Nat Rev Neurosci. Author manuscript; available in PMC 2013 October 19.

Published in final edited form as:
Nat Rev Neurosci. ; 13(7): 491–505. doi:10.1038/nrn3256.

Trends in Neurocognitive Aging

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Preface

The availability of neuroimaging technology has spurred a marked increase in the human cognitive neuroscience literature, including the study of cognitive aging. Although there is a growing consensus that the aging brain retains considerable plasticity of function, currently measured primarily by means of functional magnetic resonance imaging, it is less clear how age differences in brain activity relate to cognitive performance. The field also is hampered by the complexity of the aging process itself and the large number of factors that are influenced by age. In this review, current trends and unresolved issues in the cognitive neuroscience of aging are discussed.

Introduction

Age differences in cognitive function have been studied for many years, and it is well-established that older adults have particular difficulty with episodic memory, defined as the conscious recollection of events[1]. In the laboratory, these age differences in episodic memory are manifested by a reduced ability to learn and retrieve both non-verbal and verbal material, such as a list of words[2]. Substantial age-related differences also are seen in tasks involving working memory[3,4], attention[5–7], and task switching[8–10], all of which can be considered as types of high level "executive" functions. Older adults also are more susceptible to the effects of distracting interference during cognitive tasks[11,12] and have generally slower processing speed[13]. Nevertheless, some aspects of cognition are maintained with age, such as semantic memory, or the accumulation of knowledge about the world[14,15], and emotional regulation[16,17]. In addition, age differences in cognition are not immutable; for example, the experimental conditions under which memory is studied in older adults can be modified so that age differences are reduced or eliminated[18]. A challenge in this field has been to understand the brain mechanisms that might underlie better or worse performance in old adults.

It is on this challenge that functional and structural neuroimaging studies of aging have focused, and in the past decade functional magnetic resonance imaging (fMRI) studies have provided ample evidence of age differences in task-related brain activity[19,20]. However, the interpretation of these differences is difficult, as sometimes brain activity is reduced in older relative to younger adults, and sometimes it is increased. Decreased brain activity has typically been interpreted as a reflection of cognitive deficits in older adults[21], and increased activity has often been interpreted as compensatory[22]. However, other mechanisms may also explain age-related increases of brain activity, including a lack of efficiency in the utilization

of neural resources, or a reduction in the selectivity of responses, known as dedifferentiation[23].

Another issue is how brain activity is related to other aspects of brain aging, such as changes in structure (volumes or white matter myelination, for example), or neurotransmitters. There also is the question of how age differences in brain function might be affected by undetected neuropathological changes due to dementing illnesses. That is, some otherwise healthy older adults might eventually be diagnosed with Alzheimer's disease (AD), and the "silent" pathological processes in their brains might account for some of the age differences reported in the literature. The purpose of this review is to cover some recent developments in the field that address these longstanding issues and to discuss some interesting new trends in this area of research.

Before reviewing this work on cognitive aging and the brain, it is important to note that there is general consensus that the blood oxygen level dependent (BOLD) signal obtained from fMRI is a reasonable, although indirect, index of neural activity, especially the synaptic activity reflected in local field potentials[24,25]. In regard to the use of fMRI to study aging, peak stimulus-related BOLD responses are similar in young and older adults,[26–28] although some work has shown that the magnitude of the BOLD response can be reduced in older adults, at least in some brain regions[29]. In addition, it is important to keep in mind that there are alterations in the cerebral vasculature with age, and these have the potential to influence the BOLD signal in as yet unknown ways[30,31]. Alhough much remains to be done to understand the impact of aging on the physiology underlying the BOLD signal, the relatively small age differences noted in the properties of these signals and recent work suggesting a small vascular contribution to BOLD signals in older adults during cognitive tasks[32] encourage the continued use of this technique to study cognitive aging.

Compensation in the Older Brain

An early idea in the literature was that older adults (i.e., those above the age of 65) might be able to engage some brain areas above the level seen in younger adults (in their 20's), particularly the frontal lobes, to compensate for impaired function elsewhere in the brain [22]. In these early studies, older adults were noted to have more activity in prefrontal cortex (PFC) during memory tasks relative to younger adults[33–35], which was thought to compensate for reduced activity in visual processing regions[22,36] (a phenomenon recently termed the posterior-anterior shift with aging, or PASA[36]). This PFC activity was often bilateral in the older adults on tasks for which younger adults typically showed unilateral PFC activity, leading to the idea that the increased bilaterality of PFC activation in older adults reflects a compensatory mechanism that can aid cognitive performance[37].

A compensatory interpretation is often invoked when older adults show more activity in a brain region than younger adults whilst they perform a task at the same level as younger adults[38], or when increased activity is positively correlated with performance in older adults, but not younger adults[35,36,39–41]. Several researchers have suggested that compensatory mechanisms might still play a role even if performance in older adults is impaired[42]. For example, increased activity in an older adult might not be associated with preserved

performance on a given task to the level seen in a young adult, but this performance might be even worse without the over-recruitment. Thus, despite the continued attention that this idea has received, it is still not clear exactly which regions might act in a compensatory manner or under which conditions this might occur[43,44].

Several recent papers have provided further evidence in favor of the compensatory hypothesis. One examined age differences in inhibition using a series of tasks that assessed the ability to inhibit prepotent responses[45]. Older adults displayed more activity in a set of dorsal PFC and parietal regions, sometimes called the dorsal attention network[46,47], compared with younger adults. Importantly, activity in these attention-related regions correlated with better inhibition only in older adults. This result is consistent with the idea of a compensatory mechanism whereby additional activity in task-relevant regions increases the ability of older adults to carry out the task. Similarly, another experiment examined face perception[48] and found a set of regions in right PFC and occipital cortex where increased activity was associated with better face recognition in older adults, but not a younger group. Furthermore, in a task requiring attention to right and left visual fields[49], only old adults showed increased activity in bilateral PFC that was positively correlated with better performance. Interestingly, studies using transcranial magnetic stimulation (TMS) also have provided some support for the idea that increased bilateral PFC activation is beneficial for performance in older adults. Two studies have shown that using TMS to reduce activity in either the left PFC during encoding or the right PFC during retrieval reduces memory performance in younger adults, but has less effect in older adults, presumably because the unstimulated hemisphere can support the function when the other is inactivated [50,51]. Therefore, these studies all suggest that older adults can recruit higher levels of brain activity than young adults, often in the PFC, and that this additional activity can aid performance of the old adults who are best able to engage it.

