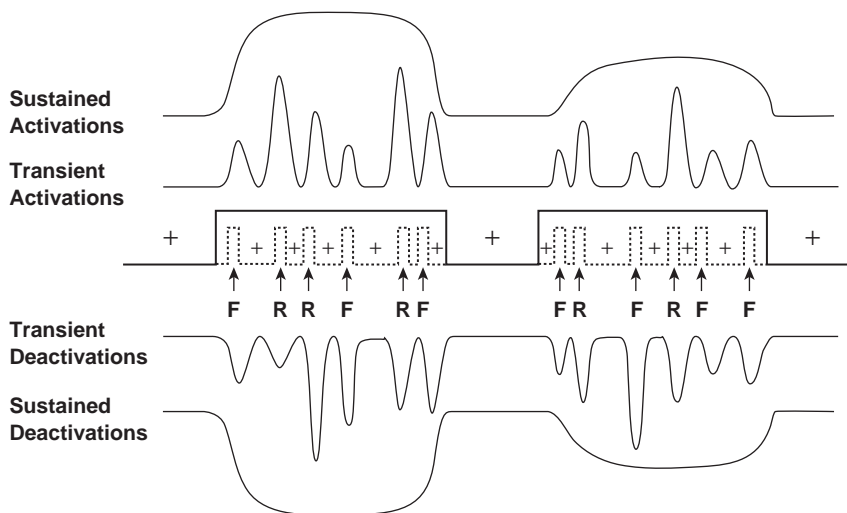


Figure 19.2 Schematic of Hybrid Blocked/Event-Related Design, Illustrating, in This Example, Modeled Responses of Sustained and Transient Activations and Deactivations in a Memory Paradigm

NOTES: Large plus signs (+) indicate between block fixation/rest periods, whereas smaller plus signs (+) indicate variable duration intertrial fixation/rest events (i.e., jitter) that allow for the deconvolution of the hemodynamic response. F = forgotten trials; R = remembered trials.

deactivate during demanding cognitive tasks, when resources are needed for efficient cognitive performance (Gusnard & Raichle, 2001; Raichle et al., 2001). Daselaar, Prince, and Cabeza (2004) found that regions of the default network, such as posterior parietal and posterior midline cortices, showed greater deactivations during encoding for stimuli that were subsequently remembered than for those that were subsequently forgotten. Regarding aging, there is evidence that deactivations of the default network during encoding are attenuated in healthy OA and even more so in adults diagnosed with mild cognitive impairment and Alzheimer's disease (AD; Celone et al., 2006; Lustig et al., 2003; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005). It is very tempting to link these two lines of evidence and suggest that a failure to deactivate the default network during encoding contributes to encoding deficits in healthy and pathological aging. However, the link we found between deactivations and successful encoding was observed for transient deactivations in an event-related design, whereas the link between aging and deactivation failure was observed for sustained deactivations in a blocked design. Thus, to link these findings it will be critical to measure both transient and sustained deactivations using a hybrid design.

Single-Trial Analysis

Single- or individual-trial analysis is a technique in which each trial (or phases within a trial)

is entered as its own regressor in the statistical analyses, as opposed to averaging trials across conditions (Rissman, Gazzaley, & D'Esposito, 2004). Thus, single-trial analysis yields an activation measure (parameter estimate) for each trial for every individual participant, which can then be linked within participants with their performance on the corresponding trial. These data can then be entered into a regression model and used to predict memory performance at the individual-trial level (Daselaar, Fleck, & Cabeza, 2006; Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006).

For instance, results of a recent event-related fMRI study compared the effects of aging on recollection-related versus familiarity-related brain activity during an episodic recognition task (Daselaar, Fleck, Dobbins, et al., 2006). The effects of aging yielded a double dissociation within the medial temporal lobe: Whereas recollection-related activity in the hippocampus was reduced by aging, familiarity-related activity in rhinal cortex was increased by aging. These results suggested that OA compensated for deficits in recollection by relying more on familiarity. Results of single-trial analysis revealed that recognition responses were determined only by hippocampal activity in YA but by hippocampal and rhinal activity in OA (see Figure 19.3), providing converging evidence for an age-related shift from recollection to familiarity-based processing in OA.

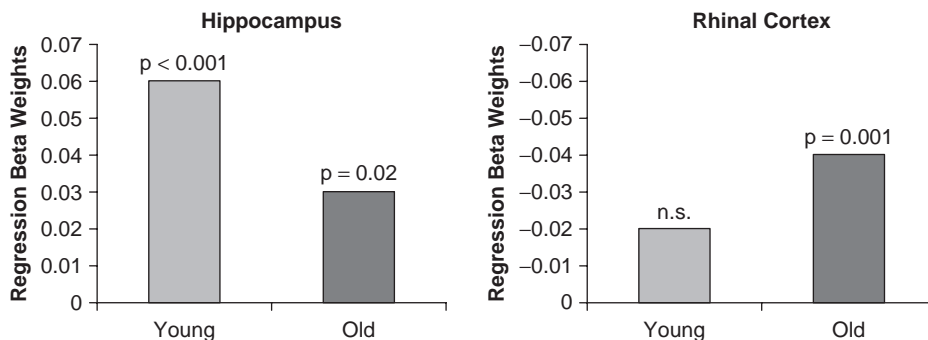


Figure 19.3 Results of Single-Trial Analysis

The results revealed that recognition responses were predicted only by hippocampal activity in young adults but by hippocampal and rhinal activity in older adults, providing evidence for an age-related shift from recollection to familiarity-based memory processing in older adults.

Functional Connectivity Analysis

It is obvious that cognition depends not only on the functions of various brain regions but also on their interactions, yet the vast majority of functional neuroimaging studies have focused on brain regions activated during a cognitive task, with very few studies addressing the issue of functional connectivity. The situation is similar among functional neuroimaging studies of cognitive aging, although it is clear that age-related cognitive decline may reflect a combination of deficits in particular regions and deficits in communications between regions. The latter idea has been described as the disconnection hypothesis (Bartzokis et al., 2004; O'Sullivan et al., 2001) and can be investigated using functional connectivity analyses.

Functional connectivity analyses can be also used to investigate compensatory mechanisms in the aging brain. For example, using functional connectivity analysis, Cabeza, McIntosh, Tulving, Nyberg, and Grady (1997) demonstrated a difference in neural networks in YA and OA, because more bilateral PFC interactions were observed in OA during episodic recall relative to YA (HAROLD pattern). In the aforementioned study by Daselaar, Fleck, Dobbins, et al. (2006), data from parametric and single-trial analyses indicated that OA rely more heavily on familiarity than recollection during a word recognition task, suggesting a top-down modulation from PFC on rhinal cortex. To explore this possibility, a functional connectivity analysis was performed in which single-trial hippocampal and rhinal activations were correlated with activations in the rest of the brain for the corresponding trials. Whereas YA showed greater correlations between the hippocampus and posterior regions (retrosplenial cortex and left parieto-temporal) that were also associated with recollection, OA showed greater connectivity between rhinal cortex and bilateral PFC regions (see Figure 19.4). The results of the functional connectivity analysis support the hypothesis that OA compensate for hippocampal deficits by relying more on rhinal cortex, possibly mediated via top-down modulation from PFC. Additional studies using functional connectivity analysis highlight the difference in effective connectivity between the hippocampus

and other brain regions in YA and OA, even under circumstances in which behavioral performance and hippocampal activation are similar (Cabeza, McIntosh, Grady, et al., 1997b; Della-Maggiore et al., 2000; Grady, McIntosh, & Craik, 2003).

