

Hemispheric Asymmetry Reduction in Older Adults: The HAROLD Model

Roberto Cabeza

Center for Cognitive Neuroscience, Duke University

This article introduces a model of the effects of aging on brain activity during cognitive performance. The model is called *Hemispheric Asymmetry Reduction in Older Adults*, or HAROLD, and it states that, under similar circumstances, prefrontal activity during cognitive performances tends to be less lateralized in older than in younger adults. This model is supported by functional neuroimaging and behavioral evidence in the domains of episodic memory retrieval, episodic memory encoding/semantic memory retrieval, working memory, perception, and inhibitory control. Age-related hemispheric asymmetry reductions may have a compensatory function or they may reflect a dedifferentiation process. Furthermore, they may have a cognitive or neural origin, as well as they may reflect regional or network mechanisms. The HAROLD model is consistent with popular cognitive aging theories, but it is a cognitive neuroscience model that integrates findings and ideas from cognitive psychology and neuroscience.

Recent functional neuroimaging evidence suggests that our brain responds to age-related changes in anatomy and physiology (for reviews, see Cabeza, 2001; Raz, 2000) by reorganizing its functions (Cabeza et al., 1997a; Grady et al., 1994). In 1997 we noted that, compared to younger adults, older adults showed a more bilateral pattern of prefrontal cortex (PFC) activity during verbal recall. We interpreted this change in prefrontal activity in older adults as reflecting functional compensation (Cabeza et al., 1997a). Since then, this age-related change has been replicated several times with different kinds of tasks and materials. By extending our earlier notions, (Cabeza, 2001; Cabeza et al., 1997a) as well as those articulated by others (Reuter-Lorenz et al., 2000), this article now proposes that the change in hemispheric asymmetry in older adults during verbal recall is reflective of a general aging phenomenon rather than a task specific occurrence. More specifically, under similar circumstances, PFC activity during cognitive performances tends to be less lateralized in older adults than in younger adults. This empirical generalization is conceptualized in terms of a model called *Hemispheric Asymmetry Reduction in the OLD* or HAROLD¹.

This article introduces the HAROLD model and has six main sections. The first section reviews functional neuroimaging evidence in various cognitive domains consistent with the model. The second section describes two different accounts of the function of age-related asymmetry reductions. According to a *compensation view*, age-related asymmetry reductions could help counteract age-related neurocognitive decline, whereas, according to a *dedifferentiation view*, they reflect a difficulty in

recruiting specialized neural mechanisms. The third section considers two different explanations of the origin of age-related asymmetry reductions. According to a *psychogenic view*, age-related asymmetry reductions originate in a change in cognitive strategies. In contrast, the *neurogenic view* posits that reduced asymmetry in old adults originate in a change in neural mechanisms. The fourth section describes two different accounts of the neural mechanisms mediating age-related asymmetry reductions. According to a *network view*, reduced asymmetry in old adults reflects a global reorganization of task-specific neurocognitive networks. According to a *regional view*, however, the age-related asymmetry reductions reflect local brain changes that are task-independent. The fifth section evaluates how age-related asymmetry reductions can be accommodated by popular cognitive aging theories, such as the *resources view*, the *speed view*, and the *inhibition view*. Finally, the last section discusses the generalizability of the HAROLD model in terms of cognition, the brain, and the elderly population.

I. Evidence of Age-Related Asymmetry Reductions

Table 1 summarizes functional neuroimaging evidence consistent with the HAROLD model in the domains of episodic memory retrieval, episodic memory encoding/semantic memory retrieval, working memory, perception, and inhibitory control. Each of the five subsections below reviews findings in one of these domains. The final subsection discusses what kind of findings can be considered as evidence for the model or as evidence against the model.

Episodic Memory Retrieval

Episodic memory refers to the encoding and retrieval of information about personally experienced past events (Tulving, 1983). In younger adults, positron emission tomography (PET)

I thank Lars Bäckman, Karen Berman, Randy Buckner, Fergus Craik, Cheryl Grady, David Madden, Lars Nyberg, Patricia Reuter-Lorenz, Naftali Raz, Glenn Stebbins, and Endel Tulving for providing unpublished manuscripts, data, figures, and/or useful comments.

This work was supported by grants to RC from the National Sciences and Engineering Research Council of Canada and the Alberta Heritage Foundation for Medical Research (Canada).

Correspondence concerning this article should be addressed to Roberto Cabeza, Center for Cognitive Neuroscience, Duke University, Box 90999, Durham, NC 27708, USA. Electronic mail may be sent to cabeza@duke.edu

¹ The name *hemispheric asymmetry reduction in old adults* is purely descriptive and neutral about whether the change is beneficial or detrimental for cognitive performance. Thus, the model could be also called *hemispheric symmetry increase in old adults*.

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

Cognitive Domain Imaging Technique: Materials/Task (Reference)	Younger		Older	
	Left	Right	Left	Right
Episodic Retrieval				
PET: Pair Cued-Recall (Cabeza et al., 1997)	-	++	+	+
PET: Stem Cued-Recall (Bäckman et al., 1997)	-	+	+	+
PET: Word Recognition (Madden et al., 1999)	-	+	++	++
PET: Face Recognition (Grady et al., 2000a)	-	++	+	+
Episodic Encoding/Semantic Retrieval				
fMRI: Word – incidental (Stebbins et al., 2000)	++	+	+	+
fMRI: Word – intentional (Logan & Buckner, 2001)	++	+	+	+
fMRI: Word – incidental (Logan & Buckner, 2001)	++	+	++	++
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 trails (Nielson et al., 2001)	-	+	+	+

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

and functional magnetic resonance imaging (fMRI) studies have associated episodic memory encoding and retrieval with prefrontal cortex (PFC) activations (for a review, see Cabeza & Nyberg, 2000). These activations tend to be left lateralized during encoding and right lateralized during retrieval, a pattern known as Hemispheric Encoding/Retrieval Asymmetry (HERA) (Nyberg, Cabeza, & Tulving, 1996a; Nyberg, Cabeza, & Tulving, 1998; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). This asymmetry has been found for both verbal and nonverbal materials (Nyberg, Cabeza, & Tulving, 1996a). Although the HERA model has received considerable support from functional neuroimaging studies with younger adults, available evidence suggests that this model does not hold to the same extent in older adults.

Cabeza et al. (1997a) investigated the effects of aging on brain activity during episodic memory encoding and retrieval. In the encoding condition, subjects studied word-pairs (e.g.,

parents-piano). In one retrieval condition, they were presented with the first word of each pair and had to recall the second word (e.g., *parents-???*). Consistent with the HERA model, PFC activity in younger adults was left lateralized during encoding and right lateralized during recall. In contrast, older adults displayed little PFC activity during encoding and a bilateral pattern of PFC activity during recall. As illustrated by Figure 1-a, PFC activity during recall was right lateralized in younger adults but bilateral in older adults. Cabeza et al. interpreted this age-related change as compensatory: To counteract neurocognitive deficits, older adults recruited both hemispheres to perform a task that basically requires one hemisphere in younger adults.

Cabeza et al. (1997a) were not alone in observing such a pattern of activation. In an independent study reported at about the same time, Bäckman and colleagues (1997) found that during word-stem cued recall (e.g., *rea* → *reason*), PFC activity was right lateralized in the young but bilateral in the old

(see Figure 1-b). Two years later, Madden et al. (1999b) found similar results using word recognition. Again, younger adults showed significant activity in right PFC, whereas older adults showed significant activity in both right and left PFC (see Figure 1-c). Madden et al.'s finding was important because it demonstrated that the age-related reduction in hemispheric asymmetry was not limited to recall tasks but also occurred for other episodic retrieval tasks, such as recognition. On the other hand, the fact that the studies by Cabeza et al., Bäckman et al., and Madden et al., employed verbal materials suggested that bihemispheric involvement in old adults is a verbal phenomenon, possibly related to the well-known left lateralization of linguistic functions. Grady et al. (2000a) recently disconfirmed this possibility. Despite using nonverbal materials, Grady et al. observed the same activation pattern evident in the three previous studies, i.e., right PFC activity in younger adults coupled with bilateral PFC activity in older adults (see Figure 1-d). In sum, an age-related reduction in hemispheric asymmetry during episodic memory retrieval has been demonstrated for different kinds of tests (recall and recognition) and different kinds of stimuli (verbal and pictorial), and hence, it appears to be a robust and general phenomenon.

Episodic Memory Encoding/Semantic Memory Retrieval

Episodic memory encoding and semantic memory retrieval are considered in the same section because they tend to co-occur during scanning and are very difficult to differentiate (Nyberg et al., 1996a; Tulving et al., 1994). When participants are asked to encode new information (*intentional learning*), they normally process it by retrieving information from semantic memory, and when they are asked to retrieve information from semantic memory, they normally encode the retrieval cues and retrieved information into episodic memory (*incidental learning*). Evidence of age-related asymmetry reductions during episodic encoding/semantic retrieval was absent for several years but was recently reported by Stebbins et al. (2000) and Logan and Buckner (2001).

Stebbins et al. (2000) examined age-related differences in PFC activity during deep (concrete/abstract) and shallow (uppercase/lowercase) incidental encoding of words. In younger adults, left PFC activity was nearly twice as large as right PFC activity. In older adults, left PFC activity was reduced but right PFC was not and, as a result, the asymmetry shown by younger adults was eliminated (see Table 1). According to the authors: "The age-associated reduction in left prefrontal activation eliminated the left hemisphere asymmetry evident in younger participants who exhibited twice as much activation in left relative to right prefrontal activation."

In Logan and Buckner et al. (2001), adults studied words for a subsequent memory test (intentional learning) or performed abstract/concrete judgments without knowing about the memory test (incidental learning). The results were consistent with the age-related hemispheric asymmetry reduction model. Younger adults showed a left lateralized pattern of PFC activity, whereas older adults showed a symmetric pattern. Interestingly, providing older adults with a semantic processing strategy (i.e., environmental support) increased their PFC activity in both hemispheres but did not increase their hemispheric asymmetry (see Table 1).

