

New visions of the aging mind and brain

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Cognitive aging is widely viewed as a process of progressive mental loss. Compelling new evidence from functional neuroimaging urges a reconsideration of this pessimistic view. In the domains of working memory and episodic memory, older adults recruit different brain regions from those recruited by younger adults when performing the same tasks. Specifically, older adults show prominent changes in the recruitment of prefrontal regions, and a conspicuous increase in the extent to which activation patterns are bilateral. These results are stimulating new hypotheses about the mechanisms underlying age-related cognitive declines and the potential for compensation. By suggesting a life-long potential for reorganization and plasticity, these discoveries might revise long-held views of functional localization.

Until the early 1990s, the lesion model was the dominant approach to the neuropsychology of aging. The goal was to determine the neural underpinnings of cognitive aging by identifying the neurological-patient population(s) whose cognitive impairments most closely resembled the 'normal' elderly profile. This approach necessarily viewed aging as a deficit-laden trajectory where cognitive abilities and their neural substrates decline progressively. However, the recent surge of neuroimaging research on the neural bases of cognitive aging is breathing new life into the aging mind. Whereas behavioral indices paint a picture of old age that is generally slower and more error-prone than youth, neuroimages portray older brain function as complexly different from younger brain function, rather than a mere reduced or depleted rendition. Across a considerable range of tasks and cognitive domains, four important trends are emerging.

- (1) Neuroimaging reveals localized regions of task-specific underactivation in older adults compared with younger adults, providing new evidence about the neural substrates of cognitive decline.
- (2) Even when behavioral performance is matched, younger and older adults show different activation patterns, suggesting that they engage different brain areas to accomplish the same tasks.
- (3) Older adults show conspicuous bilateral activation under conditions that produce highly lateralized activity in younger adults.
- (4) Some senior-specific activation patterns are related to optimal performance, suggesting compensatory potential in the aging brain.

The cognitive neuroscience of aging, and neuroimaging of older adults in particular, is still in its infancy. Nevertheless, its start has been auspicious. Functional imaging of older adults is yielding new and exciting discoveries that might change

fundamentally our conceptualization of functional brain organization across the life span. This article reviews some of these new results with a particular emphasis on neuroimaging studies of memory – the cognitive domain most vulnerable to aging and the domain where recent research efforts have been most intense.

Comparing task-related brain activity in older and younger adults yields three possible outcomes: (1) age-equivalent activity, (2) age-related underactivation in which an area is less active in older than younger adults, and (3) age-related increased activation in which an area is more active in older than younger adults. Indeed, all three patterns have been reported, with multiple patterns occurring within the same dataset. Age-related underactivation should be the predominate outcome with fMRI if aging reduces the hemodynamic response or alters its coupling to neural activity. However, the prevalence of age-equivalent patterns and increased activation in older adults suggests that this is not the case [1,2]. Moreover, orderliness of the neuroimaging evidence is stimulating new, testable hypotheses about the neural bases of cognitive aging.

Neural correlates of age-related decline

There are now several important examples of tasks that older adults perform less well than young adults do and that produce age-related underactivation in the very brain regions that have been linked to proficient performance in young adults. Age-related underactivation often involves prefrontal cortex, a general pattern that converges with one of the major conclusions from the lesion model of aging [3–5].

Our laboratory has shown, for example, that activity in left inferior frontal gyrus (IFG, at the Brodmann's 44–45 boundary) increases when young adults must resolve conflicting response tendencies in a verbal working memory task [6,7]. Older adults encounter significantly greater conflict than their younger counterparts, as indicated by their poorer behavioral performance, and they seem to lack the neural correlate of this conflict resolution. Unlike young adults, older adults do not recruit this region of IFG when conflict is high (Fig. 1). The poor performance of older adults could result from underactivation of this brain region, an interpretation that is strengthened by evidence that focal damage involving IFG selectively impairs performance in the high conflict condition [8]. Our ongoing efforts to

