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Neuroscience Frontiers of Cognitive Aging: Approaches to Cognitive Neuroscience of Aging

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Nobody would seriously challenge the idea that age-related changes in cognition are in great part a consequence of age-related changes in the brain. Yet, although both types of phenomena have been thoroughly studied in isolation, the relationships between them are not well understood. On one hand, postmortem studies, structural MRI, and resting PET studies have provided detailed information about the effects of aging on the anatomy and physiology of the brain, including grey and white matter atrophy, synaptic loss, receptor and metabolic changes, and so forth. These studies constitute the rich discipline of *neuroscience of aging*. On the other hand, behavioral studies have systematically described and analyzed the effects of aging on measures of memory, attention, executive functions, and so on. These behavioral studies comprise the fruitful discipline of *cognitive psychology of aging*. However, despite abundant evidence about cerebral aging and about cognitive aging, the link between these two domains is still missing. Fortunately, this situation is being rapidly resolved due to the birth of the new discipline of *cognitive neuroscience of aging*, which focuses on the relationships between age-related changes in the brain and age-related changes in cognition (for reviews see, Cabeza, 2001a; Cabeza, 2001b). The present chapter describes three methodological approaches of cognitive neuroscience of aging, and for each one, it underscores some interesting findings and notes some current issues.

To describe the methodological approaches to cognitive neuroscience of aging, it is useful to organize the critical variables in a simple model like the one in Figure 1. In this model, aging is assumed to affect both the brain and cognition. The distinction between brain and cognition is artificial but useful for conceptual purposes. The same can be said about the distinction between structure and processes in the brain and in cognition. Structures and processes interact with each other and differ only in degree: structures are more stable (e.g., neurons, memory stores); processes are more dynamic (e.g., blood flow, cognitive operations). The structures and processes of the brain can be assessed using *neural measures*, such as resting blood flow and structural MRI (see left side of Figure 1), whereas the structures and processes of cognition can assessed using *cognitive measures*, such as perception and memory tasks (see right side of Figure 1).

Although any change in cognition implies a change in the brain, it is useful to differentiate between two types of age effects: neurogenic and psychogenic. *Neurogenic age effects* (solid arrows in Figure 1) occur when a change in the brain causes a change in cognition. For example, age-related atrophy of prefrontal gray matter may lead to decline in working memory function. In contrast, *psychogenic age effects* (dashed arrows in Figure 1) occur when a change in cognition causes a change in the brain. For instance, age-related disuse of cognitive strategies may lead to atrophy of certain brain regions. As illustrated by Figure 1, neurogenic effects may lead to psychogenic effects and vice versa. For instance, a decline in neural function may originate a compensatory change in cognitive strategies, which in turn may initiate a change in brain function.

As noted before, the goal of cognitive neuroscience of aging is to reveal the relationships between age-related changes in the brain (neuroscience of aging) and age-related changes in cognition (cognitive psychology of aging). There are three basic methodological approaches to achieve goal. First, the *neuropsychological approach* compares cognitive changes in healthy aging and in patients with brain damage due to trauma, stroke, or degenerative disorders. Second, the *correlational approach* associates neural measures to cognitive measures that were independently obtained (see curved bi-directional arrow at the top of Figure 1). Finally, the *activation imaging approach* measures brain activity in young and older adults during cognitive performance (see arrow pointing to bi-directional links between brain and cognitive processes in Figure 1). The section below describes these three approaches, emphasizing some of the points made by Raz, by Nyberg and Bäckman, and by Bäckman et al., in their respective chapters in this book. The following section discusses the strengths and weaknesses of each approach.

Approaches to Cognitive Neuroscience of Aging

Neuropsychological approach

The neuropsychology approach to cognitive neuroscience of aging involves comparing neurocognitive changes in healthy aging to those associated with brain damage (for a review, see Prull et al., 2000). This approach is based on analogical reasoning: if patients with damage in specific brain regions display cognitive deficits that are qualitatively similar to the ones displayed by elderly adults, then age-related cognitive deficits may be related to alterations in these specific regions. In contrast, if damage of a certain brain area yields a kind of cognitive deficit that is uncommon in healthy aging, then it is unlikely that such area is a major contributor to age-related cognitive decline.