As illustrated in Table 1, the results in the episodic encoding/semantic retrieval domain support the generalizability

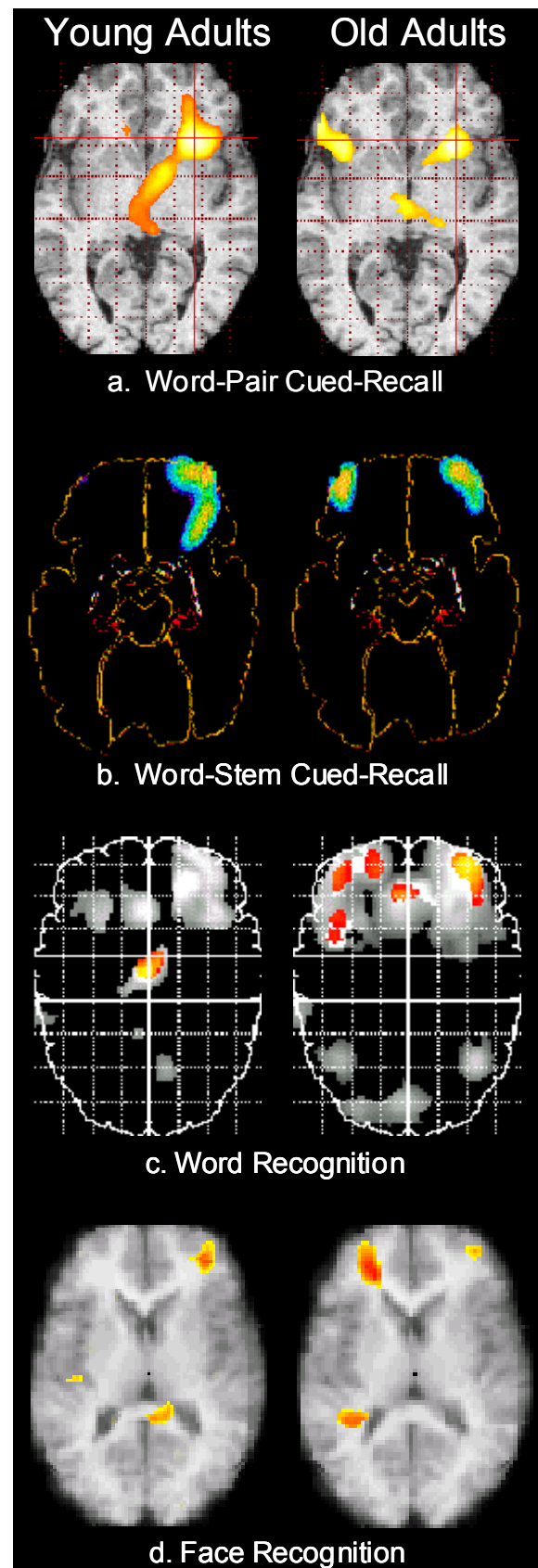


Figure 1. Results of functional neuroimaging studies in which prefrontal activity during episodic memory retrieval was right lateralized in younger adults but bilateral in older adults: (a) Cabeza et al. (1997a); (b) Bäckman et al. (1997); (c) Madden et al. (1999a); (d) Grady et al. (2000a).

of the HAROLD model in two ways. First, they demonstrate that age-related asymmetry reductions are not limited to the situation in which PFC activity is right lateralized in young adults with an age-related *increase* in left PFC activity; they may also occur when PFC activity is left lateralized in young adults with an age-related *decrease* in left PFC activity. Thus, the most parsimonious account is not one based on the specific functions of left PFC, but rather one based on the overall distribution of PFC activity across hemispheres. Second, the combined results of the intentional and incidental encoding conditions in Logan and Buckner's (2001) study demonstrate that age-related reductions in hemispheric asymmetry are robust and resist strategy manipulations that alter the overall level of PFC activity in older adults.

Working Memory

In the domain of working memory, Reuter-Lorenz et al. (2000) provided clear evidence for the HAROLD model. During working memory, PFC activity in younger adults tends to be left lateralized for verbal stimuli and right lateralized for spatial stimuli (for a review, see Smith & Jonides, 1997). Consistent with this pattern, Reuter-Lorenz et al. found that younger adults displayed significant activity in left PFC during a verbal working memory task but in right PFC during a spatial working memory task (see Figure 2). In contrast, PFC activity in older adults was significant bilaterally during both tasks (see Figure 2). Reuter-Lorenz et al. clearly noted that PFC activity during working memory was unilateral in younger adults but bilateral in older adults, and hence, like the study by Cabeza et al. (1997a), the study by Reuter-Lorenz et al. is a direct antecedent of the HAROLD model.

The recent study by Dixit et al. (2000) also found evidence for HAROLD during working memory. In this study, neural activity in younger subjects during an N-back task was greater in right PFC than in left PFC but was similar in both prefrontal cortices in a group of middle-age subjects. The fact that an age-related asymmetry reduction was found in middle-aged individuals suggests that the HAROLD pattern develops before old age.

As shown in Table 1, age-related asymmetry reductions can be found when PFC activity is right lateralized in young adults, as in the case of episodic retrieval, as well as when PFC activity is left lateralized in young adults, as in the case of episodic encoding/semantic retrieval. The results in the working memory domain indicate that this is also true when the task is constant and that it is the nature of the information processed that affects the lateralization of PFC. In other words, the working memory data demonstrate that age-related asymmetry reductions may be found not only for process-related hemispheric asymmetries (e.g., episodic retrieval vs. semantic retrieval) but also for stimuli-related hemispheric asymmetries (e.g., verbal vs. spatial working memory).

Perception

One of the first activation studies of cognitive aging was the study by Grady et al. (1994) on visual perception. During face matching, older adults showed weaker activity than younger adults in the occipital cortex but stronger activity in more anterior brain regions, including PFC. In the second experiment of this study, PFC activity during face matching was found in the right hemisphere in young adults but in both hemispheres in

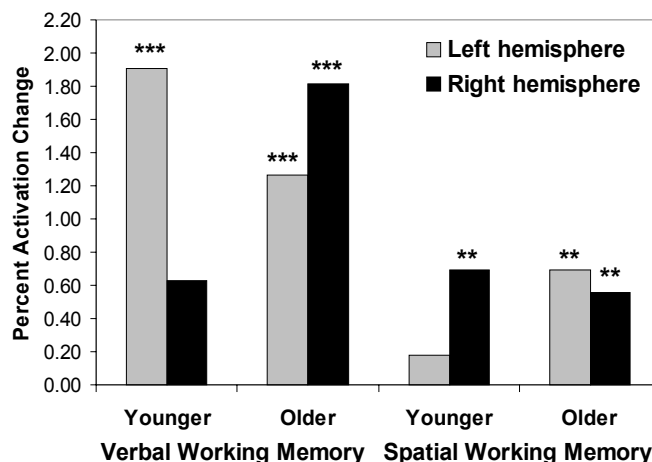


Figure 2. Left and right PFC activity in young and old adults during verbal and spatial working memory tasks (from Reuter-Lorenz et al., 2000). Asterisks denote significant difference from zero (one-tailed tests): ** $p < .03$; *** $p < .001$.

older adults. This result suggests that age-related asymmetry reductions can be found not only for higher-order cognitive operations, such as episodic and working memory processes, but also for simple cognitive processes, such as face matching.

In a more recent study by Grady and collaborators (2000b), age-related asymmetry reductions during face matching were also found. In this study, face matching was investigated for both degraded and nondegraded faces. In both conditions, right hemisphere activity was greater in younger than in older adults. According to the authors: "This finding, coupled with that of greater left-hemisphere activation in older adults, may indicate a more bilateral involvement of the brain in nondegraded face matching with increasing age" (p. 180).

In the perception domain, the HAROLD model is supported not only by functional neuroimaging evidence but also by behavioral evidence. Reuter-Lorenz et al. (1999) investigated the effects of aging on a task in which subjects matched two letters projected either to the same visual field (hemisphere) or to the opposite visual field (hemisphere). There were three levels of complexity: low (physical matching with one distractor), medium (physical matching with three distractors letters), and high (name matching with three distractors). In young adults, within-hemisphere matching was faster when complexity was low, across-hemisphere matching was faster when complexity was high, and they were equivalent when complexity was medium. These results are consistent with the idea that at high levels of complexity the benefits of engaging resources from both hemispheres outweigh the costs of interhemispheric communication (Banich, 1998). In old adults, the benefits of bilateral processing were evident at lower levels of complexity and they showed an advantage for across-hemisphere matching in both medium and high complexity conditions. Thus, the results of Reuter-Lorenz et al. (1999) suggest that older adults may benefit from bihemispheric processing at levels of task complexity for which unilateral processing seem to be enough in young adults.

Inhibition

Finally, there is also evidence consistent with the HAROLD model in the domain of inhibitory control. A popular method to study inhibitory control is the *Go/No-go* task, in which subjects

must respond to targets (*Go* trials) while inhibiting prepotent responses to distractors (*No-go* trials). An fMRI study that investigated this paradigm (Garavan, Ross, & Stein, 1999) associated response inhibition with a network of regions strongly lateralized to the right hemisphere, including PFC and parietal regions. Thus, in young adults, inhibitory control was associated with right PFC activity (see Table 1). Nielson et al. (2001) investigated the same paradigm in a group of older adults. In older adults, inhibitory control elicited significant activity not only in right PFC but also in left PFC (see Table 1). As noted later, age-related increases in the left hemisphere were also found in the parietal cortex, suggesting that the HAROLD model may generalize beyond PFC.

Appraisal

In summary, the HAROLD model is supported by evidence in the domains of episodic memory retrieval, episodic encoding/semantic retrieval, working memory, perception, and inhibitory control. In the case of episodic memory retrieval, in which PFC activity in young adults tended to be right lateralized, age-related asymmetry reductions typically involved an increase in left PFC activity. In the case of episodic encoding/semantic retrieval, in which PFC activity in young adults tended to be left lateralized, age-related asymmetry reductions involved a decrease in left PFC activity or an increase in right PFC activity. In the case of working memory, age-related asymmetry reductions usually involved an increase in activation in the hemisphere that was less activated in younger adults. Finally, in the case of perception and inhibitory control, the age-related asymmetry reduction primarily involved increases in left PFC.

Thus, the HAROLD model is consistent with a variety of age-related changes in activity (see two rightmost columns in Table 1). As the example in Figure 3 illustrates, this diversity may be a consequence of the use of brain images that display differences in activations only if they exceed a certain significance threshold. The plot in this figure demonstrates the basic finding supporting the HAROLD model; i.e., PFC activity is less asymmetric (or more symmetric) in older adults than in younger adults. (In the example, PFC activity in young adults is shown as right lateralized but the same arguments also apply to cases in which PFC activity in young adults is left lateralized.) The main point of Figure 3 is that the same basic activation pattern depicted in the graph may yield several different outcomes in the thresholded images (Outcomes A to E) depending on the power of the experiment and/or the significance threshold employed. In Outcome A, PFC activity is below threshold in both groups, and hence, an age-related asymmetry reduction is likely to be missed unless specifically tested. Outcomes B and C may show a significant age-related reduction in one hemisphere but are unlikely to reveal the underlying age-related asymmetry reduction. In contrast, an age-related asymmetry reduction is obvious in Outcome D where PFC activity is unilateral in young adults but bilateral in old adults. Finally, when PFC activity is significant bilaterally in both groups (Outcome E), an age-related asymmetry reduction is not obvious, but it may be detected for example because PFC older adults show weaker PFC activity in one hemisphere but stronger PFC activity in the contralateral hemisphere. Several studies have shown this pattern (Anderson et al., 2000; Grady et al., 1998; Nagahama et al., 1997; Rypma, Prabhakaran,

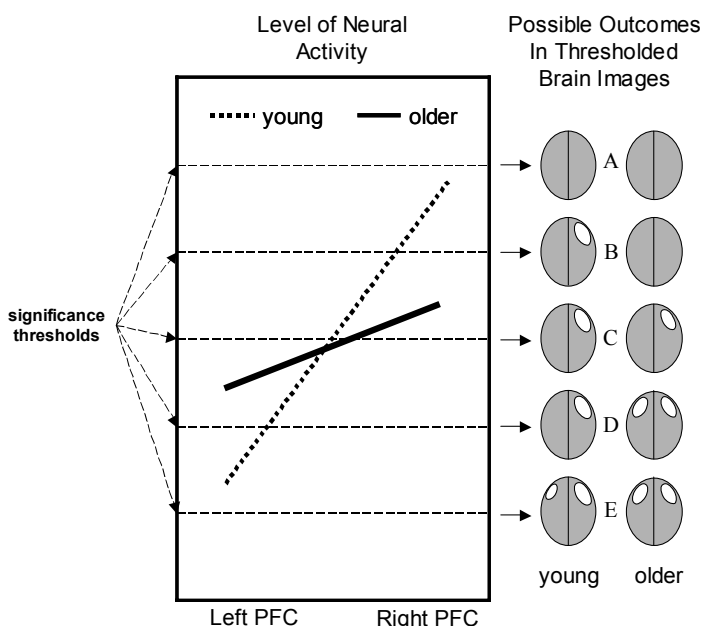


Figure 3. Simulated data illustrating an age-related hemispheric asymmetry reduction, and the corresponding brain images at different significance thresholds.