By contrast, other work has provided evidence that over-recruitment of brain activity does not necessarily lead to better task performance. For example, some researchers[42,52,53] have suggested that when performance is matched between age groups, over-recruitment reflects less efficient use of neural resources in the older group, not compensation. In addition, more activation in old adults can sometimes be associated with poorer, not better, performance[54]. Recent studies have reported greater activity in the PFC during memory encoding[55] or retrieval[56] in older adults, both of which were correlated with poorer memory. Similarly, higher activity in a distributed set of regions, including PFC and parietal cortex, in old adults compared to young adults[57,58] was found to be correlated with slower and more variable reaction times on a set of visual tasks. To complicate matters further, some of these regions associated with slower responses in older adults are very similar to the fronto-parietal regions reported to support better inhibitory function in older adults[45] (see above), suggesting that the association between activity in a given brain region and performance in older adults is task specific, response specific (e.g., accuracy vs. response time), or both (Figure 1).

Together, these results suggest that increased activity in older relative to younger adults can be associated with better performance on some tasks, but that this additional activity is not always compensatory (in the sense that it is directly related to better task performance). In

some cases, over-recruitment of brain areas may reflect a greater demand on neural resources or less efficient use of them, and may or may not be related specifically to individual differences in behavior. One explanation for this is the 'partial compensation hypothesis'[55], whereby over-recruitment of the right PFC during memory encoding may aid old adults in carrying out the encoding task because of less effective use of the left PFC, which would normally carry out this task [21,59,60]. However, this additional right PFC activity during encoding cannot compensate for a reduction in encoding effectiveness of the left PFC, and so does not provide a benefit for subsequent memory of the encoded items. This is similar to the idea that over-recruitment might help cognition in a general way, but may not be related to performance on a specific task[42]. Regardless, the papers cited in this section indicate that one should be careful about interpreting age increases in brain activity as compensatory without sufficient evidence from behavior to support such an interpretation.

Potential explanations for compensatory activity

One idea is that older adults shift from proactive strategies early in a decision process to reactive strategies that occur later. Support for this idea was reported in an experiment[61] that found PFC activity in young adults during the early phase of memory retrieval trials, and PFC activity in older adults that occurred later in time. Another experiment examining task switching found that younger adults showed sustained PFC activity throughout the period in which they had to switch between tasks, whereas older adults showed transient increases to cues indicating that a switch was required[62]. This pattern suggests that cognitive control is engaged differently with aging, and also supports the notion of a shift from proactive control to a more reactive strategy that occurs in response to task demands. A similar proactive/reactive age difference was reported for the medial temporal lobes (MTL) in older adults during a memory task[63]. Younger adults had more activity in these regions during preparation for memory retrieval, whereas older adults showed more activity during retrieval. These studies suggest that a shift in the timing of resource engagement is required to deal with the influence of age on proactive strategies that make these less effective or accessible, and that compensation in aging may have a temporal component to it.

Another idea to explain compensatory activity is the 'Compensation-Related Utilization of Neural Circuits hypothesis', or CRUNCH[64]. The idea of CRUNCH is that more neural resources are recruited by older adults at low levels of cognitive load, i.e., when tasks are easier, than in younger adults, who don't need them[53]. At higher levels of load, this compensatory mechanism is no longer effective, leading to equivalent or less activation in older adults relative to young. Data consistent with this idea have been reported in PFC[65], and in both PFC and parietal cortex[66,67] during working memory tasks that varied in the number of items that had to be kept in mind. In these studies, older adults had more activation at low levels of working memory load, where performance was equivalent to that of younger adults, but less activity and lower accuracy at higher loads. This kind of result also has been found during episodic memory tasks[68]; younger adults showed recruitment of bilateral PFC during a difficult version of the memory task, whereas older adults showed activation of these areas for both easy and difficult versions of the task. All of these studies are consistent with CRUNCH (Figure 2), which suggests that the relationship between brain activity and cognitive load is "S" shaped and plateaus at higher levels of load regardless of

age. The older adult curve would be shifted to the left relative to younger adults, such that older adults would have greater brain activity at lower levels of load, and reach their plateau at levels where younger adults are still able to increase their brain activity. According to this hypothesis, old adults engage neural resources, such as the PFC, at lower task loads to compensate for less effective use of these resources, or perhaps because of degraded input to the PFC[64], thus shifting the curve leftward. Although this idea has considerable appeal, and may be able to account for both the age-related increases and decreases of brain activity described in the literature, it is not clear if one would need to see recruitment of a unique region in older adults in order to interpret this activity as compensatory. That is, the engagement at lower load of the same region active in younger adults at higher loads might reflect an increase in the "normal" inter-individual variability in the brain/load function that must exist even in young adults, rather than compensation per se.

Dedifferentiation

The concept of dedifferentiation was originally proposed to explain the increased correlations among behavioral measures in older adults[69], but was adopted by neuroimagers because it also seemed to characterize brain activity in older adults. Early examples included bilateral prefrontal activity associated with abilities that typically yield lateralized activity in younger adults[37,70], more diffuse activation patterns[71], and less selective activity in task-relevant regions across a variety of tasks[22,72,73]. Like the idea of compensation, dedifferentiation continues to be a viable explanation for some age differences in brain activity.