The patient populations that are most often compared to healthy elderly are frontal-lobe patients, Parkinson's Disease (PD) patients, medial temporal lobe (MTL) amnesics, and

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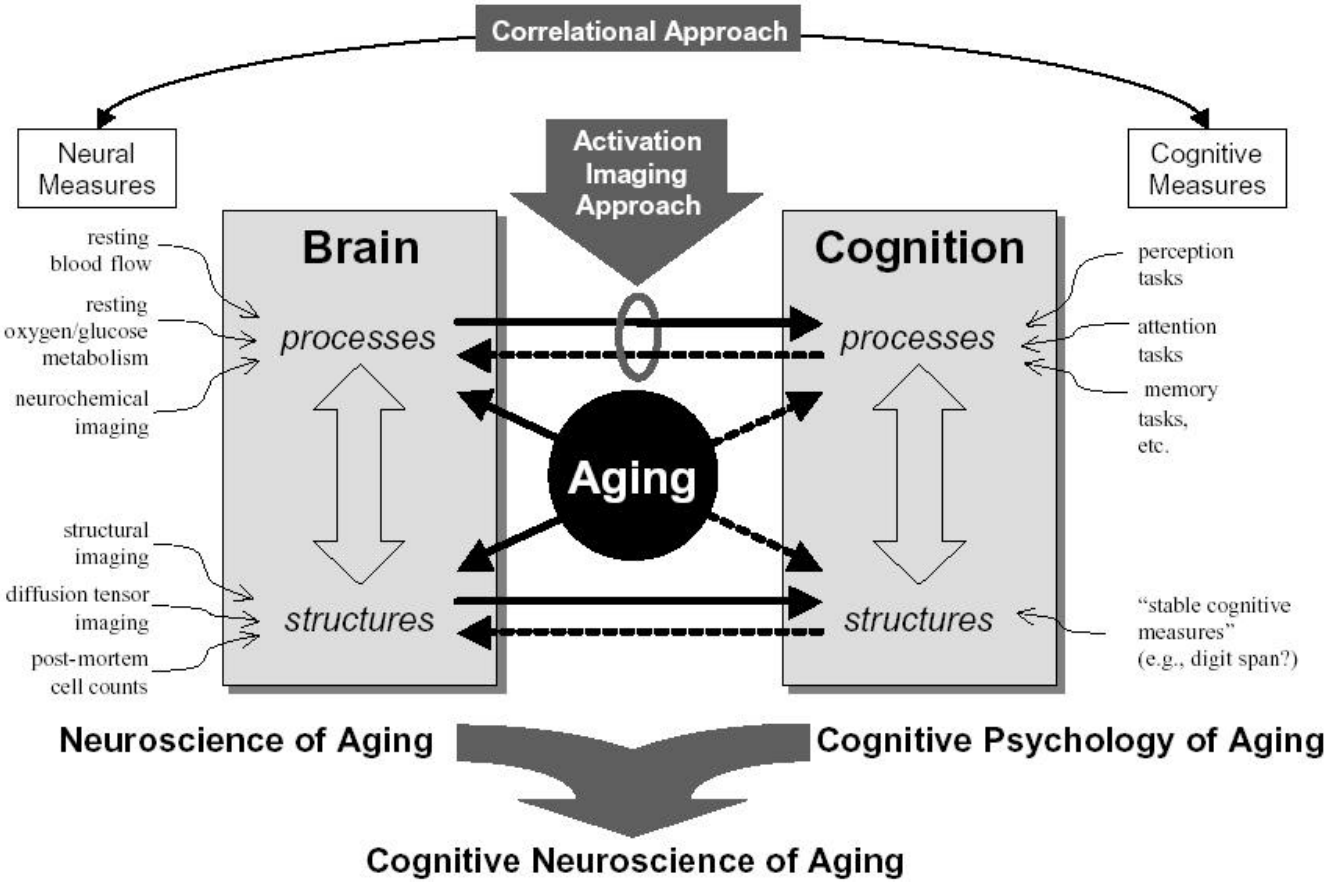


Alzheimer's Disease (AD) patients. Frontal-lobe patients show in augmented fashion many of the cognitive deficits displayed by healthy elderly, including difficulties with recall, context memory, working memory, and executive functions (for a review, see Moscovitch & Winocur, 1995). This pattern provides support to the idea that frontal dysfunction plays an important role in the cognitive deficits observed in healthy aging (for a review, see West, 1996). Likewise, PD patients also show cognitive deficits that resemble those of healthy aging (for a review, see Prull et al., 2000), suggesting that dopamine deficits contribute to age-related cognitive decline. As described later, this idea has received strong support from receptor imaging studies. In contrast with frontal and PD patients, cognitive deficits in MTL amnesics tend to differ from those of healthy elderly. For example, whereas amnesics can show severe episodic memory deficits in both strategic and associative retrieval tasks (e.g., Haist et al., 1992), healthy older adults are usually impaired in strategic tasks, such as context memory, but little in associative tasks, such as recognition (for a review, see Spencer & Raz, 1994). Thus, frontal damage and PD seem to provide better models for healthy aging than MTL amnesia, suggesting that frontal deficits and dopamine dysfunction may play a more important role in age-related cognitive decline than MTL dysfunction.