Desmond, & Gabrieli, in press) but are not listed as evidence for the HAROLD model because they did not explicitly report an age-related asymmetry reduction. Therefore, age-related asymmetry reductions are easier to detect in Outcomes D and E, and this explains why Table 1 consists mainly of these two types of outcomes. However, age-related asymmetry reductions could be responsible for Outcomes A, B, and C in many studies, but were simply not detected.

Having specified what types of findings are *consistent* with the HAROLD model, it is important to identify what types of findings are *inconsistent* with this model. As illustrated by Figure 3, Outcomes A (e.g., Madden et al., 1996), B (e.g., Grady et al., 1995), C (e.g., Madden et al., in press), or E (e.g., Grady et al., 1999) are not necessarily inconsistent with the model. Thus, there is only one case in which thresholded images are inconsistent with the HAROLD model: when PFC activity is bilateral in young adults but unilateral in old adults. To our knowledge, only one study has reported such a finding (Iidaka et al., 2001). In this study, however, the effects of aging on PFC activity were nonsignificant.

As noted above, in the case of Outcomes A, B, and C, age-related asymmetry reductions are unlikely to be detected unless a specific test is performed. A good test is to draw region-of-interests (ROI) in homologous PFC regions in both hemispheres and calculate a *lateralization index* (e.g., Blanchet et al., 2001) such as $[(\text{right ROI} - \text{left ROI}) / (\text{right ROI} + \text{left ROI})] \times 100$. This lateralization index varies from -100, for a completely left lateralized activation, to 100, for a completely right lateralized activation, with 0 representing perfect symmetry. If the absolute value of the lateralization index is greater for younger adults than for older adults, the results are consistent with the HAROLD model, whereas if the absolute value of the lateralization index is similar in both groups or greater in older adults, the model is disconfirmed.

II. Function of Age-Related Asymmetry Reductions

A question one may ask is whether age-related reductions in lateralization have a function or whether they are merely a byproduct of the effects of aging on the brain without any specific purpose. As an example of the first alternative, one may propose that asymmetry reductions play a compensatory role in the aging brain (*compensation view*). As an example of the second alternative, one may propose these reductions reflect an age-related difficulty in engaging specialized neural mechanisms. Borrowing a term from the psychometric literature, this notion may be called the *dedifferentiation view*. The two sections below review evidence for the compensation and dedifferentiation views.

Compensation view

In 1997, we proposed a compensation view of the HAROLD model by suggesting that increased bilaterality in old adults could help counteract age-related neurocognitive deficits (Cabeza et al., 1997a). This account is consistent with several lines of evidence, including evidence about the relation of brain activity and cognitive performance and evidence about the recovery of function following brain damage.

Relation of brain activity and cognitive performance. Strong support for the compensation view is provided by evidence that bilateral activity in older adults is associated with enhanced cognitive performance. A good example of this kind of evidence was provided by the aforementioned study by Reuter-Lorenz et al. (2000). In that study, older adults who displayed a bilateral pattern of PFC activity were *faster* in the verbal working memory task than those that did not. If bilateral activity leads to faster reaction times, then it is reasonable to suggest that it plays a compensatory role in the aging brain.

The compensation view is also buttressed by evidence that the brain regions showing additional activity in older adults are likely to enhance performance in the task investigated. For example, there is evidence that left PFC can contribute to episodic retrieval performance. First, although PFC activity during episodic retrieval is usually right lateralized, left PFC activations have also been found in many studies and seem to be associated with demanding retrieval tasks (Nolde, Johnson, & Raye, 1998). Since the same tasks tend to be more demanding for older than for younger adults, then it is possible that old adults recruit left PFC in order to cope with increased retrieval demands. Second, left PFC has been associated with semantic retrieval (Cabeza & Nyberg, 2000) and semantic retrieval can contribute to episodic retrieval (Cabeza, Anderson, Kester, Lennartsson, & McIntosh, in press; Cabeza et al., 1997a).

Recovery of function after brain damage. Evidence for the compensation view of the HAROLD model is also provided by research on the recovery of function after brain damage. Before describing this research, it is important to emphasize that the effects of normal aging on neurocognitive function are very different from those of pathological brain damage. Whereas the effects of aging on cognitive performance (e.g., Park et al., 2000), brain structure (e.g., Raz et al., 1997), and brain function (e.g., Esposito, Kirby, Van Horn, Ellmore, & Faith Berman, 1999) develop gradually during several decades, the initial effects of brain damage occur very rapidly (e.g., trauma, stroke). Whereas aging produces only a mild-to-moderate decrement in cognitive performance, pathological brain damage can

completely obliterate one or more cognitive functions. Whereas aging tends to affect several cognitive functions (episodic memory, working memory, attention, etc.), the effects of brain damage are sometimes very specific (e.g., production aphasia). However, despite all these differences, it is reasonable to assume that several of the same compensatory mechanisms apply to both age-related and pathology-related neurocognitive dysfunction. To illustrate this point with an analogy, a walking stick (a compensatory device) may alleviate locomotion deficits in both healthy older adults and brain-damaged patients, even if the nature and origin of the locomotion deficits are quite different in the two cases.

In this sense, the compensation view of the HAROLD model is indirectly supported by evidence that recovery of function after unilateral brain damage is facilitated by the recruitment of homologous regions in the unaffected hemisphere. For example, the recovery from aphasia following lesions in left PFC (e.g., Broca's area) may be aided by the involvement of the homologous right PFC areas. Since peri-lesion areas are usually engaged as well, this shift leads to bilateral activity during tasks that are normally mediated by unilateral activity. If bihemispheric activity plays a compensatory role in brain-damaged patients, it is reasonable to assume it also plays a compensatory role in older adults. Aging involves protracted anatomical and physiological neural deterioration and the slowness of this process is likely to favor a progressive neurocognitive adaptation.

Evidence of involvement of the unaffected hemisphere during the recovery of motor functions after monohemispheric stroke has been found with a variety of techniques, including cortical potentials (Honda et al., 1997); transcranial magnetic stimulation (Cicinelli, Traversa, & Rossini, 1997; Netz, Lammers, & Homberg, 1997), Doppler ultrasonography (Silvestrini, Cupini, Placidi, Diomedi, & Bernardi, 1998), Xenon-133 (Brion, Demeurisse, & Capon, 1989), and PET (Di Piero, Chollet, MacCarthy, Lenzi, & Frackowiak, 1992; Honda et al., 1997). According to Netz et al. (1997), motor outputs in the unaffected hemisphere are significantly changed after stroke, including the unmasking of ipsilateral corticospinal projections. Silvestrini et al. (1998) point out that activation ipsilateral to the side of the body affected cannot be considered a transient phenomenon because it is still evident several months after a stroke. The damaged hemisphere may also show changes, such as an enlargement of the hand motor area (Cicinelli et al., 1997). In fact, favorable clinical evolution of motor deficits has been associated with bilateral increase in cerebral activity during motor performance (Silvestrini et al., 1998).

The involvement of the healthy hemisphere has also been found during the recovery of language abilities. Again, the evidence was provided by a variety of methods, including finger tapping (Klingman & Sussman, 1983), cortical potentials (Thomas, Altenmuller, Marckmann, Kahrs, & Dichgans, 1997), Doppler ultrasonography (Silvestrini, Troisi, Matteis, Razzano, & Caltagirone, 1993); Xenon-133 (Demeurisse & Capon, 1991); PET (Buckner, Corbetta, Schatz, Raichle, & Petersen, 1996; Engelen et al., 1995; Ohyama et al., 1996; Weiller et al., 1995), and fMRI (Cao, Vikingstad, Paige George, Johnson, & Welch, 1999; Thulborn, Carpenter, & Just, 1999). For example, a language-related negative cortical potential that is normally left lateralized was found bilaterally in a group of aphasic patients,

which suggests that the right hemisphere is also involved (Thomas et al., 1997). A longitudinal study using Doppler ultrasonography found that after a period of speech therapy word fluency in a group of aphasic patients was associated with a bilateral increase in flow velocity (Silvestrini et al., 1993). A recent fMRI study reached the same conclusion; several months after a left-hemisphere stroke, better language recovery was observed in aphasic patients who showed bilateral activations (Cao et al., 1999).

Dedifferentiation view

The idea that age-related decreases in lateralization are a mere byproduct of aging without any specific function is implied by the hypothesis of an age-related dedifferentiation of cognitive abilities (for a review, see Li & Lindenberger, 1999). It has been suggested that there is a gradual evolution from an amorphous general ability into a group of distinct cognitive aptitudes during child development (Garrett, 1946), and that during aging different functions come to require similar executive or organizing resources (Balinsky, 1941; Baltes & Lindenberger, 1997). In other words, a process of functional *differentiation* during childhood is reversed by a process of functional *dedifferentiation* during aging.

The dedifferentiation hypothesis is primarily supported by evidence that correlations among different cognitive measures, and between cognitive and sensory measures, tend to increase with age. For example, Baltes and Lindenberger (1997) found that median intercorrelations between five cognitive measures increased from 0.37 in younger adults to 0.71 in older adults (see also, Babcock, Laguna, & Roesch, 1997; Mitrushina & Satz, 1991). The same study also showed that the average proportion of individual differences in intellectual functioning related to sensory functioning increased from 11% in adulthood to 31% in old age (see also, Birren, Riegel, & Morrison, 1962; Granick, Kleban, & Weiss, 1976; Salthouse, Hancock, Mainz, & Hambrick, 1996).