NOVEL IMAGING DOMAINS

Neurotransmitter Imaging

Imaging of neurotransmitter systems has become more prevalent with advances in PET radioligand development. Early neurotransmitter imaging studies, while representing significant methodological advances, suffered from cross-binding with multiple receptors, for example, serotonin (5-HT) and dopamine (DA; Iyo & Yamasaki, 1993; Wong et al., 1984). Although deficits in cholinergic function in aging and AD are well documented (e.g., Davies & Maloney, 1976; Strong, 1998), few *in vivo* neuroimaging studies have addressed the issue. Two PET studies have reported negative relationships between age and serotonin receptor density (Meltzer et al., 1998; Rosier et al., 1996). A more recent report found no correlation between cognitive function and serotonin receptor density (Borg, Andree, Lundberg, Halldin, & Farde, 2006). Because of limited data, in this section we focus primarily on imaging the DA system.

DA systems are critical for higher-order cognitive functions. For example, cognitive deficits are often observed in Parkinson's disease patients, whose DA deficit is attributed to cell loss in the substantia nigra, a major source of DA production. The role of DA in cognition is also supported by ontogenetic (Pendleton, Rasheed, Roychowdhury, & Hillman, 1998) and phylogenetic evidence (for a discussion of the role of DA in the evolution of human intelligence, see Previc, 1999) and by computational models (Li, Lindenberger, & Sikstrom, 2001). There are two main families of DA receptors, D₁ and D₂. In the presynaptic terminal, the DA transporter (DAT) protein regulates synaptic DA concentration. Radioligands have been developed to bind to the D₁ (e.g., Farde, Halldin, Stone-Elander, & Sedvall, 1987) or D₂ (Farde,

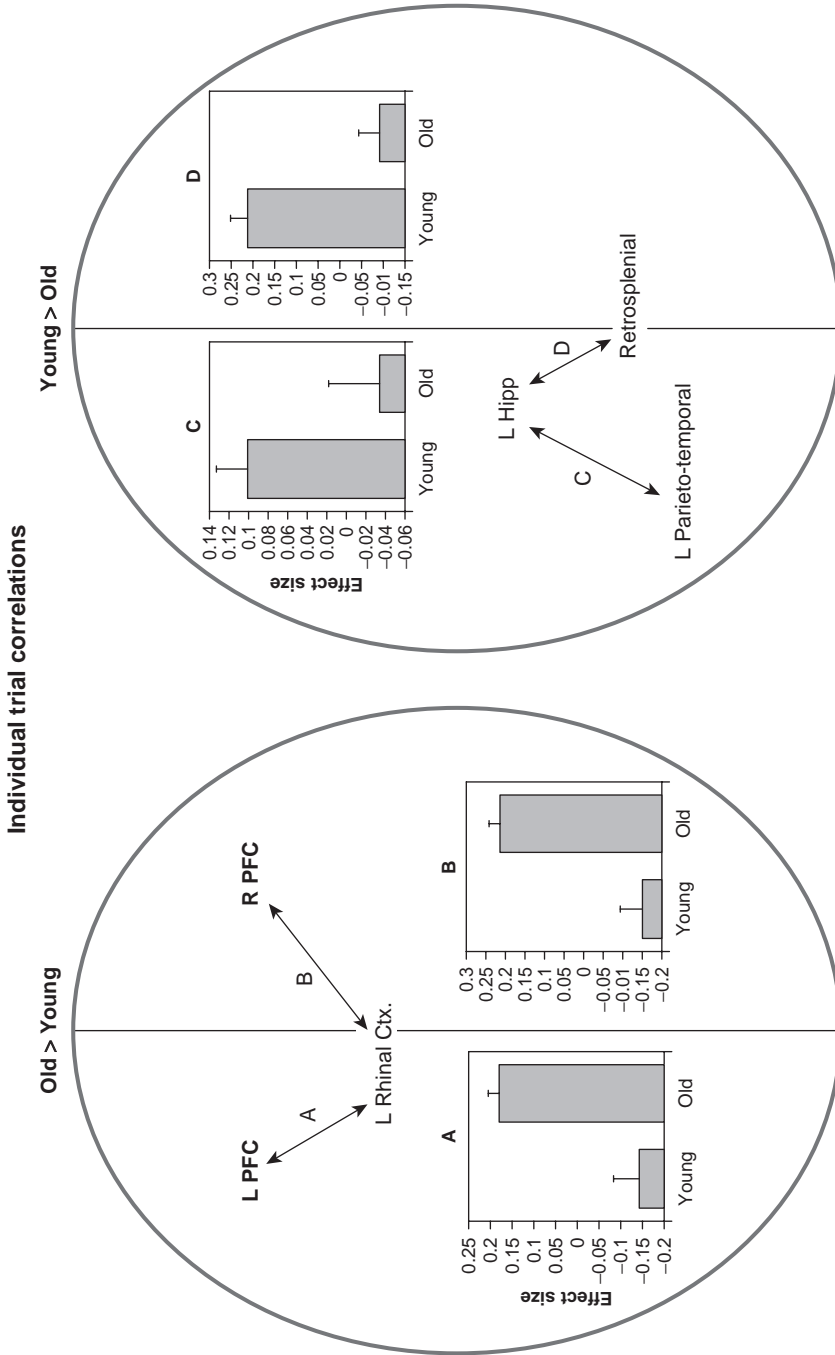


Figure 19.4 Correlation Analyses Using Individual Trial Activity

The analyses showed an age-related increase in functional connectivity within a rhinal–bilateral frontal network (A, B) coupled with an age-related decrease in connectivity within a hippocampal–retrosplenial/parietotemporal network.

SOURCE: From “Effects of Healthy Aging on Hippocampal and Rhinal Memory Functions: An Event-Related fMRI Study,” by S. M. Daselaar, M. S. Fleck, I. G. Dobbins, D. J. Madden, and R. Cabeza, 2006, *Cerebral Cortex*, 16, p. 1779. Copyright 2006 by Oxford University Press. Adapted with permission.

NOTE: L = left; R = right; PFC = prefrontal cortex; Ctx. = cortex; Hipp = hippocampus.

Hall, Ehrin, & Sedvall, 1986) receptor and DAT (Erixon-Lindroth et al., 2005; for a recent review of DA imaging, see Brooks, 2006).