In contrast, memory deficits in AD patients have been strongly associated with MTL dysfunction, as reviewed in the chapter by Bäckman, Small, and Fratiglioni in this volume. These authors note that cognitive deficits in AD are global but tend to be more pronounced in episodic memory. They relate this pattern to evidence that episodic memory is critically dependent on the hippocampal complex, which is the region showing the earliest brain changes in AD. However, episodic memory measures do not provide a simple tool for early diagnosis of AD. For example, Bäckman and collaborators (Bäckman et al., 2000b; Small et al., 2000) found that although pre-clinical AD individuals were impaired in episodic memory measures compared to healthy older adults, the size of these impairments remained quite stable until the period just preceding diagnosis. In their chapter, Bäckman et al. point out that this finding is paradoxical, given the wealth of evidence that the brain changes that lead to AD start several decades before the diagnosis. According to these authors, one possible explanation is that the brain can counteract slowly occurring neural changes until a certain threshold is reached. As discussed later, one way in which the aging brain may counteract neural changes is by recruiting both cerebral hemispheres for tasks that require basically one hemisphere in young adults (Cabeza, 2002).

One of the main questions of the neuropsychology approach is whether analogous patterns of cognitive decline in healthy older adults and in brain-damaged patients reflect not only similarities in the regions involved but also similarities in neural mechanisms. Obviously, the mechanism of frontal dysfunction is different in the case of healthy aging and in the case of frontal damage due to trauma or stroke. In the case of PD and AD, however, a clear boundary between healthy and pathological mechanisms is not always clear. In the case of AD, in particular,

such boundary may not exist. Actually, it is possible to think that there is a continuum from older adults without cognitive impairment to those with AD, with older adults with mild cognitive impairment (MCI) in the middle. As noted by Bäckman et al. in their chapter, the histopathological features of AD, senile plaques and neurofibrillary tangles, can be found among older adults with intact cognitive functions. A possible explanation is that different individuals vary in terms of "brain reserve" (Katzman, 1993), and only when these reserves are exhausted, dramatic declines in cognitive performance are observed. At any rate, regardless whether healthy aging and AD are seen as two different phenomena or as two stages of the same continuum, it is clear that comparing healthy older adults to brain damaged patients can yield important insights concerning the neural correlates of cognitive aging.

Correlational approach

The correlational approach involves associating a neural measure, such as structural imaging measures (see left side of Figure 1), to a cognitive measure, such as memory performance (see right side of Figure 1). Instead of neural measures, some studies have correlated employed behavioral tests assumed to be sensitive to the function of a certain brain region, such as the so-called "frontal lobe tests" (e.g., Wisconsin Card Sorting Task—WCST). Since the relationship between these tests and the anatomical and functional integrity of the brain region of interest is uncertain, the usefulness of this type of studies has been limited. In contrast, studies using direct neural measures, such as *in vivo* structural, neurochemical, blood flow, and metabolism imaging, can provide a more direct link between cerebral and cognitive aging. Correlational studies using structural and neurochemical imaging were respectively reviewed in the chapters by Naftali Raz and by Nyberg and Bäckman.

As reviewed by Raz, the effects of aging on brain structure have been observed primarily as volume decreases and white matter deterioration. Age-related decreases in brain volume tend to be large in the prefrontal cortex (PFC), moderate in the striatum, MTL, and the cerebellum, and minimal in the visual cortex. Age-related reductions in the integrity of white matter can be observed as white matter hyperintensities (WMH) in MRI images, and these changes are also greater anterior in brain regions. Raz points out that age-related changes in brain structure are relevant to cognitive neuroscience of aging as long as they can be linked to age-related changes in cognitive performance. He reviews examples of studies linking age-related changes in brain structure to age-related changes in measures of executive functions, motor skill learning, and cognitive skill learning (Raz, 2000). In one study, PFC volume and prefrontal WMH volume were independently associated with age-related deficits in executive functions (Gunning-Dixon & Raz, submitted). In another study, cerebellar and putamen volumes were associated age-related deficits in motor skill learning (Raz et al., 2000). Finally, in a third study, PFC volume was associated with age-related decreases in cognitive skill learning (Head et al., in press). These studies are excellent examples of how correlational studies can link age-related deficits in cognitive performance to anatomical deterioration in specific brain regions. Future challenges in this domain include conducting longitudinal studies (e.g., Raz, 2002) and using new statistical techniques to analyze correlational data (e.g., McArdle et al., submitted)