Li and Lindenberger (1999) proposed a cognitive neuroscience theory relating three age-related phenomena: (1) decline in cognitive performance; (2) increase in correlations among cognitive/sensory measures; and (3) increase in intra- and inter-subject variability. The theory assumes that catecholamines (epinephrine, norepinephrine, and dopamine) sharpen the signal-to-noise ratio of neuronal activity (Servan-Schreiber, Printz, & Cohen, 1990), and hence, the decline in catecholamine concentration during aging tends to increase "neural noise" in the aging brain. The authors conducted simulation studies showing that this mechanism could account for both intra-subject and inter-subject variability, as well as for an increase in correlations among cognitive/sensory measures (Li & Lindenberger, 1999).

Appraisal

In summary, the compensation view and the dedifferentiation view are both supported by empirical evidence. The compensatory view is consistent with evidence that bilateral activation in old adults is associated with improved cognitive performance and that bihemispheric involvement facilitates recovery of function following brain damage. The dedifferentiation view is consistent with evidence that inter-measure correlations tend to increase with age.

The compensation and dedifferentiation views are not incompatible. For example, it is possible to argue that neurocognitive dedifferentiation plays a compensatory role in the aging brain. More specifically, although the dedifferentiation view implicitly assumes that higher inter-measure correlations reflect an age-related deficit, to date there is no clear evidence that this is the case. For example, there is no evidence that inter-measures correlations are higher among older adults with a more pronounced level of age-related cognitive decline. Instead, one could argue that old adults' cognitive performance is actually benefited by a decrease in differentiation. Interpreted in this sense, evidence of age-related increases in inter-measure correlations would be consistent with the compensation view.

III. Origin of Age-Related Asymmetry Reductions

A second question one may ask is whether age-related reductions in lateralization have a psychological origin or a neural origin. Before describing these psychogenic and neurogenic views, it is important to note that the issue concerning the origin of age-related asymmetry reductions is orthogonal to the issue concerning their function. Thus, one may cross the compensation/differentiation distinction with the psychogenic/neurogenic distinction and, as a result, conceive four different accounts of the HAROLD model.

Psychogenic view

According to a psychogenic view, age-related changes in brain activity reflect age-related changes in cognitive architecture, such as altered cognitive structures (e.g., semantic memory network) and cognitive processes (e.g., semantic elaboration during encoding). Altered cognitive processes may reflect changes in cognitive strategies, and the notion that aging is accompanied by changes in cognitive strategies has a long tradition in cognitive aging research (Light, 1991). Thus, a psychogenic view of the HAROLD view could argue that older adults show a more bilateral pattern of brain activity than young adults because they use different cognitive strategies.

In situations in which age-related changes in cognitive strategies can be assumed to have a beneficial effect on performance, the psychogenic view may be combined with the compensation view. However, age-related strategy changes are sometimes interpreted as detrimental for performance. For example, Schacter et al. (1996) found that in a demanding stem cued-recall condition, old adults showed weaker activity than young adults in anterior PFC regions but stronger activity in Broca's area, and proposed that, instead of memory strategies mediated by anterior PFC, older adults recruited inappropriate phonological strategies mediated by Broca's area. Likewise, one could argue that age-related increases in activity in the hemisphere less activated by young adults reflect the use of inefficient strategies in older adults. The psychogenic view can also be combined with the dedifferentiation view: With aging, cognitive strategies become less specific, and hence, activation patterns become more widespread.

Neurogenic view

According to a neurogenic view, age-related changes in brain activity reflect an alteration in neural architecture, such as changes in the functions of different brain regions and/or their connections. A neurogenic account of the HAROLD model would posit that the *same* cognitive processes are mediated by a

more bilateral pattern of brain activity in older adults than in younger adults.

As in the case of the psychogenic view, the neurogenic view may be combined with either the compensation or the dedifferentiation accounts of the HAROLD model. A neurogenic account of compensation is that an age-related reduction in hemispheric asymmetry is an adaptation of the aging brain that has beneficial effects on cognitive performance. In contrast, a neurogenic account of dedifferentiation is that an age-related asymmetry reduction reflects the disintegration of brain systems without a beneficial outcome.

The neurogenic view of the HAROLD model can be supported by evidence linking age-related reductions in lateralization to the effects of aging on basic neural mechanisms or to the behavior of neural networks. For example, there is evidence that dopamine function in the striatum show hemispheric asymmetries (de la Fuente-Fernandez, Kishore, Calne, Ruth, & Stoessl, 2000; Larisch et al., 1998) and that age-related changes in dopamine function play an important role in age-related cognitive decline (Bäckman et al., 2000; Volkow et al., 1998). Thus, the neurogenic view of the HAROLD model would be bolstered by evidence that aging attenuates hemispheric asymmetries in dopamine function. The neurogenic view is also consistent with computational models showing that damaging neural networks can alter hemispheric asymmetry. For example, Levitan and Reggia (1999) investigated a neural network consisting of left and right hemisphere regions connected through the corpus callosum and found that, in the case of asymmetric networks, a lesion in one hemisphere resulted in increased map formation and organization in the contralateral, intact hemispheric region. They also found that diffuse lesions in the dominant side of asymmetric networks resulted in less lateralization. Even if this study did not investigate diffuse bilateral damage resembling the one associated with aging, its results suggest that under certain conditions hemispheric asymmetry reductions may reflect adaptations of neural networks rather than changes in cognitive strategies.

Appraisal

Determining whether age-related differences in activation reflect changes in cognitive architecture or changes in neural architecture is a very thorny problem (for a discussion of this issue in studies with brain-damaged patients, see Price & Friston, 2001). When interpreting age-related changes in brain activity, one question is particularly difficult to answer: Did young and older adults engage different brain regions to perform the *same* cognitive operations, or did they recruit different brain regions to perform *different* cognitive operations? Of course, the main problem is how to determine exactly the cognitive processes engaged by young and older adults, since cognitive tasks can be performed in many different ways and introspective reports provide very limited information about the actual cognitive operations recruited by human subjects.

However, a few pieces of evidence tend to favor the neurogenic view. First, the neurogenic view can more easily account for age-related asymmetry reductions during simple tasks such as face matching tasks (Grady et al., 1994; Grady et al., 2000b). In general, evidence of age-related changes in activity during tasks in which cognitive strategies play little or no role (e.g., sensory discrimination: Della-Maggiore et al.,

2000) tends to support the neurogenic view. Second, the combined results of the intentional and incidental learning conditions in Logan and Buckner (2001) indicates that age-related asymmetry reductions are resistant to strategy manipulations, even if these manipulations affect the overall level of PFC activity in young and older adults.

IV. Neural Mechanisms of Age-Related Asymmetry Reductions

A third question one may ask is whether age-related reductions in lateralization reflect a global transformation of the neural network underlying task performance or whether they reflect a regional phenomenon limited to the specific brain areas showing the effect. These network and regional views, which account for the neural mechanisms of age-related asymmetry reductions at the systems level, are described below.

Network view

If one assumes that cognitive performance is mediated by a network of highly interconnected regions, the effects of aging on the anatomical and physiological integrity of the brain can be expected to affect not only the function of specific brain areas but also the interactions between these areas. According to this view, an age-related increase in activation in a certain brain region (e.g., left PFC during episodic retrieval) is not independent of the effects of aging on other brain regions mediating the task, but rather is the result of a global network change. This network view of the HAROLD model receives support from two types of evidence.

First, this view is supported by evidence that age-related changes in activity are task-specific. If age-related changes in brain activity reflect a network transformation, and if different tasks involve different networks, then these age-changes should vary depending on the nature of the task. The strongest proof that the effects of aging on brain activity are task-specific is evidence that the same brain region can show an age-related increase in activation or an age-related decrease in activation depending on the task. For example, in the aforementioned study by Cabeza et al. (1997a), bilateral PFC activity during a recall task occurred in old adults because left PFC activity during this task was significant in older adults but not in younger adults (see Figure 4-a). However, during the encoding task, the same left PFC region (Area 47) was significantly active in younger adults but not in older adults (see Figure 4-a). Actually, brain activity in left Area 47 showed the striking crossover dissociation depicted in Figure 4-b. It is difficult to account for this task x age interaction in terms of local neural phenomena because the same region was less activated or more activated in older adults depending on the task. In contrast, this kind of interaction suggests a global change in which the same region can play different roles in the two age groups depending on its interactions with other regions within the network subserving the task.

Second, the network view of the HAROLD model is also supported by evidence that aging affects not just regional brain activity in particular brain regions but the *interactions* between different regions within the network. The effects of aging on functional interactions between brain regions can be studied using covariance analyses (Grady et al., 1995; Horwitz, Duara, & Rapoport, 1986; McIntosh et al., 1999) and structural equation modeling (Cabeza, McIntosh, Tulving, Nyberg, & Grady,

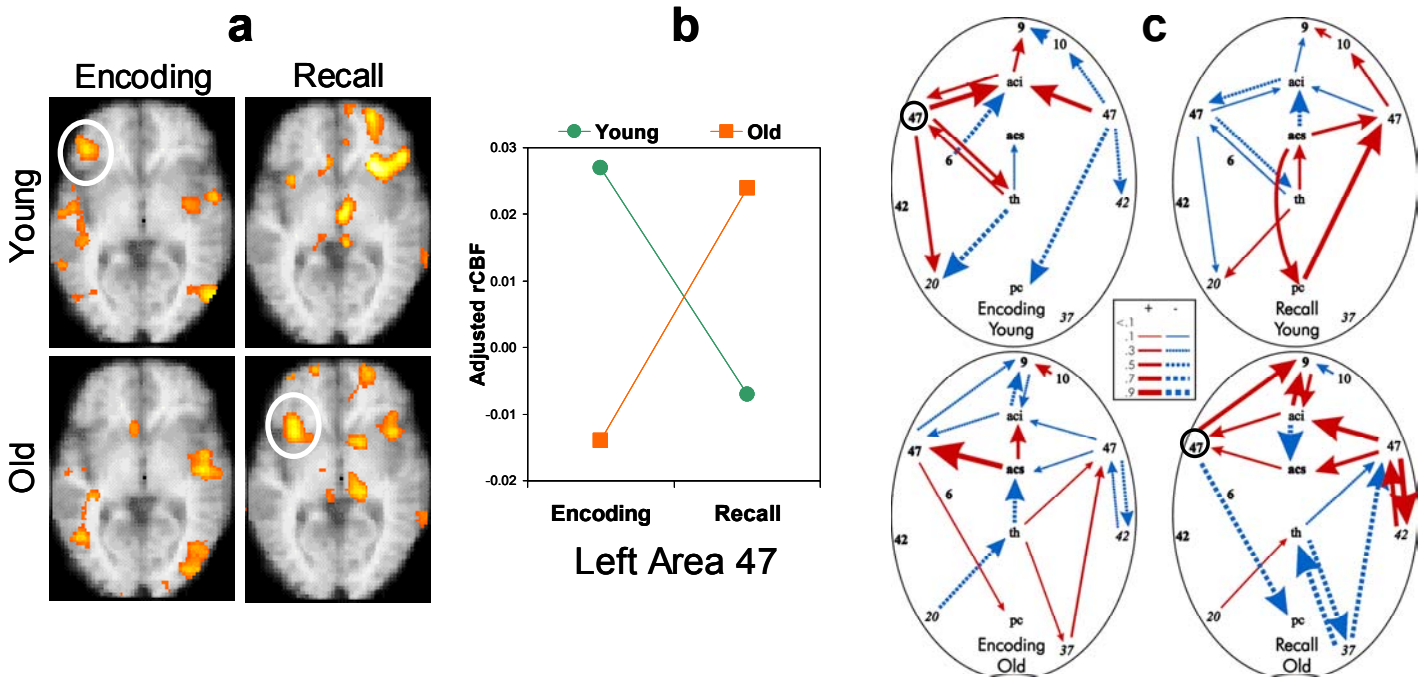


Figure 4. Evidence for the network view of the HAROLD model. (a) Brain activity in young and old adults during word-pair encoding and recall. (b) Left ventrolateral PFC (Area 47) as a function of task and group. (c) Main results of structural equation modeling of encoding and recall activity in young and old adults (from Cabeza et al., 1997b)