In vivo studies using PET and single photon emission computed tomography (SPECT) have found loss of striatal D₁ and D₂ receptor binding across adulthood, with age-related decreases ranging between 7% and 10% per decade (Antonini & Leenders, 1993; Ichise et al., 1998; Suhara et al., 1991; Wang et al., 1998) and, in striatal DAT binding, with rates of decline of 4.4% to 8% per decade (Rinne, Sahlberg, Ruottinen, Nagren, & Lehtikoinen, 1998; van Dyck et al., 1995). DA loss has been observed in frontal, temporal, and occipital cortices as well as the hippocampus and thalamus (Inoue et al., 2001; Kaasinen et al., 2000). Given the role of fronto-striatal circuits in cognition (Cummings, 1993), striatal DA deficits could account for age-related cognitive deficits associated with PFC dysfunction. Indeed, age-related deficits in striatal DA have been associated with reductions in episodic memory (Backman et al., 2000; Erixon-Lindroth et al., 2005), executive function (Erixon-Lindroth et al., 2005; Mozley, Gur, et al., 2001; Volkow, Gur, et al., 1998), and motor performance (Mozley, Gur, et al., 2001; Wang et al., 1998), and striatal DA markers have been shown to predict cognitive performance after controlling for the effects of age (Backman et al., 2000; Volkow, Gur, et al., 1998). Furthermore, reductions in striatal DA function have been shown to mediate age-related cognitive deficits (Erixon-Lindroth et al., 2005).

Future research in DA imaging will continue to address neurochemical relationships to cognitive function. One issue that remains to be addressed is the lack of differential age or neuroanatomical effects between D₁ and D₂ imaging, despite differences in preferential localization of D₁ and D₂ within striatal circuitry. Research with larger sample sizes, comparative DA imaging, and inclusion of cognitive measures may elucidate age-related changes within specific striatal circuits.

Imaging Alzheimer's Disease Biomarkers

AD is characterized by the presence of beta-amyloid plaques and tau neurofibrillary tangles. Because of recent advances in radioligand

development (for a review, see Mathis, Wang, & Klunk, 2004), *in vivo* neuroimaging of AD neuropathology is now possible (see Figure 19.5; for review of AD neuropathology imaging technologies, see Bacskai, Klunk, Mathis, & Hyman, 2002). Thus far in humans, *in vivo* imaging of AD biomarkers has used PET, and primarily two radioligand tracers, either Pittsburgh Compound B (PIB) or FDDNP (for a conceptual discussion of quantification of amyloid burden, see Shoghi-Jadid et al., 2005). PIB and FDDNP differ on the basis of whether the tracer binds only beta-amyloid (PIB) or whether it binds beta-amyloid plaques and tau neurofibrillary tangles (FDDNP). Imaging results are typically reported in terms of residence time or standard uptake value, which are based on ratios of the amount of tracer detected in a given brain region relative to a region typically unaffected by AD, such as the pons or cerebellum. Longer residence times or greater standard uptake values indicate binding of the tracer and are assumed to reflect greater density of AD neuropathology.

At present, we are aware of only four AD biomarker imaging studies in humans. The initial report used PET with FDDNP, which is reported to bind beta-amyloid plaques and tau neurofibrillary tangles (Shoghi-Jadid et al., 2002). The results indicated increased residence time of the probe in medial temporal lobe (MTL) regions of probable AD patients relative to control participants, and residence times correlated with scores on the Mini-Mental State Exam, immediate verbal recall, and delayed figure recall. Brain regions exhibiting increased residence times appeared to match those showing glucose hypometabolism as measured by FDG (glucose) PET. In another study, Klunk et al. (2004) reported increased retention of a beta-amyloid probe (PIB) in association cortices of AD patients relative to control participants, corresponding to postmortem assessments of plaque accumulation in AD. Equivalent probe retention was observed in brain regions typically preserved in AD. Furthermore, probe retention was inversely correlated with glucose metabolism, consistent with the observations of Shoghi-Jadid et al. (2002). Using a novel beta-amyloid tracer and PIB, Verhoeff et al. (2004) reported results consistent with those of Klunk et al. (2004).

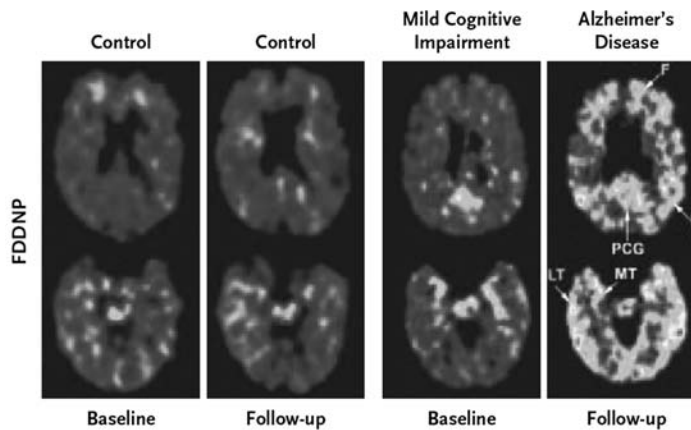


Figure 19.5 Example of FDDNP–Positron Emission Tomography Scans in a Representative Control Participant at Baseline and 2-Year Follow-Up and a Patient With Mild Cognitive Impairment Who Developed Alzheimer’s Disease

SOURCE: Adapted from Small, G. W., Kepe, V., Ercoli, L. M., Siddarth, P., Bookheimer, S. Y., Miller, K. J., et al. (2006). PET of brain amyloid and tau in mild cognitive impairment. *New England Journal of Medicine*, 355(25), 2652–2663. Copyright © 2006 Massachusetts Medical Society. All rights reserved.

NOTE: Light gray areas correspond to high FDDNP values. F = frontal; P = parietal; PCG = posterior cingulate; LT = lateral temporal; MT = medial temporal.

In the most comprehensive AD biomarker imaging study to date, structural MRI, FDG (glucose) PET, and FDDNP PET were performed on participants (age range: 49–84 years) classified as normal, with mild cognitive impairment, or with AD, on the basis of comprehensive neuropsychological testing (Small et al., 2006). Results indicated that FDDNP PET more accurately distinguished among unimpaired participants, those with mild cognitive impairment, and those with AD than FDG PET and MRI (volume of the medial temporal lobes). In the only participant for whom postmortem data were available, binding of FDDNP PET corresponded well to beta-amyloid and tau immunohistochemical staining. Finally, in a small subset of participants for whom follow-up data (mean duration: 2 years) were available, the three participants exhibiting cognitive deterioration also exhibited increases in FDDNP binding from 5.5% to 11%, whereas minimal increases in FDDNP binding (less than 3%) were observed in 9 cognitively stable control participants.

There are several challenges facing the utility of amyloid imaging, namely development of a

probe that crosses the blood–brain barrier and binds selectively to AD neuropathology (Nichols, Pike, Cai, & Innis, 2006). Accumulation of the radioligand is typically not specific to beta-amyloid, because the probe initially accumulates the most in the pons, an area typically unaffected by AD, and least in the hippocampus, one of the areas most affected by AD. Over time, however, the pattern reverses, as the probe clears from the pons yet remains in the hippocampus. Concerns regarding the ratio of the imaging probe in the hippocampus relative to the pons remain (Bacskai et al., 2002), and current methods may not be sensitive to identification of AD in the prodromal phase. The current promise of amyloid imaging resides in *in vivo* assessment of drug efficacy for medications designed to reduce plaque and/or tangle burden in AD patients.