Age-related deficits in cognitive performance can be linked not only to deficits in brain anatomy but also to deficits in brain function. For example, there is now clear evidence that cognitive decline in older adults is in great part a consequence of deficits in dopamine (DA) function. As reviewed by Nyberg and Bäckman in the present volume. DA function declines during aging at a steady rate of about 10% per decade, and this decline is significantly associated with age-related deficits in cognitive performance. Reliable correlations have been found for both presynaptic (e.g., DA transporter—DAT) and postsynaptic (e.g., D_1 and D_2 receptor binding) markers of DA function. For instance, the PET studies have associated age-related deficits in striatal D_2 binding to age-related deficits in executive function and speed (Volkow et al., 1998), and episodic memory and speed (Bäckman et al., 2000a). Importantly, in these studies the association between DA function and cognitive performance remained after controlling for age.

Activation Imaging Approach

Whereas the correlational approach relates cognitive and neural measures of aging that were independently obtained, the activation imaging approach assess the effects of aging on brain activity and cognitive performance in direct relation to each other. Activation imaging studies have investigated a variety of cognitive functions (for reviews, see Cabeza, 2001a, 2001b), and those in the working memory and episodic memory domain were reviewed by the chapter by Nyberg and Bäckman. In general, lower activity in older adults has been attributed to deficits in neurocognitive processing whereas greater activity in older adults has been attributed to compensation mechanism.

Cognitive Domain Imaging Technique: Materials/Task (Reference)	**Younger**		**Older**	
	Left	Right	Left	Right
Episodic Retrieval				
PET: Word Pair Cued-Recall (Cabeza et al., 1997a)	-	++	+	+
PET: Word Stem Cued-Recall (Bäckman et al., 1997)	-	+	+	+
PET: Word Recognition (Madden et al., 1999)	-	+	++	++
PET: Face Recognition (Grady et al., 2002)	-	++	+	+
Episodic Encoding/Semantic Retrieval				
fMRI: Word – incidental (Stebbins et al., 2002)	++	+	+	+
fMRI: Word – intentional (Logan et al., 2002)	++	+	+	+
fMRI: Word – incidental (Logan et al., 2002)	++	+	++	++
fMRI: Word – SME (Morcom et al., 2002)	++	+	++	++
Working Memory				
PET: Letter DR (Reuter-Lorenz et al., 2000)	+	-	+	+
PET: Location DR (Reuter-Lorenz et al., 2000)	-	+	+	+
PET: Number N-Back: (Dixit et al., 2000)	+	+++	++	++
Perception				
PET: Face Matching (Grady et al., 1994, Exp. 2)	-	+	++	++
PET: Face Matching (Grady et al., 2000)	+	+++	++	++
Inhibitory Control				
fMRI: No-Go Trials (Nielson et al., 2002)	-	+	+	+

Note: Plus signs indicate significant activity in the left or right PFC, and minus signs indicate nonsignificant activity. The number of pluses is an approximate index of the relative amount of activity in left and right PFC in each study, and it cannot be compared across studies. DR = delayed response task; SME = subsequent memory effect

Table 1 PET/fMRI Activity in Left and Right PFC in Younger and Older Adults

The most consistent result of activation imaging studies is probably the finding that older adults tend to show a more bilateral pattern of PFC activation than young adults, a pattern known as *Hemispheric Asymmetry Reduction in Older Adults* or HAROLD model (Cabeza, 2002). Table 1 lists PET and fMRI studies consistent with this model various cognitive domains. In the case of episodic memory retrieval, in which PFC activity in young adults tends to be right lateralized, age-related asymmetry reductions involved an increase in left PFC activity. Conversely, in the case of episodic encoding/semantic retrieval, in which PFC activity in young adults tends to be left lateralized, age-related asymmetry reductions involved a decrease in left PFC activity or an increase in right PFC activity. Despite this variety of age effects, the basic outcome was always the same: PFC activity was less lateralized in older adults than in younger adults.