One way to investigate dedifferentiation is to compare the patterns of activity across tasks to see if they are more similar, i.e., less selective, in older adults. This kind of result was found in an experiment contrasting implicit memory for a sequence of repeated visual stimuli to explicit memory for a list of words[74]. Young adults showed more activity in the hippocampus for explicit learning, and more activity in the striatum for implicit learning. Older adults showed equivalent activation in these regions during the two tasks. Another experiment[75] also found that implicit memory in younger adults was accompanied by increased activity in striatum and decreased activity in the hippocampus, whereas older adults showed increases in both. Simlarly, older adults are reported to have less distinctive activity in the visual cortex during perception and working memory tasks[76,77]. In both kinds of task, old adults had less distinctive patterns of activity in occipital cortex than young adults, consistent with dedifferentiation. Interestingly, distinctiveness in PFC and parietal regions was higher in old adults compared to young adults, which was interpreted as compensation. In another study [78], young adults were found to have unique patterns of activity during retrieval of three different kinds of memory content: autobiographical (personally relevant), episodic (not personally relevant but related to stimuli seen during the experiment) and semantic memory (world knowledge). These included activity in the MTL for autobiographical retrieval, dorsolateral PFC and parietal regions during episodic retrieval, and left temporal cortex during retrieval of semantic memories. These patterns of activity were also seen in old adults, but were less distinct for the autobiographical and episodic conditions, consistent with reported age differences in autobiographical and episodic memory but maintained, or even increased, semantic memory with age. Finally, less

selective responses to specific categories of visual stimuli also have been reported[79], and are associated with measures of task switching and working memory in old adults[80]. Thus, all of these studies indicate that young adults have activation patterns that are typically quite selective for the particular stimulus features or task demands involved, whereas in older adults activation can be much less distinct, consistent with the idea of dedifferentiation across cognitive processes. These studies further suggest that the loss of selective brain responses may be a marker of a more general cognitive disruption.

Another way to assess dedifferentiation is to use adaptation, which is a reduction in the response of a given brain region, or regions, when a stimulus is presented repeatedly, relative to the first presentation[81]. Several recent studies have used this method to look at selectivity of brain responses in aging. One assessed activity in the region of the brain that is most responsive to faces, the Fusiform Face Area, or FFA[82] to faces that were the same, that had been morphed by varying amounts (similar), or that were different[83]. Young adults showed more FFA activity during presentation of morphed faces than for the same face shown repeatedly, indicating that the FFA treated morphed faces as “different” even though they were relatively similar to each other. In contrast, the older adults showed equivalent activity for same and morphed faces. Moreover, discrimination thresholds for distinguishing same from different faces were correlated with the degree of adaptation in the FFA across younger and older adults, indicating that this adaptation was important for behavior. A similar study[48] assessed adaptation in the FFA during presentation of faces that also varied in viewpoint (right/left orientation). Young adults showed the least activity when the same face was seen in the same viewpoint, more activity when the face or the viewpoint changed, and the most activity when both the face and viewpoint changed. Older adults showed no differences in activity in FFA across the conditions, and performed worse than young adults on a face-matching task involving changes in viewpoint. Adaptation in the auditory domain also has been examined[84], and, like visual adaptation, is seen more prominently in younger than in older adults. These experiments show that when adaptation is used to examine differentiation of responses in regions of cortex that respond to specific features of stimuli, regardless of modality, older age is associated with dedifferentiation of responses that are relatively selective in younger adults. Furthermore, this loss of selectivity may be associated with decrements in the ability to discriminate similarities and/or differences among these stimuli.

Brain Networks and Functional Connectivity

Cognitive neuroscientists are becoming increasingly interested in assessing the integrated activity among groups of brain regions as a way of defining brain networks (Box 1). One way of doing this is to measure the functional connectivity of a given brain region or set of regions[85,86]. Several recent studies have looked at specific functional connections during a task, and how these are affected by age. One study examined changes in brain activity during a working memory task with varying degrees of difficulty[87] and found that young adults had load-dependent increases of activity in PFC. Older adults showed relatively high levels of PFC activity across all load levels (consistent with CRUNCH, see above), and weaker functional connectivity between the premotor cortex and a left dorsolateral PFC region. Another study addressed age differences in the resolution of interference during

working memory for scenes using a delayed match-to-sample task[88]. Interference was introduced by presenting a face during the delay period and asking participants to make a gender and age judgment about it. Connectivity was measured between a brain region that responds preferentially to scenes, (the parahippocampal place area, or PPA[89]) and a region of PFC thought to be important for resolving interference. In young adults, the correlation between activity in the PPA and PFC was disrupted when the face was presented, but returned to pre-interruption levels after the face was removed, suggesting that the resumption of PPA-PFC functional connectivity resolved the interference effect. Older adults showed a similar disruption of PPA-PFC functional connectivity, but the effect persisted after the face was removed, suggesting a deficient ability to dynamically modulate network connectivity, consistent with the poorer performance of the older adults on the task in the presence of the interfering face. Both of these studies highlight the importance of functional connectivity between task-relevant regions and the influence of age on these connections, which in turn might affect behavior.

Box 1

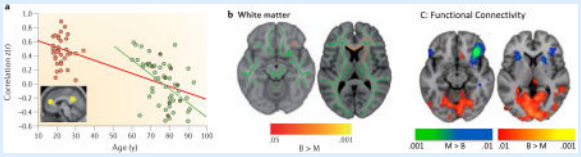
Measuring Activity in Brain Networks

There is currently much interest in using neuroimaging to assess brain networks, and a number of methods have emerged in recent years for identifying such networks and measuring individual or group differences in network integration and activity. Most of these methods are based on correlations or covariance between regional measures of activity obtained with fMRI (or some other neuroimaging technique), and range from relatively simple assessments of correlations between the time courses of two or more brain regions[105], to more complex multivariate approaches that assess brain-wide patterns of connectivity, such as independent component analysis[116], or partial least squares[198,199]. Another approach is that of graph theory[200], which uses the number of correlations that characterize various regions to identify areas with large numbers of connections (hubs) and to cluster together subgroups of regions with strong connectivity inside larger collections of areas. Some have attempted to design methods that can assign temporal or functional causality, such as dynamic causal modeling[201] and Granger causality analysis[202], but these have been somewhat controversial[203].