Imaging Genetics

Genetic information and neuroimaging have been used to identify brain-related changes in individuals at risk for disease, with most

age-relevant research to date focusing on apolipoprotein E (APOE) status, a gene in which the $\epsilon 4$ allele shows a dose-related effect on risk and age of onset of AD (Corder et al., 1993; Saunders et al., 1993). In a landmark study, Reiman and colleagues (1996) observed reductions in glucose metabolism in posterior cingulate, parietal, temporal and PFC of cognitively intact adults (50–65 years old) at risk for AD (homozygous APOE $\epsilon 4$ allele), the same regions exhibiting reductions in glucose metabolism in probable AD patients (Alexander, Chen, Pietrini, Rapoport, & Reiman, 2002; Minoshima, Frey, Foster, & Kuhl, 1995). A similar pattern of abnormal glucose reductions was observed in younger adults (20–39 years old) at risk for AD (one APOE $\epsilon 4$ allele; Reiman et al., 2004), and APOE $\epsilon 4$ gene dose (homozygotes > heterozygotes > noncarriers) has been shown to correlate with lower glucose metabolism in posterior cingulate, precuneus, and parietotemporal and frontal cortex (Reiman et al., 2005).

In addition to changes in glucose metabolism, differences in patterns of fMRI activation between APOE $\epsilon 4$ and homozygous $\epsilon 3$ carriers have been observed while scanning during an active memory task (Bookheimer et al., 2000). Despite equivalent behavioral performance (as measured outside the scanner), increased activation in the medial temporal lobes (hippocampus and parahippocampal gyrus) and PFC was observed during episodic memory encoding and recall in $\epsilon 4$ carriers relative to homozygous $\epsilon 3$ carriers. In a subset of adults tested 2 years later, subsequent verbal memory decline was associated with increased activation in the left hemisphere at baseline, which was attributed to a compensatory response. An additional report indicated that the compensatory response was specific to the requirements of the episodic memory task, because a difference in activation pattern was not observed in $\epsilon 4$ carriers and homozygous $\epsilon 3$ carriers on a working memory task (Burggren, Small, Sabb, & Bookheimer, 2002).

Whereas imaging genetics of healthy and pathological aging has primarily focused on APOE, the future of age-related imaging genetics will likely incorporate other candidate genes associated with episodic memory performance, hippocampal function, or PFC function. For example, the Ser allele of the disrupted-in-schizophrenia 1

(DISC1) gene, which is primarily expressed in the hippocampus, has been associated with reductions in hippocampal volume. Moreover, decreased hippocampal activation has been observed during a working memory (n-back) task and during episodic encoding and retrieval of neutral scenes in healthy participants with homozygous Ser alleles relative to participants with homozygous Cys alleles (Callicott et al., 2005).

The COMT (catechol-*o*-methyltransferase) gene has received a great deal of attention in schizophrenia research because of its role in metabolism of DA and associated deficits in DA and prefrontal function in schizophrenia. The Val allele of COMT catabolizes DA approximately four times faster than the Met allele, leading to the hypothesis that individuals with Val/Val alleles on the COMT gene would have lower levels of prefrontal DA and therefore experience inefficient prefrontal function and deficits on tasks of executive function. During a working memory task, increased fMRI activation (greater inefficiency) in dorsolateral PFC and anterior cingulate was observed in individuals with homozygous Val on the COMT gene relative to Val/Met individuals (Egan et al., 2001). Moreover, Val/Met COMT individuals had greater activation than Met/Met COMT. Because DA plays a critical role in cognitive function, as previously discussed, the COMT gene has implications for aging as well.

Genetic variation in brain-derived neurotrophic factor (BDNF) has also been associated with differential patterns of cognitive performance and brain activation. Decreased episodic memory performance was observed in individuals with Val/Met BDNF relative to Val/Val (Egan et al., 2003). Furthermore, Val/Met BDNF individuals failed to deactivate the hippocampus during a working memory task, whereas Val/Val BDNF patterns exhibited normal activity.

Imaging genetics studies highlight the potential utility of combining genotype and neuroimaging. In each of the aforementioned studies, groups were matched for age, education, gender, and behavioral performance, yet differences in brain activity, as measured by PET or fMRI, were associated with allelic variation. Despite equivalent cognitive task performance, functional neuroimaging can reveal biological effects of genetic variability, even

when relatively small sample sizes ($n < 20$) are used. Because of complex interactions between genes and between genes and the environment, these studies represent the beginning of a promising research endeavor. Indeed, many relatively basic questions remain unaddressed. For example, genetic variations within APOE, COMT, and BDNF, when considered in isolation, have implications for hippocampal function and episodic memory. Thus far, they have not been considered in relation to one another. Do genetic variants of COMT and BDNF elicit further inefficient processing within the hippocampus or increase risk for AD in APOE $\epsilon 4$ carriers? Indeed, as imaging genetics continues to develop, more elegant neuroimaging designs and more sophisticated questions will be addressed.

CONCLUSION

Technological advances have enabled the *in vivo* assessment of cerebral structure and function, leading to a new field of aging research, the cognitive neuroscience of aging (see Cabeza, Nyberg, & Park, 2005). As indicated in Figure 19.6, neural structure is a prerequisite for resting neural function, which in turn is a prerequisite for cognition-related activity. The imaging tools (identified in italics in the figure) provide measures of different but interconnected aspects of the neural basis of cognitive aging (identified in boldface in the figure). Indicators of neuropathological disease processes, such as plaques and tangles, are also identified in Figure 19.6, as are factors that can influence their expression, such as genotype and environment, all of which can impact cognitive function.

Clarification of brain structure–function–cognition relationships will require the integration of multiple imaging techniques, such as DTI and fMRI data. Indeed, several reports integrating DTI and fMRI were published recently (Madden et al., 2007; Oleson, Nagy, Westerberg, & Klingberg, 2003; Persson et al., 2006; Takahashi, Ohki, & Kim, 2007). Persson et al. (2006) provide a particularly nice example of multimethod imaging as they reported fMRI, DTI, structural MRI, and longitudinal data. They compared FA in regions of the corpus callosum

and fMRI activation in OA whose episodic memory performance declined across a decade relative to those whose memory performance remained stable. In memory-stable and memory-declining OA, equivalent levels of fMRI activation were found in left prefrontal regions. However, increased activation was observed in right ventral PFC in memory-declining relative to -stable OA. In the genu of the corpus callosum, FA was significantly lower in the memory decline relative to stable OA. Furthermore, FA in the genu correlated negatively with right ventral prefrontal activity; that is, decreased white matter integrity in the genu was associated with increased ventral prefrontal activity. Finally, Persson et al. (2006) reported reductions in hippocampal volume in memory-declining OA. This study highlights the richness of data that can be acquired and simultaneously assessed in a single neuroimaging study and the multiple measures that can be associated with age-related memory changes within subjects.

Although not reported by Persson et al. (2006), integration of functional connectivity analysis, which measures the relations of activations within the brain (Daselaar, Fleck, Dobbins, et al., 2006; McIntosh, 1999), with DTI tractography, could offer structurally constrained and biologically plausible models of neural networks. Combining fMRI and DTI allows one to assess the structural integrity of white matter tracts that presumably connect regions of activation identified by functional connectivity analyses.

Turning to genetic imaging, consideration of multiple genes and age-related changes represents an interesting step forward and could provide informative data into theoretical debate regarding age-related changes in cognitive function. For instance, if hippocampal dysfunction (as measured by fMRI) is observed in individuals with the Ser/Ser allele of DISC1, is hippocampal dysfunction attenuated by the Met/Met variant of COMT, which is associated with enhanced PFC function? Are individuals with the Met/Met variant of COMT more likely to exhibit neural compensation in the form of HAROLD or PASA pattern due to enhanced PFC function? Future studies aimed at addressing age-related compensation and dedifferentiation will need to address these questions.