It has been suggested that bihemispheric involvement play a compensatory role in the aging brain (Cabeza et al., 1997a). This *compensation account* is consistent with evidence that bilateral activity in older adults is associated with enhanced cognitive performance (Reuter-Lorenz et al., 2000), and that the particular brain regions showing age-related increases in activation are likely to enhance performance in the task investigated (e.g., left PFC during episodic retrieval, Nolde et al., 1998). The compensation account is also consistent with evidence that recovery of function following unilateral brain damage is associated with the recruitment of the unaffected contralateral hemisphere (e.g., Cao et al., 1999; Silvestrini et al., 1998). However, there is also an alternative view of age-related asymmetry reductions: they may reflect age-related difficulty in engaging specialized neural mechanisms (e.g., Li & Lindenberger, 1999). This *dedifferentiation account* is consistent with evidence that correlations among different cognitive measures, and between cognitive and sensory measures, tend to increase with age (Baltes & Lindenberger, 1997). Randy Buckner recently suggested that if one assumes that in young adults there is competition between the two hemispheres, an age-related decrease in lateralization could reflect an age-related reduction of interhemispheric transfer due to callosal deterioration (Buckner, 2002). Yet, the notion that in young adults the two hemispheres compete with each other is has not received strong empirical support (Chiarello & Maxfield, 1996).

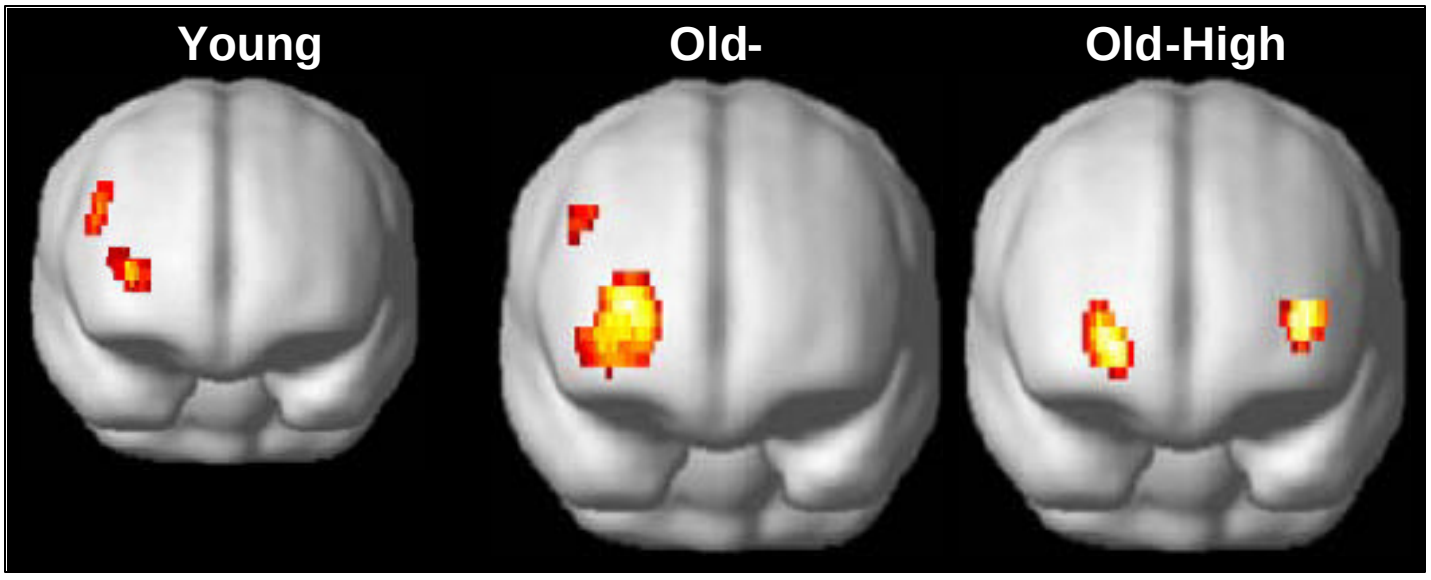
Recently, we tested compensation and dedifferentiation accounts of HAROLD using PET (Cabeza et al., 2002). Before scanning, we selected from a larger sample of older adults a group that performed as well as the young group in a battery of memory tests (old-high group), and a group that performed significantly more poorly that then young group in the same battery (old-low group). The two groups of older adults and a group of young adults were then scanned in a source memory tasks, which was known from a previous study to be associated with right PFC activity in young adults. The compensation hypothesis predicted bilateral PFC activity in old-high participants, whereas the dedifferentiation hypothesis predicted bilateral PFC in old-low participants. As illustrated by Figure 2, the results supported the compensation hypothesis. Old-low participants showed some additional PFC activity in the same hemisphere as young adults but no reduction in lateralization, whereas old-high participants showed a bilateral activation pattern. We interpreted this finding as suggesting that Old-Low participants recruited similar PFC regions as young adults but used them inefficiently, whereas Old-High participants compensated age-related memory decline by reorganizing the episodic retrieval network.