An example of the pair-wise correlation approach is shown in the Figure (panel A)[105]. In this study, the time course of resting activity in the posterior cingulate cortex, a main node of the default network (DN), was correlated with the time course of activity in the other primary network node, medial PFC (these regions are shown as yellow circles on the brain image in panel A). The correlation values are shown (panel A) for a group of older adults (green dots) and younger adults (black dots). Not only are the correlations lower in older adults, relative to the young, but are reduced with age even in the older group (note regression line shown in green). Studies assessing whole brain functional connectivity have shown age differences in global DN functional connectivity[58] (see also Figure 3), suggesting weaker network integration overall in older adults. Functional connectivity in the DN (and other networks) is weakened further in older adults with dementia[180,204]. However, recent work has shown that some imaging artifacts that are

more common in older adults, such as the influence of motion in the scanner[205], can weaken functional connectivity, so issues such as this need to be examined further.

Structural connections appear to be important for at least some of the functional connectivity seen in brain networks[206]. For example, the posterior cingulate is a hub for structural connections[207], as well as functional connections in the DN[117], and DN regions are strongly connected structurally[208]. In terms of aging, older adults with better maintained white matter show stronger functional connectivity[49]. In addition, life experience can influence this relationship between structure and function in older adults. Recently it was shown that bilingualism was associated with better white matter integrity as well as more distributed patterns of functional connectivity in older adults[209]. Bilingual older adults had better white matter integrity in a number of tracts, including the corpus callosum, as measured with DTI (see panel B in the Figure, which shows white matter tracts in green on two representative structural images, and the areas with greater integrity in bilinguals [Bi] than monolinguals [Mono] in red and yellow). The bilingual older adults also had stronger resting functional connectivity between a region of inferior PFC (circled in panel B) and posterior brain regions (red areas in panel C, where brain images correspond to the slices seen in panel B) compared to age and education-matched monolinguals, whereas monolinguals had stronger functional connectivity within PFC areas (blue regions, panel C). Since older bilinguals typically show better cognitive control than monolinguals[210], this finding suggests that better maintained white matter structure and more distributed functional connectivity support maintained cognitive function in older age. Panel A in the Figure is reproduced with permission from REF. 105; Panels B and C in the Figure are adapted from REF. 209 and reproduced with permission.



Age differences in functional connectivity during episodic memory tasks have been studied using a verbal recognition task[90]. Old adults had reduced functional connectivity within a hippocampal-parietotemporal network relative to young adults, but increased connectivity within a parahippocampal-frontal network. This result was interpreted as evidence that older adults compensate for hippocampal deficits by relying more on the parahippocampal cortex. Similar results have been reported in studies that measured brain activity during successful encoding of words[91], scenes[92] or objects[93] by comparing encoding activity for subsequently remembered versus forgotten stimuli. In these studies, functional connectivity during successful encoding between MTL regions and posterior regions, such as occipital cortex, was weaker in old adults, but connections between the MTL and the PFC were stronger in the older adults compared to a younger group. The results of these studies are reminiscent of the PASA effect involving more PFC activity in conjunction with less occipital activity[36], and suggest that successful memory encoding in older adults might be mediated by similar

posterior-to-anterior shifts in the functional connectivity of memory-related regions in the MTL.

Functional connectivity has also been studied using attentional tasks. One recent study[94] showed that attention to specific task-related cues was associated with activation of the dorsal PFC and parietal attention-related regions in both younger and older adults, but functional connectivity of these regions was higher in young adults than for older adults. Interestingly, increasing cue-related functional connectivity was associated with more efficient performance on the task. In another study[95] attention and expectancy were manipulated by predictively cueing which type of stimulus would be presented in a working memory task. When the cue indicated that a picture of a face would be presented, young adults showed greater functional connectivity between the FFA and dorsal attention regions compared to older adults, consistent with their greater memory for predictively cued faces. Both of these studies suggest that weakened functional connectivity between PFC and parietal regions may explain the reduced ability of older adults to attend to and make use of stimuli in the environment. In general, the studies in this section suggest that task-relevant functional connections between specific brain regions can be disrupted with age, and that these disruptions have a negative impact on task performance.

Another recent trend in the neuroimaging literature is to examine functional connectivity within particular large-scale brain networks, such as the default network (DN), which is active when people are resting and engaged in spontaneous thought[96–101]. In young adults, DN regions maintain strong functional interconnections during tasks requiring self-reference or theory of mind[101,102], and also during the resting state[103,104]. Several studies have found that the reduction of DN activity during externally-driven cognitive tasks is less pronounced in old adults, relative to young adults[58,105–112]. Functional connectivity of the DN also is reduced with age during working memory tasks[113] and during periods of rest[105,114–116]. These reductions in task-related deactivation and functional connectivity are seen in the two regions thought to be the major nodes of the DN, the posterior cingulate cortex (PCC) and ventromedial PFC[117], as well as in other DN regions, such as the MTL and inferior parietal lobes (see Figure 3). Interestingly, intrinsic connectivity during the resting state among nodes of the DN is related to the performance of older individuals on a variety of cognitive tasks[105,106,111,118]. Given that DN modulation is associated with the degree of task difficulty and performance[119,120], a deficit in the ability to modulate DN activity and functional connectivity with advancing age may be a mechanism for deficient resource allocation to the task at hand, accounting for some age differences in cognitive performance[108].