1997b; Esposito et al., 1999). For example, we applied structural equation modeling to the results of the aforementioned encoding/recall PET study (Cabeza et al., 1997b). We selected regions that showed main effects of age or task, or task \times age interactions, and linked them according to known neuroanatomy. The goal of this study was to account for the crossover dissociation in left Area 47 (Figure 4-b). Figure 4-c shows the main results of this path analysis. In the young group, there was a shift from positive interactions involving left PFC during encoding to positive interactions involving right PFC during recall, whereas in the old group, PFC interactions were mixed during encoding and bilaterally positive during recall. Thus, these results suggest that the age-related decrease in left prefrontal activation during encoding did not reflect a local change in the left prefrontal but a global change in memory networks. More generally, they suggest that an age-related reduction in lateralization may result from a global transformation of the neural network underlying task performance.

Regional view

The regional view assumes that bihemispheric involvement in old adults reflects the way in which specific brain regions respond to aging. For example, the age-related increase in left PFC activity during episodic retrieval would not reflect a global change of the episodic memory network, but rather it would reflect something specific about left PFC. Left PFC is associated with semantic memory retrieval (Cabeza & Nyberg, 2000) and semantic retrieval is relatively resistant to aging (Zacks, Hasher, & Li, 2000). Accordingly, the regional view could argue that old adults recruit left PFC during episodic retrieval because of the function and properties of this particular brain region.

The regional view is supported by evidence of the existence of hemispheric asymmetries in age-related neural decline. If one

hemisphere is more affected by aging than the other, then those cognitive processes that are lateralized towards the affected hemisphere would become more bilateral during the aging process. In the case of episodic memory retrieval, the regional view is consistent with evidence that the right hemisphere is more vulnerable to aging than the left hemisphere. This idea has been supported by measures of language processing (Rastatter & Lawson-Brill, 1987; Rastatter & McGuire, 1990), skill learning (Meudell & Greenhalgh, 1987; Weller & Latimer-Sayer, 1985), and visuospatial performance (Meudell & Greenhalgh, 1987). The fact that the same pattern was found in a variety of tasks suggests that the change is task-independent and does not involve a change in the specific networks underlying these tasks. For example, the regional view could argue that age-related increases in left PFC activity during episodic retrieval reflect difficulties with right hemisphere functions that are independent of episodic retrieval or the episodic retrieval network.

Appraisal

In summary, both the network view and the regional view have received some empirical support. The network view is consistent with evidence that the effects of aging on brain activity are task-specific (e.g., the same region may show age-related increases or decreases depending on the task) and that they affect not only individual regions but also the connections between them. The regional view is consistent with evidence that aging affects one hemisphere more than the other and that the same asymmetric effect can be found in a variety of different tasks.

The network and regional views of the HAROLD model are not incompatible. For example, the age-related global network reorganization proposed by the network view could originate in age-related regional changes. For example, an age-related decline in right hemisphere functions could increase old adults'

reliance on left hemisphere operations. However, the particular left hemisphere region engaged could depend on the particularities of the task and the role of other regions within the network. Eventually, the change in one network component would alter other network components and their interactions, thus resulting in a global network change. Although the theory that the right hemisphere is more vulnerable to aging than the left hemisphere has been strongly criticized (Benton, Eslinger, & Damasio, 1981; Byrd & Moscovitch, 1984; Mittenberg, Seidenberg, O'Leary, & DiGiulio, 1989; Nebes, Madden, & Berg, 1983; Obler, Woodward, & Albert, 1984), the possibility that the effects of aging are not always symmetrical cannot be completely discarded. Until additional evidence is available, it is cautious to assume that both network and regional views are partly correct.

V. Age-Related Asymmetry Reductions and Cognitive Aging Theories

Although the psychological theories of cognitive aging do not make explicit predictions concerning the neural basis of aging, some expectations may be inferred. The sections below discuss whether or not three popular cognitive aging theories, the *resources*, *speed*, and *inhibition* theories, are consistent with the HAROLD model.

Resources view

The resources view (Craik, 1983; Craik, 1986; Craik & Byrd, 1982) assumes that cognitive processes are fueled by a limited supply of attentional resources (Kahneman, 1973) and that aging further reduces this limited supply, producing deficits on demanding cognitive tasks. If one assumes that processing capacity is a property of neural units, and that aging is associated with a decline in processing capacity, then it is reasonable to also assume that older adults may recruit more neural units to generate the same amount of resources as young adults (Reuter-Lorenz et al., 1999). Old adults could accomplish this goal by engaging additional brain areas, such as homologous contralateral regions.

If recruiting additional neural units can boost processing resources, then why do young adults not take advantage of this mechanism? An answer to this question is that there is a cost associated with recruiting additional neural units. The notion of a negative trade-off of compensation is a feature of some compensation models (Bäckman & Dixon, 1992). One possibility is that recruiting both hemispheres reduces the ability of the brain to handle distracting stimuli or to perform simultaneous tasks. For example, one can speculate that one advantage of monohemispheric processing is that it leaves neural units available for processing additional information. Investigating whether old adults showing bilateral activation are more sensitive to distraction or less able to handle simultaneous tasks could test this hypothesis. There is evidence that older adults' performance is impaired by divided attention manipulations (Anderson, Craik, & Naveh-Benjamin, 1998) but the link between sensitivity to divided attention and bihemispheric processing has not been established.

Speed view

The speed view proposes that older adults' cognitive deficits are primarily a consequence of a general age-related reduction in processing speed (for a review, see Salthouse, 1996). If one

assumes that processing speed can be increased by recruiting additional neural units, then the speed view would be consistent with the HAROLD model: Old adults could counteract deficits in processing speed by recruiting additional neural units. Consistent with this idea, a recent fMRI study by Rypma and D'Esposito (2000) found that those elderly adults who showed greater PFC activity responded faster in a working memory task.

However, one can raise a similar question in regards to the speed view as was introduced for the resources view: If responses can be accelerated by recruiting additional neural units, then why do young adults not take advantage of this mechanism? The fMRI study by Rypma and D'Esposito (2000) provides an answer to this question. In this study, response speed and brain activity were positively correlated in older adults but negatively correlated in younger adults (however, see Grady et al., 1998). According to the authors, young and older adults could be at different points of a sigmoid function relating neural activity and performance such that the ideal level of neural activity for optimal performance is higher for older adults than for younger adults. This idea provides a convincing account for the existence of age-related reductions in lateralization: unilateral activity may be more efficient for younger adults, whereas bilateral activity may be more efficient for older adults.

Inhibition view

Finally, the inhibition view (Hasher & Zacks, 1988; Zacks et al., 2000) attributes age-related cognitive deficits to a decline in inhibitory control. Deficient inhibitory control allows goal-irrelevant information to gain access to working memory, and the resulting "mental clutter" impairs working-memory operations, including the encoding and retrieval of episodic information. If one assumes that PFC performs inhibitory operations (e.g., Shimamura, 1995), then the inhibition view is consistent with the HAROLD model: Older adults must recruit additional PFC regions in order to reach the same level of inhibitory control as young adults. It is important to note that this argument applies only to those regions assumed to perform inhibitory operations (inhibiting regions), such as PFC, and not to those assumed to be affected by these operations (inhibited regions).

One may again ask the same question as in the case of the resources and speed views: If inhibitory control can be increased by recruiting additional neural units, why do young adults not take advantage of this mechanism? One possible answer is that young adults do not need additional inhibitory control. If young adults are successful in inhibiting most goal-irrelevant information, further inhibitory control is unlikely to improve their performance. As discussed by Bäckman and Dixon (1992), some compensatory changes may be redundant for high-performing people.

Appraisal

In summary, the resources, speed, and inhibition theories of cognitive aging are consistent with the HAROLD model. They could argue that, in order to counteract neurocognitive deficits elderly adults increase attentional resources, processing speed, or inhibitory control by recruiting additional neural units. In terms of the HAROLD model, these three views are not incompatible. On the contrary, they could be combined to provide a better account of the HAROLD model.

It could be argued that cognitive aging theories are compatible with the HAROLD model only because they do not make specific claims about the neural basis of cognitive aging. Although it is true that the links between cognitive aging theories and the neurobiological evidence are still indirect, this situation is rapidly changing, in great part due to functional neuroimaging evidence. As the neural correlates of cognitive processes become better known, cognitive aging theories will provide more specific predictions about the HAROLD model. For example, inhibitory processes have been linked to left ventrolateral PFC activity (D'Esposito, Postle, Jonides, & Smith, 1999; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998), and age-related deficits in inhibitory control have been associated with weaker activity in this region (Jonides et al., 2000). Thus, the inhibition view of HAROLD would be supported by evidence that, under certain conditions, bilateral activity in older adults involves an inhibition-related increase in left ventrolateral PFC activity. As the neural correlates of attentional resources, inhibitory control, and processing speed are differentiated, so will the predictions that the resources, inhibition, and speed views of aging make about the HAROLD model.

VI. Generalizability of Age-Related Asymmetry Reductions

Generalizability within cognition

Although the evidence listed in Table 1 indicates that age-related asymmetry reductions occur for a variety of different cognitive functions, there are several unsolved issues regarding the generalizability of the HAROLD model within cognition. For example, it is unclear if age-related asymmetry reductions occur only for higher-order cognitive processes, such as the ones listed in Table 1, or whether they can also be found for simple sensory and motor processes. The answer to this question is informative with respect to psychogenic vs. neurogenic accounts of the HAROLD model. The psychogenic account suggests that age-related asymmetry reductions should be more likely for higher-order cognitive processes because they are more amenable to strategic control, whereas a neurogenic account suggests age-related asymmetry reductions should also occur for simple sensory/motor processes. A recent PET study investigated the effects of aging on brain activity during auditory-cued thumb-to-index tapping (Calautti, Serrati, & Baron, 2001). As expected, both groups showed sensorimotor activity in the contralateral hemisphere, i.e., left sensorimotor activity for right-hand tapping and right sensorimotor activity for left-hand tapping. Additionally, older adults showed more activity than younger adults in right dorsal PFC during right-hand tapping. Although this age-related increase in ipsilateral activity may reflect differences in the resting baseline, it suggests that the HAROLD model may generalize to simple motor processes.