Strengths and Weaknesses of Each Approach

Table 2 list some of the strengths and weaknesses of the neuropsychological, correlational, and activation imaging approaches. These strengths and weaknesses are discussed in the next three subsections.

Neuropsychological Approach

The main strength of the neuropsychological approach to cognitive neuroscience of aging is that it identifies age effects on brain regions that are *necessary* for cognitive performance. For example, evidence that both older and PD patients are impaired in strategic retrieval tasks (for a review, see Prull et al., 2000) suggests, first, that dopaminergic fronto-striatal loops are necessary for strategic memory performance, and second, that strategic memory decline in older adults is related to dopamine deficits. This brings us to a second strength of the neuropsychological approach: it clarifies the neural mechanisms



for age-related neural decline. The neuropsychology approach suggest what neural mechanisms are likely (e.g., dopamine deficits), and what neural mechanisms are unlikely. For example, studies identifying differences between healthy and pathological aging (e.g., AD) can help discard hypotheses concerning neural mechanisms of cognitive decline in healthy aging.

The main weakness of the neuropsychological approach is that it cannot easily identify compensatory changes in the aging brain. When healthy older adults do not show a cognitive deficit typically observed in a certain form of brain pathology, this may be interpreted as suggesting that the neural mechanism of the pathology does not play an important role in healthy aging. Yet, it is also possible that the pathological mechanism is actually affecting normal elderly but they can compensate for it. For example, Bäckman and collaborator noted in their chapter that senile plaques and neurofibrillary tangles can be found among older adults with intact cognitive functions, and discussed that possibility that the effects of these pathological changes may be compensated by older adults for decades until a certain threshold is reached. Since the neuropsychological approach is based on behavioral performance, neural changes that decrease differences in performance are difficult to detect. In contrast, compensatory changes can be detected using activation imaging methods (e.g., Figure 2).

Another weakness of the neuropsychological approach is that it tries to clarify an obscure phenomenon (neural mechanism of cognitive changes in healthy aging) by comparing it to another obscure phenomenon (neural mechanism of cognitive changes in brain damaged populations). For example, the fact that older adults (Spencer & Raz, 1994) and frontal lobe patients (Schacter, 1987; Stuss et al., 1994) tend to be more impaired in context than in item memory suggest that age-related deficits in context memory are related to frontal dysfunction. Yet, the specific role of the frontal lobes in context memory is yet understood.

Correlational Approach

The main strength of correlational studies is that they employ neural measures that are relatively close to the neural mechanisms underlying age-related cognitive changes, such as structural and neurochemical imaging measures. Of course, changes in brain volume and neurochemical function are still removed from the original molecular causes of neural aging. Yet, these measures can be obtained *in vivo* and correlated with behavioral measures, thereby allowing the establishment of critical links between neural and cognitive aging. Another strength of the correlational approach is that correlations are likely to reflect neurogenic rather than psychogenic changes. Even though correlations do not imply causation, if the atrophy of a certain brain region is correlated with poor performance in a certain cognitive task it is reasonable to assume that brain atrophy caused poor cognitive performance rather than the other way round.

The main weakness of the correlational approach is that neural measures are related to cognitive measures only indirectly. This is particularly true in the case of structural measures. As illustrated in Figure 1, age-related changes in brain structure are likely to cognitive processes only if they are associated with changes in brain processes. However, structural changes may not lead to functional changes until a certain threshold is reached. Correlational studies may employ functional measures, such as resting blood flow and metabolism measures, but resting measures are not directly associated with cognitive performance either. For example, older adults may show reduced resting blood flow in a certain region but recruit this region as much as young adults during a cognitive challenge. Conversely, a region may not show age-related blood flow differences during rest, but these differences may become apparent under the demands of

	Strengths	Weaknesses
Neuropsychological Approach	• Identifies age effects on brain regions that are necessary for cognitive performance • Clarifies the neural mechanisms of age-related neural decline	• Cannot easily identify compensatory changes in the aging brain • Inferences about neural mechanisms are based on obscure phenomena
Correlational Approach	• Can employ neural measures are close to the neural mechanisms underlying age-related cognitive changes • Correlations are likely to reflect neurogenic rather than psychogenic changes	• Neural measures are only indirectly related to age-related changes in cognitive performance • Cannot easily identify compensatory changes in the aging brain
Activation Imaging Approach	• Age-related changes in brain activity are directly related to age-related changes in cognitive performance • Can detect compensatory changes in the aging brain.	• Brain activity measures are removed from the neural mechanisms underlying age-related cognitive changes • Age-related changes in brain activity may reflect neurogenic as well as psychogenic changes

Table 2 Examples of the strengths and weaknesses of three methodological approaches to cognitive neuroscience of aging

cognitive tasks (for a discussion, see Anderson & Craik, 2000).