Factors Influencing Age Differences in Cognition and Brain Activity

An important issue in understanding age differences in brain activity is how these are related to other factors that are affected by aging and that influence brain function, such as brain structure. It has been known for some time that gray matter structures in the brain undergo changes with aging, such as reduced volume and thinning of the cortex, particularly in the frontal lobes[121,122]. Integrity of white matter, which is typically assessed with diffusion tensor imaging (DTI)[123], also is reduced in old compared to young adults[124–126]. In addition to structural changes, age reductions in neurotransmitter binding potential and receptor

density have been found for both dopamine[127–129] and serotonin[130,131]. Finally, the incidence of dementing illnesses such as AD increases with age[132], making the impact of risk factors for AD in healthy older adults an area of interest.

Brain Structure

There is a fairly extensive literature on age differences and decline in gray and white matter structures in the brain, especially in the frontal lobes[133,134]. A longitudinal study[135] showed that both hippocampal volume and integrity of white matter in the corpus callosum were reduced in older adults and correlated with declining memory performance. Some studies[49,55] have found that age differences in activation within PFC were mediated by white matter integrity, such that more intact white matter was related to more activation, but others have failed to find this effect[94,136]. Despite this inconsistency in results, the use of DTI to assess white matter integrity holds considerable promise for the study of cognitive aging, particularly as the integrity of specific tracts has been shown to be related to speed of performance in older adults[137] or to accuracy of performance [138–140]. Of particular interest will be studies examining the relations among white matter integrity underlying specific functional networks, functional connectivity in those networks, and how these measures are related to behaviour in older adults. For example, it has been shown that stronger functional connectivity in a network involving inferior PFC was associated both with better integrity of the corpus callosum and faster response times in older adults[141] (see also Box 1).

Reduced functional activation also has been associated with age differences in gray matter volumes[142]. One recent study[143] assessed the relationship between age reductions in gray matter volume of a region in the right middle frontal gyrus (MFG) and brain activity. In young adults, larger right MFG volume was positively correlated with greater activity in bilateral dorsolateral PFC and inferior parietal cortex, both of which have been implicated in memory retrieval[144,145]. In older adults right MFG volume was not positively correlated with activity in any regions that showed correlations in young adults, but was negatively correlated with activity in several regions, including parahippocampal cortex. Less activity in these regions predicted better memory in older adults, suggesting that older adults with larger right MFG volume may be better able to compensate for the effects of age on this region by modifying activity in other brain regions to help memory retrieval. Interestingly, in this case, the compensation, if that is what it is, appears to take the form of decreased activity in some regions, which may indicate suppression of processes that would conflict with memory retrieval.

Another study[146] assessed the relation between brain activity and gray matter volume in younger and older adults across the whole brain. There was under-recruitment of occipital cortex during encoding of face-name pairs in old, compared to young adults, which was mostly accounted for by atrophy in these regions. At retrieval, older adults over-recruited a number of regions including dorsolateral PFC and parietal cortex. This over-recruitment was eliminated after accounting for volume loss in the PFC, but age differences remained in parietal cortex after accounting for the effect of age differences in volume. These results suggest that structural age changes may account for some, but not all, of the differences in brain activity between older and younger adults. Perhaps more important is the evidence that

age differences in brain structure can influence the relationship between activity in task-related brain regions and behavior, indicating a complex interplay between structure and function.

Dopamine

One of the most studied aspects of dopamine is its role in reward. Current conceptions of how reward is processed in the brain propose that a circuit of regions, including the ventral striatum and dopaminergic cells in the ventral tegmental area, is necessary for learning about and using rewards to guide behavior[147]. Several studies have shown that there are age reductions in striatal responses to learned reward[148], and reward anticipation[149]. Only one study has directly examined the relation between functional activation during reward tasks and dopamine binding levels[150]. It showed that old adults not only have less activity in the ventral striatum during reward anticipation, they also show a weaker relationship between this activity and dopamine levels in the midbrain, relative to younger adults, suggesting that age-related dysfunction in this neurotransmitter system could impact multiple everyday decisions that rely on reward processing.

The role of dopamine in non-reward tasks also has been examined. One study[151] assessed brain activity during a low-level working memory task and the influence of a common polymorphism in the gene for COMT in young and old adults. COMT is an enzyme that is thought to regulate dopamine levels in the PFC[152], and the Val(158)Met polymorphism results in differing levels of available dopamine in the brain. The Met variant is associated with lower dopamine-degrading activity relative to the Val variant, leading to greater dopamine levels. Individuals who were Met carriers showed no age difference in brain activity, whereas those with the Val allele showed a robust age difference in left PFC activity. Older adults with the Val allele, presumably those with lower dopamine levels, had higher activity than their younger counterparts. These findings suggest that the Val(158)Met polymorphism influences the activity of brain regions within working memory networks and that over-recruitment of PFC activity in older adults can be linked to specific gene effects.

Another recent study[153] measured the binding potential of dopamine, as an index of receptor density, and related it to brain activity during working memory. Young adults had increased activity in frontal and parietal regions in a high load memory condition relative to low load conditions, and these load-dependent increases were greater in younger than in older adults. Older adults showed reductions of dopamine binding potential in the caudate nucleus and dorsolateral PFC, and when the contribution of these differences in dopamine binding was accounted for, the age effects on frontal and parietal activity were eliminated or greatly reduced. These findings suggest that some of the age-related differences seen in brain activity during varying cognitive loads (see Figure 2) may be due to alterations in dopaminergic neurotransmission.

Unlike binding potential, dopamine synthesis capacity can be increased in old adults relative to younger adults[154], which could reflect an attempt to compensate for the reduced receptor density. Greater synthesis capacity in the caudate nucleus correlated with better verbal working memory performance and more PFC activity during the task in old adults[155]. However, the relationship between dopamine synthesis capacity and task-related modulation

of activity in the PCC (a default network region), is disrupted in old adults[156]. These studies suggest that age differences in dopamine synthesis capacity, as with binding potential, influence functional activity in multiple brain circuits that are relevant for working memory performance, but whether these differences have a causal role in the reduced working memory performance in older adults is still unknown.