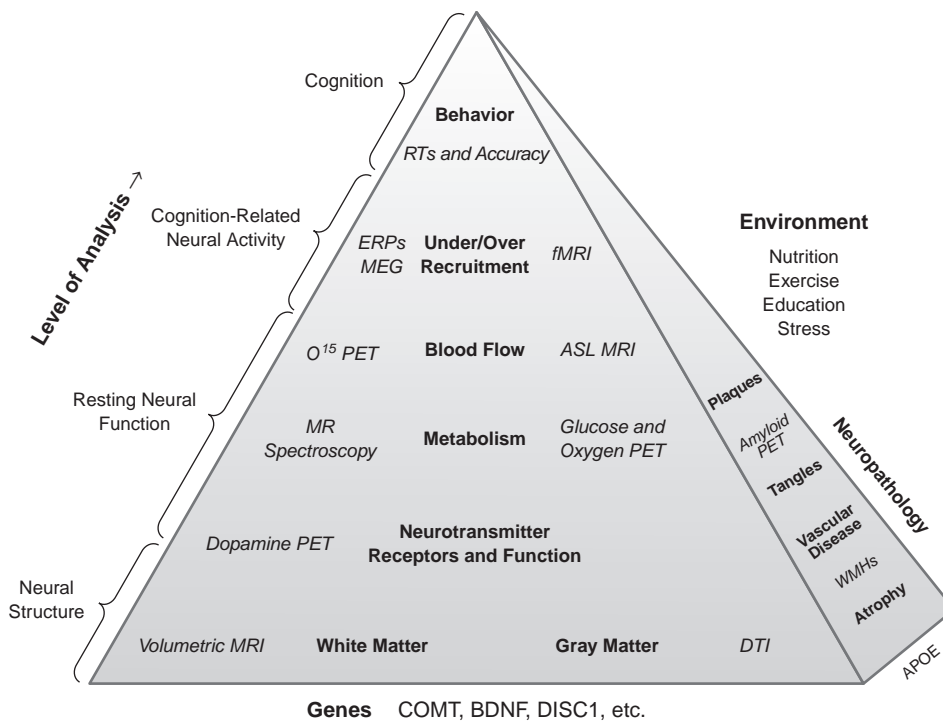


Figure 19.6 Imaging Techniques Measure Different Levels of Neural Phenomena

NOTES: Imaging tools are presented in *italics* type, whereas the phenomena they measure are presented in **boldface** type. The level of analysis is noted on the left in a hierarchical fashion, although a degree of codependence among levels is noted (e.g., gray matter structural integrity is dependent on blood flow). RT = response time; ERPs = event-related potentials; MEG = magnetoencephalography; fMRI = functional magnetic resonance imaging; PET = positron emission tomography; ASL MRI = arterial spin labeling magnetic resonance imaging; MR = magnetic resonance; DTI = diffusion tensor imaging; WMH = white matter hyperintensities; APOE = apolipoprotein E; COMT = catechol-*o*-methyltransferase; BDNF = brain-derived neurotrophic factor; DISC1 = disrupted-in-schizophrenia 1 gene.

In addition, although we have discussed age-related changes and resting DA imaging studies, DA activation imaging studies have yet to be applied to issues regarding healthy aging. Thus far, DA activation imaging studies have measured DA release while playing a video game (Koepp et al., 1998), learning a motor sequencing task (Lawrence & Brooks, 1999), and performing a rewarded or unrewarded visual search task (Sawamoto et al., 2006). Advances in the cognitive neuroscience of aging will likely include application of DA activation imaging studies to age-related issues. An obvious important integration of techniques would be the incorporation of assessment of allelic variation of the COMT gene, which is associated with enhanced PFC function, to resting and activation DA imaging studies.

Multiple noninvasive *in vivo* neuroimaging techniques are available to assess the integrity of the human brain across the life span. Neuroimaging remains a rapidly developing field, with breakthroughs in PET and MRI methods and design continuing to provide novel images of physiological indicators of brain function. Data derived from structural, resting functional, activation, neuropathological, and genetic imaging methods have revealed significant age-related changes throughout the brain. Based on the level of the neural indicator that each technique measures, these imaging methods have complementary strengths and weaknesses. The major challenge for the field of cognitive neuroscience of aging will be the simultaneous assessment of data collected from

these various imaging techniques to identify the causal relationship between changes in cerebral and cognitive function. One way to address this issue is through the use of a combination of imaging techniques and, furthermore, to interpret the results of imaging studies within a given modality in relation to those attained from complementary imaging modalities.

REFERENCES

- Alexander, G. E., Chen, K., Pietrini, P., Rapoport, S. I., & Reiman, E. M. (2002). Longitudinal PET evaluation of cerebral metabolic decline in dementia: A potential outcome measure in Alzheimer's disease treatment studies. *American Journal of Psychiatry*, *159*, 738–745.
- Anderson, N. D., Iidaka, T., Cabeza, R., Kapur, S., McIntosh, A. R., & Craik, F. I. (2000). The effects of divided attention on encoding- and retrieval-related brain activity: A PET study of younger and older adults. *Journal of Cognitive Neuroscience*, *12*, 775–792.
- Antonini, A., & Leenders, K. L. (1993). Dopamine D2 receptors in normal human brain—Effect of age measured by positron emission tomography (PET) and [C-11] raclopride. In *Alzheimer's disease: Amyloid precursor proteins, signal transduction, and neuronal transplantation* (pp. 81–85). New York: New York Academy of Sciences.
- Backman, L., Ginovart, N., Dixon, R. A., Wahlin, T. B., Wahlin, A., Halldin, C., et al. (2000). Age-related cognitive deficits mediated by changes in the striatal dopamine system. *American Journal of Psychiatry*, *157*, 635–637.
- Bacskai, B. J., Klunk, W. E., Mathis, C. A., & Hyman, B. T. (2002). Imaging amyloid-beta deposits in vivo. *Journal of Cerebral Blood Flow and Metabolism*, *22*, 1035–1041.
- Bartzokis, G., Cummings, J. L., Sultzer, D., Henderson, V. W., Nuechterlein, K. H., & Mintz, J. (2003). White matter structural integrity in healthy aging adults and patients with Alzheimer disease—A magnetic resonance imaging study. *Archives of Neurology*, *60*, 393–398.
- Bartzokis, G., Sultzer, D., Lu, P. H., Nuechterlein, K. H., Mintz, J., & Cummings, J. L. (2004). Heterogeneous age-related breakdown of white matter structural integrity: Implications for cortical “disconnection” in aging and Alzheimer's disease. *Neurobiology of Aging*, *25*, 843–851.
- Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, *66*, 259–267.
- Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system—A technical review. *NMR in Biomedicine*, *15*, 435–455.
- Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., et al. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *New England Journal of Medicine*, *343*, 450–456.
- Borg, J., Andree, B., Lundberg, J., Halldin, C., & Farde, L. (2006). Search for correlations between serotonin 5-HT1A receptor expression and cognitive functions—A strategy in translational psychopharmacology. *Psychopharmacology*, *185*, 389–394.
- Brooks, D. J. (2006). Dopaminergic action beyond its effects on motor function: Imaging studies. *Journal of Neurology*, *253*, 8–15.
- Burggren, A. C., Small, G. W., Sabb, F. W., & Bookheimer, S. Y. (2002). Specificity of brain activation patterns in people at genetic risk for Alzheimer disease. *American Journal of Geriatric Psychiatry*, *10*, 44–51.
- Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*, 85–100.
- Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage*, *17*, 1394–1402.
- Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., et al. (1997). Age-related differences in neural activity during memory encoding and retrieval: A positron emission tomography study. *Journal of Neuroscience*, *17*, 391–400.
- Cabeza, R., McIntosh, A. R., Grady, C. L., Nyberg, L., Houle, S., & Tulving, E. (1997). Age-related changes in neural interactions during memory encoding and retrieval: A network analysis of PET data. *Brain and Cognition*, *35*, 369–372.
- Cabeza, R., McIntosh, A. R., Tulving, E., Nyberg, L., & Grady, C. L. (1997). Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport*, *8*, 3479–3483.
- Cabeza, R., Nyberg, L., & Park, D. C. (Eds.). (2005). *Cognitive neuroscience of aging: linking cognitive and cerebral aging*. New York: Oxford University Press.