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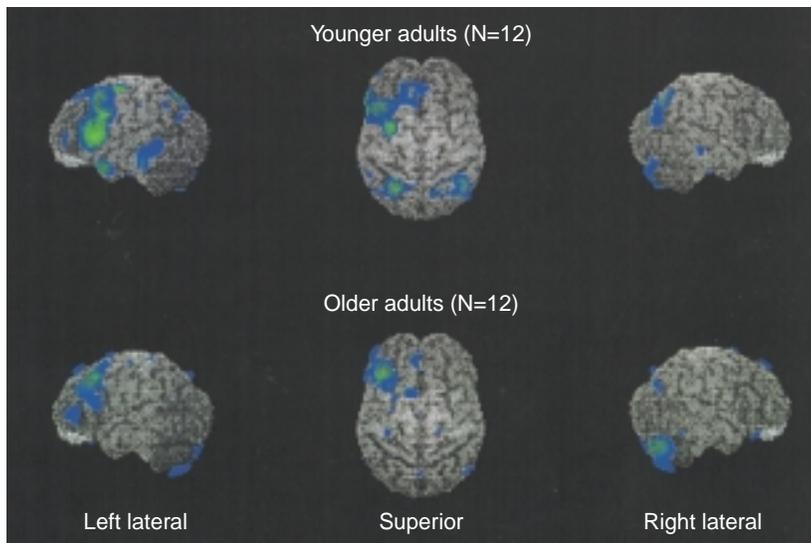


Fig. 1. Difference images for younger and older adults from the subtraction of the low conflict condition from the high conflict condition in Ref. [6]. The younger adults activate an inferior region of left prefrontal cortex that is not activated by older adults performing the same verbal working memory task. This age-related underactivation is associated with poorer performance by older adults in the high conflict condition. When the high or low conflict conditions are compared with the minimal-memory control condition (not shown), older adults have bilateral prefrontal activation whereas for younger adults the activation is left lateralized (see Ref. [23] and Box 1).

characterize the function of left IFG, including its possible role in age-related inhibitory deficits [9], should yield further insight into the cognitive operations that might be particularly vulnerable to aging.

Studies of episodic memory offer other rich examples of focal age-related underactivations that might reveal why older memory sometimes fails [10]. In the basic task, participants study a list of items (e.g. words or faces) and then perform a recognition test after a delay of several minutes. Here older adults usually remember fewer items than younger adults do and their brains behave differently as well. When studying words, younger adults recruit an anterior ventral region (BA 45/47) and a more posterior dorsal region (BA 6/44) of left prefrontal cortex. Face encoding activates an additional right prefrontal site (BA 6/44). Indeed, activation in these prefrontal areas during encoding predicts that an item will subsequently be remembered. Several laboratories have reported significantly weaker encoding-related activations in older adults, suggesting that prefrontal underactivation contributes to age-related declines in episodic memory [10–16].

Although the cause of age-related left prefrontal underactivation is currently uncertain, there are some tantalizing possibilities. For example, when younger adults study word pairs while performing an auditory discrimination task, they show reduced left prefrontal activity that resembles the underactivation seen in older adults [17]. This result suggests that aging might deplete attentional resources much like divided attention does in younger adults [18]. The resource-reduction hypothesis, originally proposed

by Fergus Craik and his collaborators [19], suggests that the proper cognitive strategies could recruit sufficient resources to ameliorate the effects of aging. Some behavioral evidence bears this out. Engaging in elaborative encoding, for example by making animacy judgements, improves aging memory and can sometimes reduce age differences in performance [20]. Moreover, providing this kind of 'environmental support' for aging memory can lead to greater activation of prefrontal regions, resulting in near age-equivalent activation levels in some studies (Fig. 2; see also [11, 15]). Thus, older adults can activate the requisite brain regions and engage in effective semantic processing when given the appropriate strategies [12, 16]. However, their failure to self-initiate elaborative encoding is associated with under-recruitment of left prefrontal areas that have been linked to successful memory in younger adults.

Importantly, however, providing strategies to improve aging memory does not simply make brain activity young again. Under conditions that equate younger and older performance, age differences in brain activity are still apparent.

Older brains process differently

Neuroimaging reveals that older brains do things differently, even when performance is comparable to that of younger adults. In their pioneering work Cheryl Grady and colleagues obtained PET measurements while older and younger adults matched faces or locations [21]. Although older adults were slower, accuracy levels were equivalent and accompanied by pronounced age differences in brain activation: older adults activated dorsal (parietal) and ventral (temporal) sites for both tasks, whereas younger adults showed the expected ventral activation for faces and dorsal activation for locations. Furthermore, evidence for more widespread activation in older adults continues to emerge, particularly in studies of memory.

