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...
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 increased 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; Sahill 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 palladium 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. 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 popu-
lation, because follow-up data collection is neg-
atively impacted by mortality in OA, morbidity
in middle-aged adults, and mobility in YA (the
"three M's"; see Raz, 2005, or additional dis-
cussion). 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 rela-
tionship between longitudinal changes in cogni-
tive function and neural structure.

**Diffusion Tensor Imaging**

The development of diffusion tensor imaging (DTI) represents a significant advance in neu-
roimaging 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 deter-
mined 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 mea-
sures 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 indica-
tors of frontal lobe white matter (e.g., FA val-
ues) have been associated with measures of
processing speed and reasoning (Stebbins,
Carillo, et al., 2001; Stebbins, Poldrack, et al.,
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 mea-
sures for the various fiber tracts passing through
a region-of-interest, these measures can be pro-
vided 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 val-
ues 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 partici-
ants (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 seg-
ment 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, uncinate 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,
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

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 mm³.
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, Iidaka 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 encoding activity, possibly due to a decline 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...
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](image)

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.


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, & Lehikoinen, 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 Baeski, 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).
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 ε4 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 ε4 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 ε4 allele; Reiman et al., 2004), and APOE ε4 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 ε4 and homozygous ε3 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 ε4 carriers relative to homozygous ε3 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 ε4 carriers and homozygous ε3 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 catalyzes 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 \(\varepsilon_4\) 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.
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