322 • BIOLOGICAL INDICATORS AND HEALTH-RELATED PROCESSES

- Callicott, J. H., Straub, R. E., Pezawas, L., Egan, M. F., Mattay, V. S., Hariri, A. R., et al. (2005). Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proceedings of the National Academy of Sciences, USA*, *102*, 8627–8632.
- Celone, K. A., Calhoun, V. D., Dickerson, B. C., Atri, A., Chua, E. F., Miller, S. L., et al. (2006). Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: An independent component analysis. *Journal of Neuroscience*, *26*, 10222–10231.
- Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., et al. (1993, August 13). Gene dose of apolipoprotein-E type-4 allele and the risk of Alzheimer's disease in late-onset families. *Science*, *261*, 921–923.
- Corouge, I., Gouttard, S., & Gerig, G. (2004). A statistical shape model of individual fiber tracts extracted from diffusion tensor MRI. In D. R. Haynor, P. Hellier, C. Barillot (Eds.), *Medical Image Computing and Computer-Assisted Intervention—MICCAI 2004: 7th International Conference Saint-Malo, France, September 26-29, 2004, Proceedings, Part II* (pp. 671–679). Berlin: Springer-Verlag.
- Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology*, *50*, 873–880.
- Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: Recollection, familiarity, and novelty. *Journal of Neurophysiology*, *96*, 1902–1911.
- Daselaar, S. M., Fleck, M. S., Dobbins, I. G., Madden, D. J., & Cabeza, R. (2006). Effects of healthy aging on hippocampal and rhinal memory functions: An event-related fMRI study. *Cerebral Cortex*, *16*, 1771–1782.
- Daselaar, S. M., Prince, S. E., & Cabeza, R. (2004). When less means more: Deactivations during encoding that predict subsequent memory. *Neuroimage*, *23*, 921–927.
- Davies, P., & Maloney, A. J. F. (1976). Selective loss of central cholinergic neurons in Alzheimer's disease. *The Lancet*, *2*, 1403–1403.
- Davis, S., Dennis, N. A., Daselaar, S., Fleck, M. S., & Cabeza, R. (in press). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex*.
- de Leon, M. J., Convit, A., Wolf, O. T., Tarshish, C. Y., DeSanti, S., Rusinek, H., et al. (2001). Prediction of cognitive decline in normal elderly subjects with 2-[F-18]fluoro-2-deoxy-D-glucose/positron-emission tomography (FDG/PET). *Proceedings of the National Academy of Sciences USA*, *98*, 10966–10971.
- Della-Maggiore, V., Sekuler, A. B., Grady, C. L., Bennett, P. J., Sekuler, R., & McIntosh, A. R. (2000). Corticolimbic interactions associated with performance on a short-term memory task are modified by age. *Journal of Neuroscience*, *20*, 8410–8416.
- Dennis, N. A., Daselaar, S., & Cabeza, R. (2006). Effects of aging on transient and sustained successful memory encoding activity. *Neurobiology of Aging*, *28*(11) 1749–1758.
- Donaldson, D. I. (2004). Parsing brain activity with fMRI and mixed designs: What kind of a state is neuroimaging in? *Trends in Neurosciences*, *27*, 442–444.
- Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mattay, V. S., Straub, R. E., et al. (2001). Effect of COMT Val(108/158) Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences, USA*, *98*, 6917–6922.
- Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*, 257–269.
- Erixon-Lindroth, N., Farde, L., Wahlin, T. B. R., Sovago, J., Halldin, C., & Backman, L. (2005). The role of the striatal dopamine transporter in cognitive aging. *Psychiatry Research: Neuroimaging*, *138*, 1–12.
- Farde, L., Hall, H., Ehrin, E., & Sedvall, G. (1986, January 17). Quantitative-analysis of D2 dopamine receptor-binding in the living human brain by PET. *Science*, *231*, 258–261.
- Farde, L., Halldin, C., Stone-Elander, S., & Sedvall, G. (1987). PET analysis of human dopamine receptor subtypes using C-11 SCH 23390 and C-11 raclopride. *Psychopharmacology*, *92*, 278–284.
- Freyhan, F. A., Woodford, R. B., & Kety, S. S. (1951). Cerebral blood flow and metabolism in psychoses of senility. *Journal of Nervous and Mental Disease*, *113*, 449–456.
- Grady, C. L., Bernstein, L. J., Beig, S., & Siegenthaler, A. L. (2002). The effects of encoding