We studied spatial working memory by having participants remember the locations of three dots that appeared on a screen for 0.5 s [22]. Three seconds later, a probe circle appeared and the participant indicated whether it encompassed one of the remembered locations. We compared the brain activity in groups of older and younger adults who performed this task with equal accuracy (~ 90% correct). Both groups activated regions of left and right parietal cortex that are associated with spatial processing. In addition, younger adults activated a network of right frontal regions, including supplementary motor cortex (BA6), ventral prefrontal cortex (PFC, BA 47) and dorsolateral PFC (DLPFC, 46/9), that have been associated with rehearsal of spatial information. Older adults activated these right frontal regions along with a homologous network of left hemisphere sites. Thus, older adults engaged more brain regions compared with younger adults performing the same task.

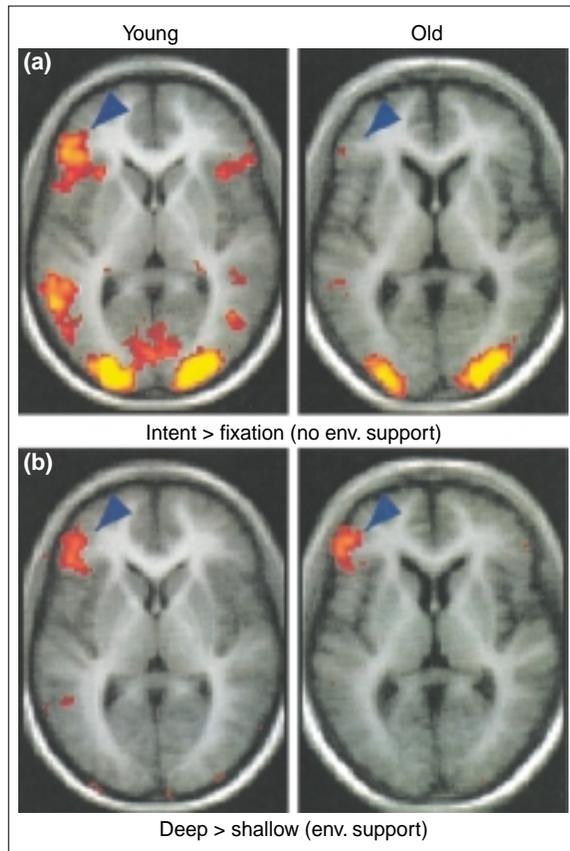


Fig. 2. The blood oxygenation-level dependent (BOLD) response of younger and older adults in two encoding conditions from the second experiment reported by Logan *et al.* [16]. (a) The left prefrontal underactivation of older adults in the encoding phase of a memory task. They were instructed to study words for subsequent recognition, but not given any explicit strategy (environmental support) for encoding the words. (b) Older adults can activate this brain region when given environmental support in the form of instructions to process the words semantically. Age differences in performance and activation patterns were reduced by providing this support.

An analogous study of verbal working memory showed complementary results: younger adults activated a highly lateralized network of left hemisphere areas, whereas older adults activated regions in both hemispheres, including DLPFC sites that were less active in the younger group [22]. This tendency for older adults to have greater bilateral activation is an important trend observed in several recent neuroimaging investigations (see Box 1, Fig. 1).

Interpreting the significance of activation patterns that are unique to older adults is one of the important challenges facing cognitive neuroscience research on aging. Perhaps older adults use different cognitive strategies than their younger counterparts. Yet, to date, debriefing protocols and error patterns offer no definitive support for this possibility in our working memory studies or in those from other laboratories [22–25]. Similarly, comparable semantic clustering strategies emerged in a verbal list learning task that yields age-specific activation patterns [26]. Moreover, McIntosh and colleagues reported age-specific activation patterns during a perceptual

matching task that minimized strategy variations by using sine-wave gratings of varying frequency [27]. Threshold setting ensured age-equivalent performance, whereas brain images revealed different neurocognitive routes for younger and older adults. Both groups activated the same basic network, but older adults uniquely recruited medial temporal and DLPFC areas. Measures of network activation correlated positively with performance, suggesting compensatory contributions in the older group.