Two studies have manipulated dopamine levels directly to assess the relationship between dopamine, aging and cognition. Dopamine depletion in young adults (by blocking dopamine D1 receptors) resulted in reduced activation in frontal and parietal regions during a high-load working memory task to levels similar to those seen in older adults[157]. Performance also was lower in young adults after D1 blockade, although still better than that seen in older adults. However, when a dopamine agonist was administered to old adults, to test the idea that boosting dopamine function would induce similar brain activity to that observed in young adults when carrying out episodic memory tasks, an enhancement, rather than a reduction, in age differences was seen[158]. Clearly much more research is required before any strong statements about the interactions among dopamine alterations and brain activity in aging can be made.

Risk Factors for Alzheimer's Disease: APOE

There is evidence that memory reductions can be seen at least 6 years prior to a diagnosis of AD[159], suggesting that pathology in memory-related regions is well advanced prior to diagnosis[160]. Therefore, it is important to assess the potential influence of AD risk on studies of "normal" aging. The impact of the different alleles of the APOE gene have been examined in this context, as the presence of one or two ε4 alleles is a known risk factor for AD[161]. Some studies have reported greater activation in memory-related areas, notably the hippocampus, in healthy old adults who were ε4 carriers compared with non-carriers of the ε4 allele[162–164], and even in young ε4 carriers relative to non-carriers[165], suggesting an increase in demand on these regions prior to the appearance of any symptoms of memory loss. However, a couple of studies[166,167] have found evidence of lower brain activity in the hippocampus of aged ε4 allele carriers during memory tasks. These inconsistent findings regarding brain activity in high-risk individuals compared to their low-risk counterparts could be due to differences in specific task demands, the influence of any number of life-style or health factors, or where in the trajectory of longitudinal change one happens to measure brain activity and cognition. For example, if a participant is on a trajectory towards eventual dementia, measuring brain activity early in this trajectory might reveal an over-recruitment of activity in a given region, whereas a later measurement might show under-recruitment. It also is possible that differential responses to cognitive load could account for over- or under-recruitment in older individuals with either high or low risk for AD (see Figure 2). It nevertheless seems clear that APOE genotype influences age-related changes in brain function, and that the altered task-related brain activity in ε4 carriers may reflect the increased vulnerability of these individuals to AD pathology and cognitive decline.

Finally, it was recently shown that over-recruitment of brain activity in older ε4 carriers is enhanced in those with greater physical activity[168]. Older adults with the ε4 allele who engaged in more physical activity had greater memory-related activation in posterior

temporal and parietal regions than non ε4-carriers or those with lower physical activity. This result is particularly interesting as these areas are some of the first regions of cortex to show metabolic deficits in early AD[169–171]. This work shows interesting influences of both APOE genotype and physical activity on memory-related brain activation in cognitively intact but genetically at-risk older adults, but it is not clear if this increase is compensatory or protective against future cognitive decline.

Risk Factors for Alzheimer's Disease: Mild Cognitive Impairment

Mild cognitive impairment (MCI) in older adults is another risk factor for AD, as a relatively high proportion of older adults with MCI, particularly those with amnestic symptoms, will progress to clinical dementia[172]. There is an extensive literature on functional and structural brain changes in MCI, much of which has shown that individuals with MCI have greater activation in the MTL during memory tasks relative to healthy older controls[173,174]. Recent research has focused on understanding what might underlie this over-activity. For example, one recent study[175] examined subregions of the hippocampus using high resolution fMRI to explore the CA3 region, thought to be involved in pattern separation during memory. Participants with MCI showed over-recruitment of the CA3 region, but not other regions, relative to controls, as well as impaired pattern separation ability, consistent with the idea of a dysfunctional encoding mechanism due to early neuropathological changes in this hippocampal region. Interestingly, healthy older adults also show memory-related deficits in CA3 function relative to younger adults[176]. Another study[177] found that over-recruitment of the hippocampus in MCI was related to cognitive load, such that it was only seen at lower levels of memory load during a paired-associates task. At higher loads, activity in the hippocampus was lower in the MCI group relative to controls, consistent with the CRUNCH hypothesis (similar results have also been reported in MCI for other brain regions[178]). These studies point both toward specific processing deficits as well an impairment in the ability to respond to increases in cognitive demand as potential explanations for MTL over-recruitment in MCI. This work also highlights the similarities between age differences in healthy older vs younger adults and differences between MCI and healthy older individuals (e.g., both can be characterized by CRUNCH and involve over-recruitment of brain activity). This similarity suggests a continuum of effects due to age and neuropathological brain changes, perhaps because both aging and risk for dementia can impact cognition in a general way that impairs the ability to respond to increasing cognitive demand.

Other recent work has emphasized how MCI affects larger scale brain networks. One such study showed that healthy older adults utilize a network of regions, including the MTL, for successful encoding[179]. Although participants with MCI showed engagement of this network, activity in it was not associated with memory performance; instead activity in a network involving anterior temporal regions thought to be involved in semantic retrieval was correlated with memory in MCI. This shift was interpreted as a compensatory response to dysfunction in the MTL. The DN also has been studied in older adults with MCI, who show weaker functional connectivity in this network compared to healty elderly, consistent with studies showing that AD patients have less deactivation of and weaker functional connectivity in the DN[109,180]. These effects of MCI have been found in the PCC[181], and in its connections to other regions[182]. In addition, DN functional connectivity is more affected

in those MCI individuals who later progress to dementia than in those who remain stable over time[183]. Indeed, the weaker functional connectivity of the DN in MCI and AD, in conjunction with the finding of amyloid deposition and other neuropathological changes in DN regions, including the MTL[160], has led to the suggestion that the DN is intimately involved in the neuropathology of AD[184]. Again, there is a similarity in the vulnerability of the DN in those with risk factors for AD (APOE, MCI) and the vulnerability seen in healthy older adults relative to young adults, suggesting that DN activity and functional connectivity in older samples might be a useful marker for predicting cognitive decline.