Generalizability within the brain

Since almost all findings of age-related asymmetry reductions have been found in PFC, the HAROLD model is currently proposed only for this brain region. However, there is no reason why this model cannot be eventually extended to other brain regions. Actually, there is some functional neuroimaging evidence suggesting that this may be possible. For example, in

the aforementioned perception PET study by Grady et al. (2000), age-related asymmetry reductions seemed to occur not only for PFC but also temporal and parietal regions. Also, in a face memory study by Grady et al. (2000a), positive correlations between temporoparietal activity and memory performance were found in the left hemisphere for young adults but bilaterally for old adults. Moreover, in the fMRI study of inhibitory control by Nielson et al. (2001), young adults showed a right lateralized fronto-parietal network, and there were age-related increases in activity not only in left PFC but also left parietal regions. Thus, several functional neuroimaging studies suggest that the HAROLD model may also apply to temporal and parietal regions.

The generalizability of HAROLD to temporal regions is also supported by an event-related potentials (ERPs) study of language processing. It is generally accepted that linguistic processing tends to be lateralized to the left hemisphere (Beaton, 1997; Benson, 1986; Epstein, 1998; Galaburda, LeMay, Kemper, & Geschwind, 1978; Ojemann, 1991; Previc, 1991; Strauss, Kosaka, & Wada, 1983; Tzourio, Crivello, Mellet, Nkanga-Ngila, & Mazoyer, 1998), and ERP studies usually show larger language-related effects over the left than over the right hemisphere scalp regions (e.g., Elmo, 1987; Nelson, Collins, & Torres, 1990). Consistent with this pattern, Bellis et al. (2000) found that in electrodes placed over temporal lobe regions an N1 effect associated with auditory processing of syllables was strongly left lateralized in both children and younger adults. In older adults, however, the N1 effect was bilateral. These results suggest that age-related asymmetry reductions also occur for language processes and support the generalizability of HAROLD model to temporal lobe regions.

At this point in time, however, the number of age-related asymmetry reductions outside PFC is too small to justify the generalization of the HAROLD model beyond this region. Like the issue of generalizability to sensorimotor processes, the issue of generalizability beyond PFC has implications for psychogenic vs. neurogenic accounts of the HAROLD model. A psychogenic account predicts that age-related asymmetry reductions should be more likely for brain regions associated with executive/strategic cognitive operations, such as PFC, whereas a neurogenic account predicts that they should also occur for brain regions associated with simpler and more automatic perceptual and motor processes, such as occipital and parietal regions.

Generalizability within the elderly population

Since most functional neuroimaging studies of cognitive aging have compared a small group of young adults and a small group of older adults, very little information is available concerning the generalizability of the HAROLD model within the elderly population. First of all, it is unknown if age-related asymmetry reductions onset in old age or before old age. Age-related asymmetry reductions have typically been observed in groups of 60-80 years-old individuals, but the PET study by Dixit et al. (2000) also found them in a group of middle-aged adults. Yet, in the study by Nielson et al. (2001), age-related changes consistent with the HAROLD model were found in old-old (mean age: 74.5) but not in young-old (mean age: 63.2) subjects. To clearly characterize the development of hemispheric asymmetry reductions one would need measure brain activity in a large group of participants evenly distributed from young to

old age (e.g., Esposito et al., 1999) and systematically measure age-related changes in hemispheric asymmetry using the lateralization index.

As in the case of onset, there is almost no information concerning the incidence of age-related asymmetry reductions within the elderly population. Given the large variability of the older adult population, it is quite possible that these changes occur for some older adults but not for others or for some older adults more than for others. Variables that are likely to affect the incidence of age-related asymmetry reductions among older adults include cognitive performance, education, frontal-lobe function, and gender.

Cognitive performance is a critical variable for two reasons. First, cognitive performance has a strong effect on brain activity. For example, brain activity has been found to vary as a function of performance measures, such as accuracy (e.g., Nyberg, McIntosh, Houle, Nilson, & Tulving, 1996b), reaction times (e.g., Madden et al., 1999a), and discrimination thresholds (e.g., McIntosh et al., 1999). The close coupling between brain activity and performance creates a chicken-egg problem: do age-related differences in performance reflect age-related differences in activation or vice versa? Thus, differences in performance between younger and older adults can confound the results of functional neuroimaging studies of aging. For example, age-related reductions in lateralization could reflect the fact that the same cognitive tasks tend to be more demanding for older than for younger adults. Second, age-related asymmetry reductions may be specific to older adults with a certain level of cognitive decline.

Education level is also a critical variable because there is a considerable amount of evidence that education modulates the effects of aging on cognition and the brain. For example, lower levels of education have been associated with increased risk of developing Alzheimer's Disease (AD) (Evans et al., 1997; Friedland, 1993; Katzman, 1993; Mortimer & Graves, 1993). According to the *reserve hypothesis* (Katzman, 1993; Satz, 1993), education contributes to the development of a reserve capacity, which attenuates the effect of age-related neural decline on cognitive abilities. Thus, it is possible that the incidence of age-related asymmetry reductions in the older adult population varies as a function of education level.

Frontal-lobe function is an important variable because age-related asymmetry reductions have been found mainly in PFC and could depend on the level of age-related neural decline in this particular region. PFC is the brain region most affected by age-related neural changes (for reviews, see Cabeza, 2001; Raz, 2000) and, according to a popular view, is the locus of age-related deficits in cognition (West, 1996). Frontal changes are variable among older adults, and there is evidence that older adults whose frontal functions are relatively preserved show less age-related cognitive decline in cognitive tasks, such as context memory (Glisky, Polster, & Routhieaux, 1995). Therefore, age-related asymmetry reductions could reflect an alteration of PFC functions that is specific to older adults with a certain level of frontal-lobe dysfunction as measured behaviorally.

Finally, gender is a variable of interest for two reasons. First, gender has been shown to modulate the effects of aging on the brain (for a review, see Coffey et al., 1998). For example, Coffey et al. (1998) found that age-related atrophy was more pronounced in men than in women (see, however, Murphy et al.,

1996; Raz, Torres, & Spencer, 1993). Second, there is evidence that gender influences the lateralization of brain activity during cognitive performance. For example, it was found that inferior frontal gyrus activity during phonological processing was left lateralized for males but bilateral for females (see however, Frost et al., 1999; Shaywitz et al., 1995). Thus, it is possible that age-related asymmetry reduction differ as a function of gender.

Conclusions

In summary, the HAROLD model is supported by functional neuroimaging and behavioral evidence in the domains of episodic memory retrieval, working memory, perception, and inhibitory control. The age-related decrease in lateralization postulated by this model may result from a global reorganization of neurocognitive networks, as well as from regional neural changes. Bilateral activity in old adults may reflect compensatory processes, as well as dedifferentiation processes. Finally, the HAROLD model is consistent with popular theories of cognitive aging. The amount of evidence supporting the HAROLD model is still quite modest, but this will probably change in the near future due to the rapid expansion of the field of functional neuroimaging of cognitive aging (Cabeza, 2001).

It seems indisputable that age-related changes in cognition are largely due to age-related changes in the brain. Yet, although cognitive aging and neural aging have been thoroughly studied in isolation, the relations between these two domains have not received enough attention. Whereas the *cognitive psychology of aging* and the *neuroscience of aging* are well-established disciplines, the *cognitive neuroscience of aging* is a relatively new approach (Cabeza, 2001). By integrating findings and ideas about cognition and the brain, the HAROLD model is an example of this new approach.

References

- Anderson, N. D., Craik, F. I. M., & Naveh-Benjamin, M. (1998). The attentional demands of encoding and retrieval in younger and older adults: I. Evidence from divided attention costs. *Psychology and Aging, 13*, 405-423.
- Anderson, N. D., Iidaka, T., McIntosh, A. R., Kapur, S., Cabeza, R., & Craik, F. I. M. (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.
- Babcock, R. L., Laguna, K. D., & Roesch, S. C. (1997). A comparison of the factor structure of processing speed for younger and older adults: Testing the assumption of measurement equivalence across age groups. *Psychology & Aging, 12*, 268-276.
- Bäckman, L., Almkvist, O., Andersson, J., Nordberg, A., Winblad, B., Reineck, R., & Langstrom, B. (1997). Brain activation in young and older adults during implicit and explicit retrieval. *Journal of Cognitive Neuroscience, 9*, 378-391.
- Bäckman, L., & Dixon, R. (1992). Psychological compensation: A theoretical framework. *Psychological Review, 112*, 259-283.
- Bäckman, L., Ginovart, N., Dixon, R. A., Wahlin, T. B., Wahlin, A., Halldin, C., & Farde, L. (2000). Age-related cognitive deficits mediated by changes in the striatal dopamine system. *American Journal of Psychiatry, 157*, 635-637.