This is not to say that older and younger adults always use similar strategies – in fact, they do not, as evidenced by the failure of older adults to engage elaborative encoding without environmental support. When this support is provided, age-equivalent activation sometimes results, for example in left inferior PFC regions for a verbal memory task. However, some age-related activations seem to be unaffected by strategy change. For example, Logan and colleagues report right frontal activation that is unique to older adults and evident regardless of whether they engaged in semantic processing [16]. Rather than reflecting strategy variations, this right frontal activation seems to be characteristic of older brains engaged in episodic encoding.

Could it be compensation?

Age-equivalent performance accompanied by age-specific activation patterns emerges when older adults are selected because of their high performance or when task demands are appropriately adjusted. One provocative interpretation of this disparity between behavior and neural activity is that regions uniquely recruited by older adults are serving a ‘compensatory’ function. In particular, additional brain regions might be brought on-line in older adults to mediate task-relevant cognitive operations and enable optimal performance [13,28–29]. The compensatory-recruitment hypothesis underscores the potential for brain plasticity over the life span.

Although compensatory recruitment in aging is one of several possible interpretations, there is evidence in its favor. At least three reports find that age-related overactivation is correlated with higher performance among the older subsample [23,27,30]. Furthermore, one recent study examined encoding-related activation patterns that predict subsequent ‘successful’ memory in younger and older adults [31]. As expected, left prefrontal activity predicted subsequent memory in young adults. For older adults, left and right prefrontal activity predicted subsequent memory. Similarly, older adults classified as high performers with standard memory indices show greater frontal bilaterality on a source memory task compared with low performers [32]. These results are consistent with the compensatory-recruitment hypothesis and challenge the idea that additional recruitment adversely affects performance.

The compensatory-recruitment hypothesis provokes the question of what the older brain is

Box 1. Laterality and brain aging

The lateralization of cortical functions is a prominent yet poorly understood characteristic of human brain organization. Although hemispheric specialization develops from infancy through adolescence, it is clearly present at birth [a]. Thus new evidence that lateralization changes in later life is both startling and provocative.

The idea that laterality holds clues to aging is not a new one: for several decades, disproportionate aging of the right hemisphere was a leading account of cognitive decline [b]. Nevertheless, the new evidence distinguishes itself from that original hypothesis in important ways. First, age-related bilaterality characterizes processes that are right lateralized in younger adults, in addition to those that are left lateralized. Our neuroimaging results from analogous verbal and spatial working memory tasks clearly illustrate that age-related bilaterality is reciprocal: for young adults (ages 18–25) the verbal task activated a network of left frontal areas, whereas the spatial task activated a right frontal network [c]. Older adults (ages 62–73) activated a bilateral, and in some respects indistinguishable, frontal network for both tasks.

In an excellent review [d], Roberto Cabeza described the bilaterality trend evident in this and other studies as hemispheric asymmetry reduction in older adults (or HAROLD) (Fig. 1). Future research will determine whether any

asymmetries exist in the lateralization of processes for which older adults activate bilaterally. For example, studies of early childhood lesions suggest greater plasticity for language than spatial abilities [e]. Should similar constraints operate in later life, the patterns of age-related compensation and decline might prove to be asymmetrical.

A second important distinction is that increased bilaterality is not simply a correlate of cognitive decline. The pattern emerges even when age differences in performance are minimized. However, age differences in speed often persist despite comparable accuracy levels. Longer processing times could result if the elderly rely on a more distributed neural network. Nevertheless, there are a host of reasons for proposing that, at least in some task contexts, bilaterality is a good thing (see main article). In addition, there are clear indications that homologous cortical loci show greater than normal recruitment and might contribute to recovery of function following brain damage [f,g]. Latent potential of the nonspecialized hemisphere might be a source of neural resilience across the life span.

The advantages of bilateral processing are evident in the younger brain as well. Using divided-visual-field studies, Marie Banich and her collaborators show that as task demands increase, performance is optimized when the left and right hemispheres are engaged in the

task [h,i]. We also found this result in older adults, but at lower levels of task complexity than young adults [j]. This pattern suggests that greater bilaterality is associated with greater resource demands and more cognitive effort for older adults compared with younger adults performing the same tasks.