Related to this last point, another weakness of the correlational approach is one previously noted for the neuropsychological approach: they cannot easily detect compensatory changes in the aging brain. Since the effects of neural changes on behavior are modulated by compensatory changes, this limitation could partly explain inconsistencies in studies correlating structural and behavioral measures. For example, among studies that correlated the volume of MTL structures with episodic memory performance in older adults (for a review, see Raz, 2000), some studies found a moderate positive correlation (e.g., Golomb et al., 1994), others found a lack of correlation (Raz et al., 1998), and still others found negative correlations (Kohler et al., 1998). A possible explanation of these mixed results is that MTL atrophy may be counteracted in different degrees by the recruitment of other brain regions. Since these compensatory changes are difficult or impossible using structural or resting functional measures, correlational studies can only provide a partial picture of the complex series of neural events underlying age-related changes in cognitive performance.

Activation Imaging Approach

The strengths and weaknesses of the activation imaging approach tend to be a mirror image of the strengths and weaknesses of neuropsychological and correlational approaches. For example, whereas a weakness of the correlational approach is the relatively indirect relationship between neural and cognitive measures, an important strength of the activation imaging approach is that neural and cognitive measures are acquired simultaneously and in direct relation to each other. As illustrated in Figure 1, activation imaging measures the interaction between the brain and cognition (see arrow in the middle of Figure 1). Thus, age-related differences in the performance of a particular cognitive task (e.g., reduced context memory accuracy) can be directly linked to age-related changes in brain activity (e.g., reduced frontal activity) during the performance of that particular task.

Another advantage of activation imaging is the possibility of detecting compensatory changes in the aging brain, which is something difficult to do with neuropsychological and correlational approaches. Since activation imaging can identify brain regions involved in cognitive performance, including those recruited to support cognitive performance, this approach is ideally suited for investigating compensatory changes in the aging brain. As previously discussed, there is evidence that one form of compensation displayed by older adults involves a more bilateral pattern of PFC activity (Cabeza, 2002). It would have been difficult or impossible to detect this phenomenon using only neuropsychological or correlational approaches.

Conversely, some of the weaknesses of the activation imaging approach correspond to strengths of neuropsychological and correlational approaches. For example, whereas the neural measures employed by correlational approaches (e.g., structural and neurochemical imaging) are relatively close to the original neural mechanisms underlying age-related cognitive decline, activation imaging measures are farther apart from these mechanisms. Age-related differences in activation detected PET and fMRI are the result of a complex series of neural events, and hence, linking these differences to specific neural mechanisms is a complicated task. In particular, since brain activity is the result of the interaction between the brain and cognitive processes, it is difficult to attribute age-related differences in activation to the function of a particular region. Actually, older adult may show weaker activity in a certain brain region during a particular cognitive task but greater activity in the same region during a different task (Cabeza et al., 1997b). This fact precludes a simple one-to-one association between age-related changes in activity and the functional integrity of the brain regions involved.

Another disadvantage of the activation imaging approach is that age-related changes in brain activity may reflect neurogenic as well as psychogenic changes. This is the downside of measuring brain processes in direct relation to cognitive processes. In activation studies, the relation between brain and cognitive processes is so close that the direction of causal effect is unclear: do older adults perform differently because their brain activity is dissimilar, or is their brain activity dissimilar because they perform differently? In Figure 1, this "chicken-and-egg" problem is illustrated by the oval that surrounds neurogenic and psychogenic arrows. Activation imaging does not measure the effect of the brain on cognition or the effect of cognition on the brain, but both simultaneously. Psychogenic effects of brain activity include differences in cognitive strategies and levels of performance (Cabeza, 2001b). Differences in cognitive strategies can be attenuated by using very simple tasks (e.g., McIntosh et al., 1999) or by manipulating strategies (e.g., Logan et al., 2002), and differences in performance can be reduced by matching (Cabeza et al., 1997a) or manipulating (Cabeza et al., 2000) performance levels. As discussed in the section below, another way of disambiguating age-related differences in activation is to relate these differences to structural and/or neurochemical imaging measures.