- Balinsky, B. (1941). An analysis of the mental factors of various groups from nine to sixty. *Genetic Psychology Monographs*, 23, 191-234.
- Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging? *Psychology and Aging*, 12, 12-21.
- Banich, M. T. (1998). The missing link: The role of interhemispheric interaction in attentional processing. *Brain and Cognition*, 36, 128-157.
- Beaton, A. A. (1997). The relation of planum temporale asymmetry and morphology of the corpus callosum to handedness, gender, and dyslexia: A review of the evidence. *Brain & Language*, 60, 255-322.
- Bellis, T. J., Nicol, T., & Kraus, N. (2000). Aging affects hemispheric asymmetry in the neural representation of speech sounds. *Journal of Neuroscience*, 20, 791-797.
- Benson, D. F. (1986). Aphasia and the lateralization of language. *Cortex*, 22, 71-86.
- Benton, A. L., Eslinger, P. J., & Damasio, A. R. (1981). Normative observations on neuropsychological test performances in old age. *Journal of Clinical Neuropsychology*, 3, 33-42.
- Birren, J. E., Riegel, K. F., & Morrison, D. F. (1962). Age differences in response speed as a function of controlled variation of stimulus conditions: Evidence of a general speed factor. *Gerontologia*, 6, 1-18.
- Blanchet, S., Desgranges, B., Denise, P., Lechevalier, B., Eustache, F., & Faure, S. (2001). New questions on the hemispheric encoding/retrieval asymmetry (HERA) model assessed by divided visual-field tachistoscopia in normal subjects. *Neuropsychologia*, 39, 502-509.
- Brion, J. P., Demeurisse, G., & Capon, A. (1989). Evidence of cortical reorganization in hemiparetic patients. *Stroke*, 20, 1079-1084.
- Buckner, R. L., Corbetta, M., Schatz, J., Raichle, M. E., & Petersen, S. E. (1996). Preserved speech abilities and compensation following prefrontal damage. *Proceedings of the National Academy of Sciences USA*, 93, 1249-53.
- Byrd, M., & Moscovitch, M. (1984). Lateralization of peripherally and centrally masked words in young and elderly people. *Journal of Gerontology*, 39, 699-703.
- Cabeza, R. (2001). Functional neuroimaging of cognitive aging. In R. Cabeza & A. Kingstone (Eds.), *Handbook of functional neuroimaging of cognition*. (pp. 331-377). Cambridge, MA: MIT Press.
- Cabeza, R., Anderson, N. D., Kester, J., Lennartsson, E. R., & McIntosh, A. R. (in press). Involvement of prefrontal regions on episodic retrieval: Evidence for a generate-recognize asymmetry model. *Brain & Cognition*.
- Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., Jennings, J. M., Houle, S., & Craik, F. I. M. (1997a). 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., Tulving, E., Nyberg, L., & Grady, C. L. (1997b). Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport*, 8, 3479-3483.
- Cabeza, R., & Nyberg, L. (2000). Imaging Cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, 12, 1-47.
- Calautti, C., Serrati, C., & Baron, J.-C. (2001). Effects of age on brain activation during auditory-cued thumb-to-index opposition: A positron emission tomography study. *Stroke*, 32, 139-146.
- Cao, Y., Vikingstad, E. M., Paige George, K., Johnson, A. F., & Welch, K. M. A. (1999). Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke*, 30, 2331-2340.
- Cicinielli, P., Traversa, R., & Rossini, P. M. (1997). Post-stroke reorganization of brain motor output to the hand: A 2-4 month follow-up with focal magnetic transcranial stimulation. *Electroencephalography & Clinical Neurophysiology*, 105, 438-450.
- Coffey, C. E., Lucke, J. F., Saxton, J. A., Ratcliff, G., Units, L. J., Billig, B., & Bryan, R. B. (1998). Sex differences in brain aging. *Archives of Neurology*, 55, 169-179.
- Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. *Philosophical Transactions of the Royal Society, London, Series B*, 302, 341-359.
- Craik, F. I. M. (1986). A functional account of age differences in memory. In F. Lix & H. Hagendorf (Eds.), *Human memory and cognitive capabilities, mechanisms, and performances*. (pp. 499-422). North-Holland: Elsevier Science Publishers B. V.
- Craik, F. I. M., & Byrd, M. (1982). Aging and cognitive deficits: The role of attentional resources. In F. I. M. & S. Trehub (Eds.), *Aging and cognitive processes* (pp. 191-211). New York: Plenum.
- de la Fuente-Fernandez, R., Kishore, A., Calne, D. B., Ruth, T. J., & Stoessl, A. J. (2000). Nigrostriatal dopamine system and motor lateralization. *Behavioural Brain Research*, 112, 63-68.
- Della-Maggiore, V., Sekuler, A. B., Grady, C. L., Bennett, P. J., Sekuler, R., & McIntosh, A. R. (2000). Cortic limbic interactions associated with performance on a short-term memory task are modified by age. *Journal of Neuroscience*, 20, 8410-8416.
- Demeurisse, G., & Capon, A. (1991). Brain activation during a linguistic task in conduction aphasia. *Cortex*, 27, 285-294.
- D'Esposito, M., Postle, B. R., Jonides, J., & Smith, E. E. (1999). The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI. *Proceedings of the National Academy of Sciences USA*, 96, 7541-7519.
- Di Piero, V., Chollet, F. M., MacCarthy, P., Lenzi, G. L., & Frackowiak, R. S. (1992). Motor recovery after acute ischaemic stroke: A metabolic study. *Journal of Neurology, Neurosurgery & Psychiatry*, 55, 990-996.
- Dixit, N. K., Gerton, B. K., Dohn, P., Meyer-Lindenberg, A., & Berman, K. F. (2000). Age-related changes in rCBF activation during an N-Back working memory paradigm occur prior to age 50. Paper presented at the Human Brain Mapping Meeting.
- Elmo, T. (1987). Hemispheric asymmetry of auditory evoked potentials to comparisons within and across phonetic categories. *Scandinavian Journal of Psychology*, 28, 251-266.
- Engelien, A., Silbersweig, D., Stern, E., Huber, W., Doring, W., Frith, C., & Frackowiak, R. S. (1995). The functional

anatomy of recovery from auditory agnosia. A PET study of sound categorization in a neurological patient and normal controls. *Brain*, 118, 1395-1409.

Epstein, C. M. (1998). Transcranial magnetic stimulation: Language function. *Journal of Clinical Neurophysiology*, 15, 325-332.

Esposito, G., Kirby, G. S., Van Horn, J. D., Ellmore, T. M., & Faith Berman, K. (1999). Context-dependent, neural system-specific neurophysiological concomitants of ageing: Mapping PET correlates during cognitive activation. *Brain*, 122, 963-979.

Evans, D. A., Hebert, L. E., Beckett, L. A., Scherr, P. A., Albert, M. S., Chown, M. J., Pilgrim, D. M., & Taylor, J. O. (1997). Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. *Archives of Neurology*, 54, 1399-1405.

Friedland, R. P. (1993). Epidemiology, education, and the ecology of Alzheimer's disease. *Neurology*, 43, 246-249.

Frost, J. A., Binder, J. R., Springer, J. A., Hammeke, T. A., Bellgowan, P. S., Rao, S. M., & Cox, R. W. (1999). Language processing is strongly left lateralized in both sexes. Evidence from functional MRI. *Brain*, 122, 199-208.

Galaburda, A. M., LeMay, M., Kemper, T. L., & Geschwind, N. (1978). Right-left asymmetries in the brain. *Science*, 199, 852-856.

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proceedings of the National Academy of Sciences of the United States of America*, 96, 8301-8306.

Garrett, H. E. (1946). A developmental theory of intelligence. *American Psychologist*, 1, 372-378.

Glisky, E. L., Polster, M. R., & Routhieux, B. C. (1995). Double dissociation between item and source memory. *Neuropsychology*, 9, 229-235.

Grady, C. L., Bernstein, L. J., Beig, S., & Siegenthaler, A. L. (2000a). The effects of encoding strategy on age-related changes in the functional neuroanatomy of face memory. *Manuscript submitted for publication*.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., Pietrini, P., Wagner, E., & Haxby, J. V. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *Journal of Neuroscience*, 14, 1450-1462.

Grady, C. L., McIntosh, A. R., Bookstein, F., Horwitz, B., Rapoport, S. I., & Haxby, J. V. (1998). Age-related changes in regional cerebral blood flow during working memory for faces. *Neuroimage*, 8, 409-425.

Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., Pietrini, P., Schapiro, M. B., & Haxby, J. V. (1995). Age-related reductions in human recognition memory due to impaired encoding. *Science*, 269, 218-221.

Grady, C. L., McIntosh, A. R., Horwitz, B., & Rapoport, S. I. (2000b). Age-related changes in the neural correlates of degraded and nondegraded face processing. *Cognitive Neuropsychology*, 217, 165-186.

Grady, C. L., McIntosh, A. R., Raja, M. N., Beig, S., & Craik, F. I. M. (1999). The effects of age on the neural correlates of episodic encoding. *Cerebral Cortex*, 9, 805-814.

Granick, S., Kleban, M. H., & Weiss, A. D. (1976). Relationships between hearing loss and cognition in normally hearing aged persons. *Journal of Gerontology*, 31, 434-440.

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension and aging: A review and a new view. *Psychology of Learning and Motivation*, 22, 193-225.

Hertzog, C., & Hultsch, D. F. (2000). Metacognition in adulthood and old age. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (2nd ed.) . (pp. 417-466). Mahwah, NJ: Erlbaum.

Honda, M., Nagamine, T., Fukuyama, H., Yonekura, Y., Kimura, J., & Shibasaki, H. (1997). Movement-related cortical potentials and regional cerebral blood flow in patients with stroke after motor recovery. *Journal of the Neurological Sciences*, 146, 117-126.

Horwitz, B., Duara, R., & Rapoport, S. I. (1986). Age differences in intercorrelations between regional cerebral metabolic rates for glucose. *Annals of Neurology*, 19, 60-67.

Iidaka, T., Sadato, N., Yamada, H., Murata, T., Omori, M., & Yonekura, Y. (2001). An fMRI study of the functional neuroanatomy of picture encoding in younger and older adults. *Cognitive Brain Research*, 11, 1-11.

Jonides, J., Marshuetz, C., Smith, E. E., Reuter-Lorenz, P. A., Koeppe, R. A., & Hartley, A. (2000). Brain activation reveals changes with age in resolving interference in verbal working memory. *Journal of Cognitive Neuroscience*, 12, 188-196.

Jonides, J., Smith, E. E., Marshuetz, C., Koeppe, R. A., & Reuter-Lorenz, P. A. (1998). Inhibition in verbal working memory revealed by brain activation *Proceedings of the National Academy of Sciences USA*, 95, 8410-8413.

Kahneman, D. (1973). *Attention and effort*. Englewood Cliffs, NJ: Prentice-Hall.

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology*, 43, 13-20.

Klingman, K. C., & Sussman, H. M. (1983). Hemisphericity in aphasic language recovery. *Journal of Speech & Hearing Research*, 26, 249-256.

Larisch, R., Meyer, W., Klimke, A., Kehren, F., Vosberg, H., & Muller-Gartner, H. W. (1998). Left-right asymmetry of striatal dopamine D2 receptors. *Nuclear Medicine Communications*, 19, 781-787.

Levitan, S., & Reggia, J. A. (1999). Interhemispheric effects on map organization following simulated cortical lesions. *Artificial Intelligence in Medicine*, 17, 59-85.

Li, S.-C., & Lindenberger, U. (1999). Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems and dedifferentiation of cognitive abilities in old age. In L.-G. Nilsson & H. J. Markowitsch (Eds.), *Cognitive Neuroscience of Memory* (pp. 103-146). Seattle, WA, US: Hogrefe & Huber Publishers.

Light, L. L. (1991). Memory and aging: Four hypotheses in search of data. *Annual Review of Psychology*, 42, 333-376.

Logan, J. M., & Buckner, R. L. (2001). *Age-related changes in neural correlates of encoding*. Paper presented at the Eighth Annual Meeting of the Cognitive Neuroscience Society, New York.

Madden, D. J., Gottlob, L. R., Denny, L. L., Turkington, T. G., Provenzale, J. M., Hawk, T. C., & Coleman, R. E. (1999a). Aging and recognition memory: Changes in regional cerebral

blood flow associated with components of reaction time distributions. *Journal of Cognitive Neuroscience*, 11, 511-520.

Madden, D. J., Turkington, T. G., Coleman, R. E., Provenzale, J. M., DeGrado, T., R., & Hoffman, J. M. (1996). Adult age differences in regional cerebral blood flow during visual word identification: Evidence from $H_2^{15}O$ PET. *Neuroimage*, 3, 127-142.