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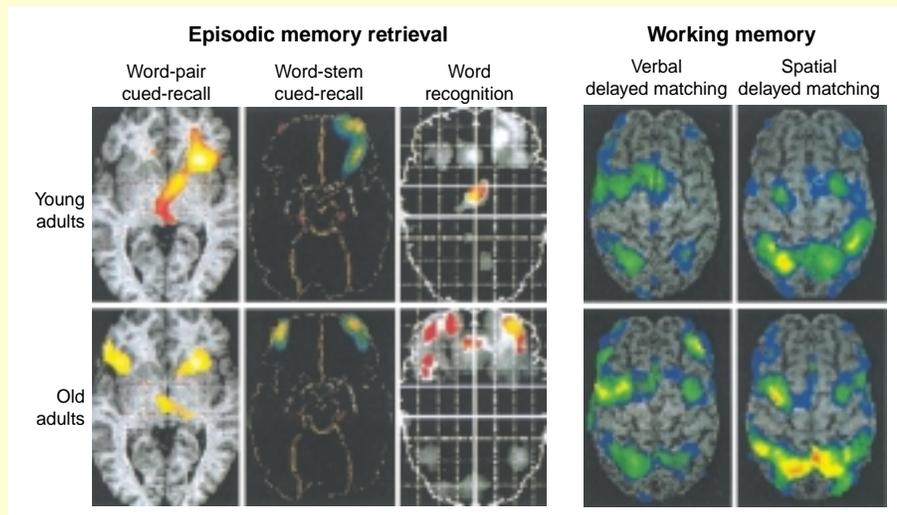


Fig. 1. Results from four neuroimaging studies included in a recent review by Cabeza [d] that examined age differences in episodic or working memory. Across all the experimental conditions, there is lateralized activity, especially in anterior brain regions, in younger adults, and bilateral activity under the same task conditions in older adults [c,k–m].

compensating for. One straightforward idea is that new areas are brought on-line to compensate for declines in other areas. Opposing this possibility, age-related overactivation is not always accompanied by underactivation in other brain regions [16,22]. However, declining neural efficiency might not be detectable by current scanning measures. A related possibility is that additional sites are recruited because older adults encounter more difficulty and expend more effort on tasks

compared with younger adults. Indeed, at a general level, the additional recruitment evident in older brains resembles the response of younger brains to increased task difficulty. For example, increased working memory load can increase activation in homologous sites, resulting in a more bilateral pattern of brain activity [33,34]. In working memory tasks and other tasks as well, increased difficulty can recruit additional brain regions [35–39]. Older adults show both patterns.

Box 2. Computational models of neurocognitive aging

The emergence of new computational models of aging that are neurobiologically informed is a clear sign that the cognitive neuroscience of later life is coming of age. These new models go beyond previous formal models by proposing explicit neural mechanisms to account for the effects of aging on performance. Li *et al.* [a] describe a neural network model that simulates the well-documented decline in dopaminergic modulation that accompanies normal aging. The consequence in their model is increased neural noise and a corresponding decrease in the distinctiveness of representations. Their simulations capture important features of aging performance including declines in learning rate and increased susceptibility to interference.

In a related model, Braver and his colleagues [b] posit that age-related decline in the prefrontal dopamine system is the neural substrate underlying decreased processing of contextual information in older adults. In their view, contextual processing is critical to implementing cognitive control and its decline has far-reaching effects on the functional integrity of cognition in the aging brain. This model is informed by neuroimaging evidence demonstrating the effects of contextual cues on cognitive control in younger adults and makes explicit, testable predictions about the behavioral and neuroimaging consequences of aging.

Cognitive aging will be further elucidated by the recent extension of the executive-process interactive control (EPIC) model to older adults [c]. This unified computational theory proposes to distinguish hardware versus software changes in aging and can be fruitfully applied to cognitive neuroscience investigations of aging.

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For example, young adults show increased activity in DLPFC when working memory tasks include contextual coding and scheduling demands. DLPFC activity also increases with increasing memory load or retention interval. We find that older adults recruit DLPFC for working memory tasks that do not activate this area in younger adults [23]. We surmise that older adults engage executive processes to optimize the maintenance of items in working memory. Furthermore, compensatory recruitment of DLPFC might have a cost: when executive control is explicitly required, as in task switching, recruitment of DLPFC to mediate maintenance leaves fewer neural resources available to mediate other executive demands [40,41]. Consequently, older adults show a disproportional decline on some executive processing tasks, whereas performance on simple storage tasks is relatively spared.