Influence of Training on the Aging Brain

The influence of expertise on the adult brain has been demonstrated[185,186] (see Box 1 for an example of how a lifelong experience can influence brain structure and function), but less is known about how short-term behavioral training can affect brain activity in older adults. This question is important because it has implications for rehabilitating cognitive decline in older people. A few neuroimaging studies have looked at this issue and their results are intriguing. One study provided training to older adults on a divided attention task in five one-hour sessions over a two-week interval and found improved performance and reduced age differences in brain activity that were apparent prior to training[187]. PFC activity that was greater in older adults prior to training was reduced to the level seen in younger adults after training, presumably because the practice on the two tasks had reduced the effort required to carry them out simultaneously, reducing the need for PFC mediated cognitive control. Similarly, a reduction in the amplitude of an electrophysiological evoked response during a working memory task was reported in older adults after 10 hours of perceptual discrimination training, and this reduction predicted the increase in accuracy on the working memory task that was achieved after training[188].

Increased activity in older adults after episodic memory training has been reported in a study[189] that scanned young and old adults during encoding of words to assess baseline age differences. The older adults then underwent two training sessions (for a total of 2.5 hours), in which they were trained on the use of three different learning strategies and then allowed to use the strategy of their choice to learn lists of words. A post training fMRI session was then carried out in the older group. Older adults' reported use of the strategies during the encoding condition at the second fMRI session coincided with an elimination of the pre-training age differences in word memory. Training also increased older adults' brain activity in the left frontal and temporal regions that have been previously associated with verbal processing and successful encoding[70,190,191]. These increases of brain activity were correlated with the degree of improvement in memory after training, suggesting a direct role for training in influencing both brain function and behavior. These training studies suggest that increased brain activity after even limited training could be due to the adoption of a different strategy, whereas decreased brain activity after training is more likely due to a practice-related increase of efficiency on a task[187].

Conclusions

There are a number of issues in the aging literature that have yet to be resolved satisfactorily, including that of compensatory brain activity. For example, over-recruitment of brain activity in older adults has been interpreted as compensation both when there was a positive correlation between activity and behavior[39], and when this correlation was negative[146]. Although it seems unlikely that both positive and negative correlations could be compensatory, perhaps a more careful and consistent definition of what is 'compensatory' is needed. One model[192] defines three different types of compensation. When there is a mismatch between available cognitive resources and current task demands, this leads to the recruitment of additional neural resources, reflected in increased brain activity. At this point, without a link to behavior, the over-recruitment is called "attempted compensation". The increase in brain activity may be associated with better task performance, in which case it is defined as "successful compensation", or not ("unsuccessful compensation"). In this model, determining the relationship between the engagement of additional neural resources and task performance is critical for determining whether the compensation has been successful or not. Adopting terms such as unsuccessful or partial compensation, to make a clear distinction between these phenomena and successful compensation, where over-recruitment is clearly linked to better performance, may help to remove discrepancies in the literature and clarify the compensatory role of various regions. In addition, others have suggested[23] that the term "compensation" should be used only for those instances in which old adults recruit brain activity that is not seen in younger adults, and the engagement of this area or areas is directly correlated with better performance only in the older adults and not in the young (i.e., there is a unique pattern of neural activity that supports task performance in an age-specific manner).

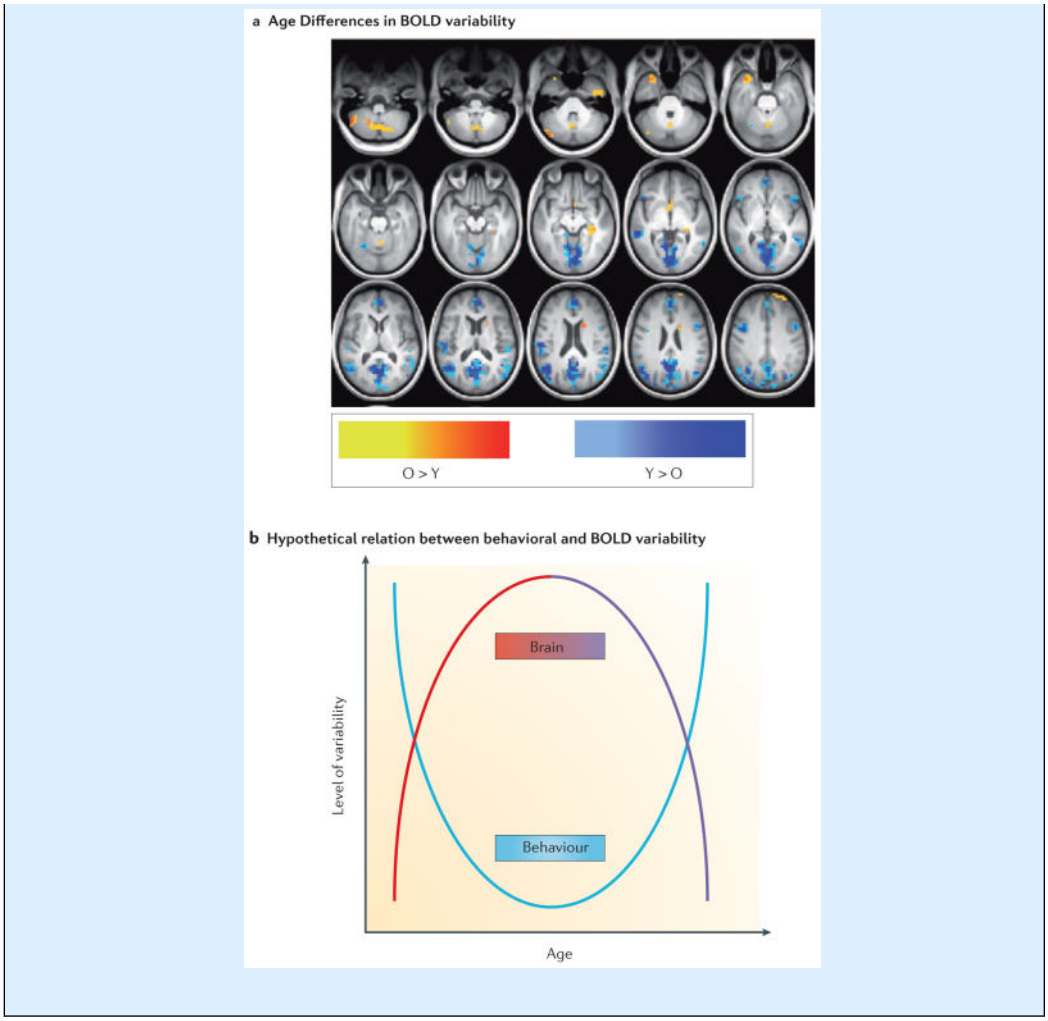
Another initiative that would be welcome in this field is the use of lifespan studies to identify the changes that occur, both in cognitive processes and the brain mechanisms underlying them, from childhood to old age. Such developmental changes could take a variety of forms, including both linear and non-linear changes. There is recent evidence suggesting that some behavioral and brain trends in development might take different forms (see Box 2), indicating that much could be learned about the links between brain and behavior using a comprehensive lifespan approach. In addition, longitudinal studies will be important for understanding brain aging. Although cross-sectional studies are easier to carry out, and have contributed most of what we know to date about aging of the brain, they are vulnerable to cohort effects, and longitudinal studies are necessary for identifying the effects of aging within individuals. There have been a few longitudinal studies of brain function in older adults, which have shown decreased task-related activity over time[193], both decreases and increases, depending on the specific brain region and cognitive demands[194,195], and a greater decline of activity in older individuals with risk factors for AD[196]. With so few data points it is difficult to come to any strong conclusions about change over time, highlighting the need for these kinds of studies.