Madden, D. J., Turkington, T. G., Provenzale, J. M., Denny, L. L., Hawk, T. C., Gottlob, L. R., & Coleman, R. E. (1999b). Adult age differences in functional neuroanatomy of verbal recognition memory. *Human Brain Mapping*, 7, 115-135.

Madden, D. J., Turkington, T. G., Provenzale, J. M., Denny, L. L., Langley, L. K., Hawk, T. C., & Coleman, R. E. (in press). Aging and attentional guidance during visual search: Functional neuroanatomy by positron emission tomography. *Psychology and Aging*.

McIntosh, A. R., Sekuler, A. B., Penpeci, C., Rajah, M. N., Grady, C. L., Sekuler, R., & Bennett, P. J. (1999). Recruitment of unique neural systems to support visual memory in normal aging. *Current Biology*, 9, 1275-1278.

Meudell, P. R., & Greenhalgh, M. (1987). Age related differences in left and right hand skill and in visuo-spatial performance: their possible relationships to the hypothesis that the right hemisphere ages more rapidly than the left. *Cortex*, 23, 431-445.

Mitrushina, M., & Satz, P. (1991). Analysis of longitudinal covariance structures in assessment of stability of cognitive functions in elderly. *Brain Dysfunction*, 4, 163-173.

Mittenberg, W., Seidenberg, M., O'Leary, D. S., & DiGiulio, D. V. (1989). Changes in cerebral functioning associated with normal aging. *Journal of Clinical & Experimental Neuropsychology*, 11, 918-932.

Mortimer, J. A., & Graves, A. B. (1993). Education and other socioeconomic determinants of dementia and Alzheimer's disease. *Neurology*, 43, S39-S44.

Murphy, D. G. M., DeCarli, C., McIntosh, A. R., Daly, E., Mentis, M. J., Pietrini, P., Szczepanik, J., Schapiro, M. B., Grady, C. L., Horwitz, B., & Rapoport, S. I. (1996). Age-related differences in volumes of subcortical nuclei, brain matter, and cerebro-spinal fluid in healthy men as measured with magnetic resonance imaging (MRI). *Archives of General Psychiatry*, 63, 585-594.

Nagahama, Y., Fukuyama, H., Yamaguchi, H., Katsumi, Y., Magata, Y., Shibasaki, H., & Kimura, J. (1997). Age-related changes in cerebral blood flow activation during a card sorting test. *Experimental Brain Research*, 114, 571-577.

Nebes, R. D., Madden, D. J., & Berg, W. D. (1983). The effect of age on hemispheric asymmetry in visual and auditory identification. *Experimental Aging Research*, 9, 87-91.

Nelson, C. A., Collins, P. F., & Torres, F. (1990). The lateralization of language comprehension using event-related potentials. *Brain & Cognition*, 14, 92-112.

Netz, J., Lammers, T., & Homberg, V. (1997). Reorganization of motor output in the non-affected hemisphere after stroke. *Brain*, 120, 1579-1586.

Nielson, K. A., Langaneker, S. A., & Garavan, H. P. (2001). Differences in the functional neuroanatomy of inhibitory control across the adult lifespan. *Manuscript submitted for publication*.

Nolde, S. F., Johnson, M. K., & Raye, C. L. (1998). The role of prefrontal cortex during tests of episodic memory. *Trends in Cognitive Sciences*, 2, 399-406.

Nyberg, L., Cabeza, R., & Tulving, E. (1996a). PET studies of encoding and retrieval: The HERA model. *Psychonomic Bulletin & Review*, 3, 135-148.

Nyberg, L., Cabeza, R., & Tulving, E. (1998). Asymmetric frontal activation during episodic memory: What kind of specificity? *Trends in Cognitive Sciences*, 2, 419-420.

Nyberg, L., McIntosh, A. R., Houle, S., Nilson, L.-G., & Tulving, E. (1996b). Activation of medial temporal structures during episodic memory retrieval. *Nature*, 380, 715-717.

Obler, L. K., Woodward, S., & Albert, M. L. (1984). Changes in cerebral lateralization in aging. *Neuropsychologia*, 22, 235-40.

Ohshima, M., Senda, M., Kitamura, S., Ishii, K., Mishina, M., & Terashi, A. (1996). Role of the nondominant hemisphere and undamaged area during word repetition in poststroke aphasics. *Stroke*, 27, 897-903.

Ojemann, G. A. (1991). Cortical organization of language. *Journal of Neuroscience*, 11, 2281-2287.

Park, D. C., Davidson, N., Lautenschlager, G., Smith, A. D., Smith, P., & Hedden, T. (2000). Models of visuospatial and verbal memory across the adult life span. *Manuscript submitted for publication*.

Previc, F. H. (1991). A general theory concerning the prenatal origins of cerebral lateralization in humans. *Psychological Review*, 98, 299-334.

Price, C. J., & Friston, K. J. (2001). Functional neuroimaging of neuro-psychologically impaired patients. In R. Cabeza & A. Kingstone (Eds.), *Handbook of functional neuroimaging of cognition*. (pp. 379-399). Cambridge, MA: MIT Press.

Rastatter, M. P., & Lawson-Brill, C. (1987). Reaction times of aging subjects to monaural verbal stimuli: some evidence for a reduction in right-hemisphere linguistic processing capacity. *Journal of Speech & Hearing Research*, 30, 261-267.

Rastatter, M. P., & McGuire, R. A. (1990). Some effects of advanced aging on the visual-language processing capacity of the left and right hemispheres: Evidence from unilateral tachistoscopic viewing. *Journal of Speech & Hearing Research*, 33, 134-140.

Raz, N. (2000). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition (2nd ed.)*. (pp. 1-90). Mahwah, NJ: Erlbaum.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., Loken, W. J., Thornton, A. E., & Acker, J. D. (1997). Selective aging of the human cerebral cortex observed in vivo: Differential vulnerability of the prefrontal gray matter. *Cerebral Cortex*, 7, 268-282.

Raz, N., Torres, I. J., & Spencer, W. D. (1993). Pathoclysis in aging human cerebral cortex: Evidence from in vivo MRI morphometry. *Psychobiology*, 21, 151-160.

Reuter-Lorenz, P., Jonides, J., Smith, E. S., Hartley, A., Miller, A., Marshuetz, C., & Koeppe, R. A. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of Cognitive Neuroscience*, 12, 174-187.

- Reuter-Lorenz, P. A., Stanczak, L., & Miller, A. C. (1999). Neural recruitment and cognitive aging: Two hemispheres are better than one, especially as you age. *Psychological Science*, 10, 494-500.
- Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nature Neuroscience*, 3, 509-515.
- Rypma, B., Prabhakaran, V., Desmond, J. D., & Gabrieli, J. D. E. (in press). Age differences in prefrontal cortical activity in working memory. *Psychology and Aging*.
- Salthouse, T. A. (1996). The processing speed theory of adult age differences in cognition. *Psychological Review*, 103, 403-428.
- Salthouse, T. A., Hancock, H. E., Meinz, E. J., & Hambrick, D. Z. (1996). Interrelations of age, visual acuity, and cognitive functioning. *Journal of Gerontology: Psychological Sciences*, 51B, 317-330.
- Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for the threshold theory. *Neuropsychology*, 7, 273-295.
- Schacter, D. L., Savage, C. R., Alpert, N. M., Rauch, S. L., & Albert, M. S. (1996). The role of hippocampus and frontal cortex in age-related memory changes: A PET study. *Neuroreport*, 7, 1165-1169.
- Servan-Schreiber, D., Printz, H. W., & Cohen, J. D. (1990). A network model of catecholamines effects: Gain, signal-to-noise ratio, and behavior. *Science*, 249, 892-895.
- Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Constable, R. T., Skudlarski, P., Fulbright, R. K., Bronen, R. A., Fletcher, J. M., Shankweiler, D. P., Katz, L., et al. (1995). Sex differences in the functional organization of the brain for language. *Nature*, 373, 607-609.
- Shimamura, A. P. (1995). Memory and frontal lobe function. In M. S. Gazzaniga (Ed.), *The Cognitive Neurosciences* (pp. 803-814). Cambridge, MA: MIT Press.
- Silvestrini, M., Cupini, L. M., Placidi, F., Diomedi, M., & Bernardi, G. (1998). Bilateral hemispheric activation in the early recovery of motor function after stroke. *Stroke*, 29, 1305-1310.
- Silvestrini, M., Troisi, E., Matteis, M., Razzano, C., & Caltagirone, C. (1993). Correlations of flow velocity changes during mental activity and recovery from aphasia in ischemic stroke. *Neurology*, 50, 191-195.
- Smith, E. E., & Jonides, J. (1997). Working memory: a view from neuroimaging. *Cognitive Psychology*, 33, 5-42.
- Stebbins, G. T., Carrillo, M. C., Dorman, J., Dirksen, C., Desmond, J., Turner, D. A., Bennett, D. A., Wilson, R. S., Glover, G., & Gabrieli, D. E. (2000). Aging effects on memory encoding in the frontal lobes. *Manuscript submitted for publication*.
- Strauss, E., Kosaka, B., & Wada, J. (1983). The neurobiological basis of lateralized cerebral function. A review. *Human Neurobiology*, 2, 115-127.
- Thomas, C., Altenmuller, E., Marckmann, G., Kahrs, J., & Dichgans, J. (1997). Language processing in aphasia: Changes in lateralization patterns during recovery reflect cerebral plasticity in adults. *Electroencephalography & Clinical Neurophysiology*, 102, 86-97.
- Thulborn, K. R., Carpenter, P. A., & Just, M. A. (1999). Plasticity of language-related brain function during recovery from stroke. *Stroke*, 30, 749-754.
- Tulving, E. (1983). *Elements of Episodic Memory*. Oxford: Oxford University Press.
- Tulving, E., Kapur, S., Craik, F. I. M., Moscovitch, M., & Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proceedings of the National Academy of Sciences USA*, 91, 2016-2020.
- Tzourio, N., Crivello, F., Mellet, E., Nkanga-Ngila, B., & Mazoyer, B. (1998). Functional anatomy of dominance for speech comprehension in left handers vs right handers. *Neuroimage*, 8, 1-16.
- Volkow, N. D., Gur, R. C., Wang, G. J., Fowler, J. S., Moberg, P. J., Ding, Y. S., Hitzemann, R., Smith, G., & Logan, J. (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.
- Weiller, C., Isensee, C., Rijtsjes, M., Huber, W., Müller, S., Bier, D., Dutschka, K., Woods, R. P., Noth, J., & Diener, H. C. (1995). Recovery from Wernicke's Aphasia: A positron emission tomography study. *Annals of Neurology*, 37, 723-732.
- Weller, M. P., & Latimer-Sayer, D. T. (1985). Increasing right hand dominance with age on a motor skill task. *Psychological Medicine*, 15, 867-872.
- West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin*, 120, 272-292.
- Zacks, R. T., Hasher, L., & Li, K. Z. H. (2000). Human memory. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition (2nd ed.)*. (pp. 293-357). Mahwah, NJ: Erlbaum.