Could it be dedifferentiation?

Dedifferentiation refers to the proposal that aging reverses the trend toward increasing specialization of neural systems that characterizes early development [42]. The dedifferentiation hypothesis was invoked to explain the increasing correlation among diverse behavioral and sensory performance measures across the life span [43]. In the brain-imaging domain, dedifferentiation might explain the tendency of older adults to recruit additional areas of activation. The prevalence of bilateral rather than lateralized activity in older adults invites the notion of dedifferentiation. In contrast with the compensatory

view of additional activation, dedifferentiation implies a breakdown in the optimal state of neurological organization. Both processes could be occurring and they could be causally related: compensation could lead to dedifferentiation or vice versa [29]. A future challenge is to determine when age-related activation patterns signal compensation, declining functional specialization, or some combination.

Another variant of the dedifferentiation hypothesis is reminiscent of an idea originally proposed by Marcel Kinsbourne [44]: age-related overactivation is nonselective, reflecting a reduced ability to achieve task-relevant focal activation and to suppress task-irrelevant areas. One particularly clear example of this pattern comes from a PET study of 41 volunteers, aged 20–80 years, performing the Wisconsin Card Sorting Task [45]. The steady performance decline across this age range was accompanied by a progressive decrease in activation of left DLPFC, inferior parietal cortex, anterior cingulate, and cerebellum. These age-related decreases co-occurred with increasing activation in polar frontal cortex and right parahippocampal gyrus – areas that were deactivated by the higher performing young members of this sample.

Buckner and his colleagues [16,46] have proposed that nonselective recruitment indicates altered connectivity and possibly decreased inhibition between brain areas. Indeed, altered regional interactions are found in the aging brain. Analyses that intercorrelate activations among brain areas invariably reveal changes in the patterns of functional connectivity with age [27,45–48]. Understanding these changes might be essential to understanding age differences in regional activation. Functional interconnections found in younger adults are typically weaker in older adults [27,47–48]. The functional networks of older adults include additional regions or comprise altogether different patterns of interconnectivity compared with those in younger adults. However, the functional significance of these changes is uncertain because they arise even with age-matched performance and they can be associated with optimal performance [27].

Altered regional connectivity can also be assessed with behavioral measures of interhemispheric information transfer, and with diffusion tensor imaging, which assesses the integrity of white matter. This latter technique revealed that white matter loss in older adults correlated with poor performance on the trails B task – a measure of executive switching ability [49]. In addition, several laboratories have documented age-related declines in interhemispheric transmission using simple visuomotor tasks [50,51]. However, on more demanding cognitive tasks, such as letter identity matching, older adults perform optimally when interhemispheric interactions are required [29,51]. Thus, the available evidence indicates that although aging alters regional

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Questions for future research

- Do age-specific activation patterns, including bilaterality, emerge gradually across adulthood, and differ in 'young-old' versus 'old-old' adults?
- What functions correspond to region-specific underactivations and overactivations in older adults?
- Is age-related asymmetry reduction or dedifferentiation a property of all sensory, motor and cognitive domains, or is either tendency restricted to higher cognitive operations?
- Do some neural circuits possess greater equipotentiality and compensatory capacity than others?
- Do particular cognitive or neural factors promote compensation and at what cost?
- Is there a 'neural reserve' that can be brought on-line across the life span?

connectivity, these changes are not necessarily detrimental to performance. Some alterations in connectivity might result from normal age-related neurobiological declines, whereas others might reflect neurocognitive compensation for such declines.

Closing remarks

Cognitive neuroscience methods are generating exciting new evidence about the aging mind and brain. Several provocative hypotheses have already emerged about the mechanisms of cognitive decline and the possibility of compensation in later life. Although speculative, these hypotheses are testable. The problem of aging is clearly fertile ground for interdisciplinary convergence of biological, neurological, behavioral, and computational approaches (Box 2). The next decade of cognitive neuroscience promises to yield valuable new insights into the mechanisms of normal aging. Studies of aging will continue to raise important questions about the structure of the cognitive system, its variation among individuals, and the life-long potential for plasticity, compensation, and neurocognitive reorganization.

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