- task on age-related differences in the functional neuroanatomy of face memory. *Psychology and Aging*, *17*, 7–23.
- Grady, C. L., McIntosh, A. R., & Craik, F. I. M. (2003). Age-related differences in the functional connectivity of the hippocampus during memory encoding. *Hippocampus*, *13*, 572–586.
- Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., et al. (1995, July 14). Age-related reductions in human recognition memory due to impaired encoding. *Science*, *269*, 218–221.
- Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences, USA*, *100*, 253–258.
- Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience*, *2*, 685–694.
- Gutchess, A. H., Welsh, R. C., Hedden, T., Bangert, A., Minear, M., Liu, L. L., et al. (2005). Aging and the neural correlates of successful picture encoding: Frontal activations compensate for decreased medial-temporal activity. *Journal of Cognitive Neuroscience*, *17*, 84–96.
- Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., et al. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: Evidence from diffusion tensor imaging. *Cerebral Cortex*, *14*, 410–423.
- Ichise, M., Ballinger, J. R., Tanaka, F., Moscovitch, M., St. George-Hyslop, P. H., Raphael, D., et al. (1998). Age-related changes in D2 receptor binding with iodine-123-iodobenzofuran SPECT. *Journal of Nuclear Medicine*, *39*, 1511–1518.
- Inoue, M., Suhara, T., Sudo, Y., Okubo, Y., Yasuno, F., Kishimoto, T., et al. (2001). Age-related reduction of extrastriatal dopamine D2 receptor measured by PET. *Life Sciences*, *69*, 1079–1084.
- Iyo, M., & Yamasaki, T. (1993). The detection of age-related decrease of dopamine-D1, dopamine D-2 and serotonin 5-HT2 receptors in living human brain. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *17*, 415–421.
- Kaasinen, V., Vilkmann, H., Hietala, J., Nagren, K., Helenius, H., Olsson, H., et al. (2000). Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. *Neurobiology of Aging*, *21*, 683–688.
- Kety, S. S. (1956). Human cerebral blood flow and oxygen consumption as related to aging. *Journal of Chronic Disease*, *3*, 478–486.
- Kety, S. S., & Schmidt, C. F. (1945). The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. *American Journal of Physiology*, *143*, 53–66.
- Kety, S. S., & Schmidt, C. F. (1948). The nitrous oxide method for the quantitative determination of cerebral blood flow in man—Theory, procedure and normal values. *Journal of Clinical Investigation*, *27*, 476–483.
- Klunk, W. E., Engler, H., Nordberg, A., Wang, Y. M., Blomqvist, G., Holt, D. P., et al. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology*, *55*, 306–319.
- Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T., et al. (1998, July 16). Evidence for striatal dopamine release during a video game. *Nature*, *393*, 266–268.
- Lawrence, A. D., & Brooks, D. J. (1999). Neural correlates of reward processing in the human brain: A PET study. *Neurology*, *52*, A306–A306.
- LeBihan, D. (2003). Looking into the functional architecture of the brain with diffusion MRI. *Nature Reviews Neuroscience*, *4*, 469–480.
- Li, S. C., Lindenberger, U., & Sikstrom, S. (2001). Aging cognition: From neuromodulation to representation. *Trends in Cognitive Sciences*, *5*, 479–486.
- Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Underrecruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. *Neuron*, *33*, 827–840.
- Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., et al. (2003). Functional deactivations: Change with age and dementia of the Alzheimer type. *Proceedings of the National Academy of Sciences, USA*, *100*, 14504–14509.
- Madden, D. J., Spaniol, J., Whiting, W. L., Bucur, B., Provenzale, J. M., Cabeza, R., et al. (2007). Adult age differences in the functional neuroanatomy of visual attention: A combined fMRI and DTI study. *Neurobiology of Aging*, *28*(3), 459–476.

324 • BIOLOGICAL INDICATORS AND HEALTH-RELATED PROCESSES

- Madden, D. J., Whiting, W. L., Huettel, S. A., White, L. E., MacFall, J. R., & Provenzale, J. M. (2004). Diffusion tensor imaging of adult age differences in cerebral white matter: Relation to response time. *Neuroimage*, *21*, 1174–1181.
- Mathis, C. A., Wang, Y., & Klunk, W. E. (2004). Imaging beta-amyloid plaques and neurofibrillary tangles in the aging human brain. *Current Pharmaceutical Design*, *10*, 1469–1492.
- McIntosh, A. R. (1999). Mapping cognition to the brain through neural interactions. *Memory*, *7*, 523–548.
- McKiernan, K. A., Kaufman, J. N., Kucera-Thompson, J., & Binder, J. R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience*, *15*, 394–408.
- Meltzer, C. C., Smith, G., Price, J. C., Reynolds, C. F., Mathis, C. A., Greer, P., et al. (1998). Reduced binding of [F-18]altanserin to serotonin type 2A receptors in aging: Persistence of effect after partial volume correction. *Brain Research*, *813*, 167–171.
- Minoshima, S., Frey, K. A., Foster, N. L., & Kuhl, D. E. (1995). Preserved pontine glucose-metabolism in Alzheimer-disease—A reference region for functional brain image (PET) analysis. *Journal of Computer Assisted Tomography*, *19*, 541–547.
- Morcom, A. M., Good, C. D., Frackowiak, R. S. J., & Rugg, M. D. (2003). Age effects on the neural correlates of successful memory encoding. *Brain*, *126*, 213–229.
- Mori, S., & van Zijl, P. C. M. (2002). Fiber tracking: Principles and strategies—A technical review. *NMR in Biomedicine*, *15*, 468–480.
- Moseley, M. (2002). Diffusion tensor imaging and aging—A review. *NMR in Biomedicine*, *15*, 553–560.
- Mozley, L. H., Gur, R. C., Mozley, P. D., & Gur, R. E. (2001). Striatal dopamine transporters and cognitive functioning in healthy men and women. *American Journal of Psychiatry*, *158*, 1492–1499.
- Nichols, L., Pike, V. W., Cai, L. S., & Innis, R. B. (2006). Imaging and in vivo quantitation of beta-amyloid: An exemplary biomarker for Alzheimer's disease? *Biological Psychiatry*, *59*, 940–947.
- Olesen, P. J., Nagy, Z., Westerberg, H., & Klingberg, T. (2003). Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. *Cognitive Brain Research*, *18*, 48–57.
- O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C. R., & Markus, H. S. (2001). Evidence for cortical “disconnection” as a mechanism of age-related cognitive decline. *Neurology*, *57*, 632–638.
- Otten, L. J., Henson, R. N., & Rugg, M. D. (2002). State-related and item-related neural correlates of successful memory encoding. *Nature Neuroscience*, *5*, 1339–1344.
- Pendleton, R. G., Rasheed, A., Roychowdhury, R., & Hillman, R. (1998). A new role for catecholamines: ontogenesis. *Trends in Pharmacological Sciences*, *19*, 248–251.
- Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L. G., Ingvar, M., et al. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral Cortex*, *16*, 907–915.
- Pfefferbaum, A., Sullivan, E. V., Hedehus, M., Lim, K. O., Adalsteinsson, E., & Moseley, M. (2000). Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magnetic Resonance in Medicine*, *44*, 259–268.
- Pfefferbaum, A., Sullivan, E. V., Rosenbloom, M. J., MATHALON, H., & Lim, K. O. (1998). A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Archives of General Psychiatry*, *55*, 905–912.
- Previc, F. H. (1999). Dopamine and the origins of human intelligence. *Brain and Cognition*, *41*, 299–350.
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, USA*, *98*, 676–682.
- Raz, N. (2000). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In F. I. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (pp. 1–90). Mahwah, NJ: Lawrence Erlbaum.
- Raz, N. (2005). The aging brain observed *in vivo*: Differential changes and their modifiers. In R. Cabeza, L. Nyberg, & D. C. Park (Eds.), *Cognitive neuroscience of aging: linking cognitive and cerebral aging* (pp. 19–57). New York: Oxford University Press.

- Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., & Acker, J. D. (1998). Neuroanatomical correlates of cognitive aging: Evidence from structural magnetic resonance imaging. *Neuropsychology, 12*, 95–114.
- Raz, N., Rodrigue, K. M., Head, D., Kennedy, K. M., & Acker, J. D. (2004). Differential aging of the medial temporal lobe—A study of a five-year change. *Neurology, 62*, 433–438.
- Raz, N., Rodrigue, K. M., Kennedy, K. M., Head, D., Gunning-Dixon, F., & Acker, J. D. (2003). Differential aging of the human striatum: Longitudinal evidence. *American Journal of Neuroradiology, 24*, 1849–1856.
- Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K. W., Bandy, D., Minoshima, S., et al. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *New England Journal of Medicine, 334*, 752–758.
- Reiman, E. M., Chen, K. W., Alexander, G. E., Caselli, R. J., Bandy, D., Osborne, D., et al. (2004). Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proceedings of the National Academy of Sciences, USA, 101*, 284–289.
- Reiman, E. M., Chen, K. W., Alexander, G. E., Caselli, R. J., Bandy, D., Osborne, D., et al. (2005). Correlations between apolipoprotein E epsilon 4 gene dose and brain-imaging measurements of regional hypometabolism. *Proceedings of the National Academy of Sciences, USA, 102*, 8299–8302.
- Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. *Journal of Neuroscience, 23*, 3295–3301.
- Rinne, J. O., Sahlberg, N., Ruottinen, H., Nagren, K., & Lehtikoinen, P. (1998). Striatal uptake of the dopamine reuptake ligand [¹¹C]beta-CFT is reduced in Alzheimer's disease assessed by positron emission tomography. *Neurology, 50*, 152–156.
- Rissman, J., Gazzaley, A., & D'Esposito, M. (2004). Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage, 23*, 752–763.
- Rodrigue, K. M., & Raz, N. (2004). Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. *Journal of Neuroscience, 24*, 956–963.
- Rombouts, S., Barkhof, F., Goekoop, R., Stam, C. J., & Scheltens, P. (2005). Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: An fMRI study. *Human Brain Mapping, 26*, 231–239.
- Rosier, A., Dupont, P., Peuskens, J., Bormans, G., Vandenberghe, R., Maes, M., et al. (1996). Visualisation of loss of 5-HT_{2A} receptors with age in healthy volunteers using [F-18]altanserin and positron emission tomographic imaging. *Psychiatry Research: Neuroimaging, 68*, 11–22.
- Salat, D. H., Tuch, D. S., Hevelone, N. D., Fischl, B., Corkin, S., Rosas, H. D., et al. (2005). Age-related changes in prefrontal white IF matter measured by diffusion tensor imaging. In J. L. Ulmer, L. Parsons, M. Moseley, & J. Gabrieli (Eds.), *White matter in cognitive neuroscience: Advances in diffusion tensor imaging and its applications* (pp. 37–49). New York: New York Academy of Sciences.
- Saunders, A. M., Strittmatter, W. J., Schmechel, D., Georgehyslop, P. H. S., Pericakvance, M. A., Joo, S. H., et al. (1993). Association of apolipoprotein-E allele epsilon-4 with late-onset familial and sporadic Alzheimers disease. *Neurology, 43*, 1467–1472.
- Sawamoto, N., Hotton, G., Pavese, N., Thielemans, K., Piccini, P., & Brooks, D. J. (2006). Neurobiological mechanism underlying decreased motivation in Parkinson's disease: A C-11-raclopride positron emission tomography study. *Neurology, 66*, A113–A113.
- Scahill, R. I., Frost, C., Jenkins, R., Whitwell, J. L., Rossor, M. N., & Fox, N. C. (2003). A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Archives of Neurology, 60*, 989–994.
- Schiavetto, A., Kohler, S., Grady, C. L., Winocur, G., & Moscovitch, M. (2002). Neural correlates of memory for object identity and object location: effects of aging. *Neuropsychologia, 40*, 1428–1442.
- Shoghi-Jadid, K., Barrio, J. R., Kepe, V., Wu, H. M., Small, G. W., Phelps, M. E., et al. (2005). Imaging beta-amyloid fibrils in Alzheimer's disease: A critical analysis through simulation of amyloid fibril polymerization. *Nuclear Medicine and Biology, 32*, 337–351.
- Shoghi-Jadid, K., Small, G. W., Agdeppa, E. D., Kepe, V., Ercoli, L. M., Siddarth, P., et al. (2002). Localization of neurofibrillary tangles

326 • BIOLOGICAL INDICATORS AND HEALTH-RELATED PROCESSES

- and beta-amyloid plaques in the brains of living patients with Alzheimer disease. *American Journal of Geriatric Psychiatry*, 10, 24–35.
- Small, G. W., Kepe, V., Ercoli, L. M., Siddarth, P., Bookheimer, S. Y., Miller, K. J., et al. (2006). PET of brain amyloid and tau in mild cognitive impairment. *New England Journal of Medicine*, 355, 2652–2663.
- Stebbins, G. T., Carillo, M. C., Medina, D., deToledo-Morrell, L., Klingberg, T., Poldrack, R. A., et al. (2001). Frontal white matter integrity in aging and its role in reasoning performance: A diffusion tensor imaging study. *Society for Neuroscience Abstracts*, 456, 3.
- Stebbins, G. T., Poldrack, R. A., Klingberg, T., Carrillo, M. C., Desmond, J. E., Moseley, M. E., et al. (2001). Aging effects on white matter integrity and processing speed: A diffusion tensor imaging study. *Neurology*, 56, A374–A375.
- Strong, R. (1998). Neurochemical changes in the aging human brain: Implications for behavioral impairment and neurodegenerative disease. *Geriatrics*, 53, S9–S12.
- Suhara, T., Fukuda, H., Inoue, O., Itoh, T., Suzuki, K., Yamasaki, T., et al. (1991). Age-related changes in human D1 dopamine receptors measured by positron emission tomography. *Psychopharmacology*, 103, 41–45.
- Takahashi, E., Ohki, K., & Kim, D. S. (2007). Diffusion tensor studies dissociated two fronto-temporal pathways in the human memory system. *Neuroimage*, 34, 827–838.
- van Dyck, C. H., Seibyl, J. P., Malison, R. T., Laruelle, M., Wallace, E., Zoghbi, S. S., et al. (1995). Age-related decline in striatal dopamine transporter binding with iodine-123-beta-CITSPECT. *Journal of Nuclear Medicine*, 36, 1175–1181.
- Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: Review and meta-analysis. *Neuropsychologia*, 42, 1394–1413.
- Verhoeff, N., Wilson, A. A., Takeshita, S., Trop, L., Hussey, D., Singh, K., et al. (2004). In-vivo imaging of Alzheimer disease beta-amyloid with [C-11]SB-13 PET. *American Journal of Geriatric Psychiatry*, 12, 584–595.
- Visscher, K. M., Miezin, F. M., Kelly, J. E., Buckner, R. L., Donaldson, D. I., McAvoy, M. P., et al. (2003). Mixed blocked/event-related designs separate transient and sustained activity in fMRI. *Neuroimage*, 19, 1694–1708.
- Volkow, N. D., Gur, R. C., Wang, G. J., Fowler, J. S., Moberg, P. J., Ding, Y. S., et al. (1998). Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. *American Journal of Psychiatry*, 155, 344–349.
- Wang, Y., Chan, G. L., Holden, J. E., Dobko, T., Mak, E., Schulzer, M., et al. (1998). Age-dependent decline of dopamine D1 receptors in human brain: A PET study. *Synapse*, 30, 56–61.
- Wong, D. F., Wagner, H. N., Dannals, R. F., Links, J. M., Frost, J. J., Ravert, H. T., et al. (1984, December 21). Effects of age on dopamine and serotonin receptors measured by positron emission tomography in the living human-brain. *Science*, 226, 1393–1396.
- Xu, D. R., Mori, S., Solaiyappan, M., van Zijl, P. C. M., & Davatzikos, C. (2002). A framework for callosal fiber distribution analysis. *Neuroimage*, 17, 1131–1143.