Summary and Conclusions

In summary, the new discipline of cognitive neuroscience of aging tries to establish links between age-related changes in the brain and age-related changes in cognition using three main methodological approaches.

First, the neuropsychological approach compares cognitive changes in healthy aging and in patients with brain damage due to trauma, stroke, or degenerative disorders. This approach includes studies investigating similarities and differences between healthy aging and AD (reviewed Bäckman et al., in this volume). The neuropsychological approach can identify age effects on regions necessary for performance and clarify the mechanisms of age-related neural decline, but it has difficulties identifying compensatory changes in the aging brain and is based on comparing aging to other unclear phenomena.

Second, the correlational approach associates cognitive measures to neural measures that were independently obtained. This approach includes studies correlating cognitive measures with structural imaging measures (reviewed by Raz, in this volume), as well as those correlating cognitive measures and dopamine imaging measures (reviewed by Nyberg and Bäckman, in this volume). The correlational approach employs neural measures that are close to the neural mechanisms underlying age-related cognitive changes and can isolate neurogenic effects, but the measures it investigates are only indirectly related to cognitive performance and relatively insensitive to compensatory changes.

Finally, the activation imaging approach measures brain

activity in young and older adults during cognitive performance. This approach includes studies investigating age-related changes brain activity during episodic memory and working memory performance (reviewed by Nyberg and Bäckman, in this volume). The activation imaging approach investigates neural measures that are directly related to cognitive performance and can detect compensatory changes in the aging brain, but the measures it employs are removed from basic neural mechanisms and are sensitive to both neurogenic and psychogenic effects

It is clear that the three approaches to cognitive neuroscience of aging have complementary strengths and weaknesses. The neuropsychological approach can clarify the neural mechanisms of age-related neural decline but it cannot easily identify compensatory changes in the aging brain. The activation imaging approach can identify compensatory changes in the aging brain but has difficulties differentiating neurogenic and psychogenic effects. Etcetera. Thus, one way of addressing the limitations of available approaches it to combine them in a way in which the strengths of an approach counteract the weakness of another approach.

A powerful strategy is to combine neuropsychological and activation imaging approaches, and compare healthy older adults and brain-damaged patients using PET or fMRI (Bäckman et al., 1999; Bookheimer et al., 2000). The activation imaging approach can help with the identification of compensatory changes, and the neuropsychological approach can help with the interpretation of activation results. For example, in a PET study investigating episodic retrieval in healthy older adults and early AD patients (Bäckman et al., 1999), AD patients failed to show a left hippocampal activation displayed by healthy older adults, but recruited fronto-parietal-cerebellar network typically associated with episodic retrieval, and displayed increases in PFC activity possibly associated with functional compensation. These results support the idea that the degree of MTL dysfunction is a critical difference between healthy and pathological aging, and the notion that compensatory changes in brain activity may partially counteract cognitive decline in AD patients.

Another powerful strategy is to integrate correlational and activation imaging approaches, and combine resting imaging measures with activation imaging measures. Combining structural and activation imaging is an important goal of cognitive neuroscience of aging, not only because volumetric measures should be used to adjust activation measures, but also because volumetric data could help disambiguate activation imaging data. For example, the issue about whether hemispheric asymmetry reductions in older adults reflect compensation or dedifferentiation could be investigated by correlating activity in the regions showing age-related increases with volumetric data. If decreased lateralization is correlated with decreased brain volume, then it is more likely to reflect dedifferentiation rather than compensation. Combining neurochemical imaging measures with activation imaging measures is another challenge for the future of cognitive neuroscience of aging. As mentioned before, age-related dopamine decline can account for a large portion of older adults' deficits in cognitive performance (Bäckman et al., 2000a). A strong relationship has been demonstrated between age-related decreases in dopamine function and age-related decreases in frontal and cingulate metabolism (Volkow et al., 2000), and it is quite likely that dopamine measures will be also strongly associated with activation imaging measures. One can envisage future studies in which age-related differences in brain activity are directly associated with age-related differences in brain anatomy and function, thereby linking activation findings to specific neural mechanisms.

Thus, cognitive neuroscience of aging is a new discipline with a very promising future. Its rapid growth during the last decade is likely to become even more intense as the three basic methodological approaches develop and new approaches are introduced. Ultimately, many different methods will be combined to achieve a move complete picture of age-related neurocognitive changes. This is definitely a neuroscience frontier in cognitive aging research.

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