Box 2

Assessing Behavioral and Brain Trajectories over the lifespan

An example of how lifespan studies could add to our knowledge of brain-behavior interactions can be found in the study of variability. It is well known that measures of behavioral performance, such as response times, are variable both between and within individuals[120,211,212] and that behavioral variability is higher in children and older adults relative to younger adults[213–216]. In aging, behavioral variability also can serve as a marker for cognitive decline[217,218], and increases prior to death[219]. However, the relation between behavioral variability and variability in brain activity has not been extensively examined, although evidence indicates that variability in ongoing activity is important for the expression of evoked patterns of activity[220]. The use of fMRI to study brain function has relied primarily on assessing average brain activation patterns. Nevertheless, brain activity is inherently variable, and several lines of research have shown that our ability to understand important aspects of brain function is enhanced by considering the variability of brain signals[221–223]. In particular, networks that are more variable may be more robust to disruption and may explore more neural states, thus enhancing learning and promoting optimal performance[221,222,224,225].

Recent studies have shown that there are developmental increases in variability and complexity of brain activity, from childhood to the young adult ages, along with increased accuracy and stability of task performance[226]. In addition, a recent study assessed variability of the BOLD signal with age, using the standard deviation of activity in all brain voxels, and found that the majority of regions with age differences had less variability in the older group[227] (see Figure, blue regions in panel A). In addition, lower BOLD variability in these regions was associated with slower and more variable response times on cognitive tasks[57]. Thus, this accumulating evidence suggests that behavioural variability has a U-shaped function over the lifespan[216], with larger variability in children and older adults compared to young adults (see Figure, panel B), whereas variability of brain activity shows the opposite trend (inverted U shape). Lifespan studies examining this kind of question using the same behavioral and imaging paradigms from children up to older adults would shed much light on how developmental changes in brain function can impact behavior. Panel A in the Figure is adapted from REF. 227, and reproduced with permission.



Finally, it is clear that aging is influenced by a large number of factors that vary from individual to individual, including genetics and life experiences (Figure 4). Although it is probably impossible to account for all of these factors in a single study, the current trend is to include an assessment of multiple influencing factors and multiple measures of brain structure and function, as the experiments reviewed here can attest. Publicly accessible databases, such as the Alzheimer Disease Neuroimaging Initiative (ADNI)[197], that contain information on a large number of individuals collected across multiple laboratories will aid greatly in this effort. Sharing of data and meta-analyses will allow for larger scale examinations of aging effects than is possible with data from a single laboratory, and ultimately add to our knowledge in a substantial way.

Biography

Dr. Cheryl Grady is a senior scientist at the Rotman Research Institute at Baycrest, and a professor in the departments of Psychiatry and Psychology at the University of Toronto. She obtained her PhD in experimental psychology from Boston University, and her main research interest is in the cognitive neuroscience of aging, with a focus on fMRI studies of

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Online Summary

- The main challenge in the field of neurocognitive aging is to understand the brain mechanisms that might underlie age differences in cognitive performance or why some functions are maintained into older age.
- A number of ideas have been suggested to explain age differences in brain activity during cognitive tasks, including compensation, dedifferentiation, and less efficient use of neural resources. Although there is evidence to support all of these theories, there also is evidence to the contrary, and it is not yet clear if one is more characteristic of aging than the others.
- Recently there has been increasing interest in examining the effects of age on large-scale brain networks. One of these in particular, the default network, appears to be especially vulnerable to the effects of age.
- There is evidence that age differences in brain structure can influence the relationship between activity in task-related brain regions and behaviour, indicating a complex interplay between structure and function.
- There is a growing literature on how various risk factors for Alzheimer disease, such as the APOE gene and mild cognitive impairment, impact task-related brain activity in older adults. This work also highlights the similarities between age differences in healthy older vs younger adults and differences between MCI and healthy older individuals, suggesting a continuum of effects due to age and neuropathological brain changes.
- Future work should aim to more clearly define compensatory brain activity, make more use of lifespan and longitudinal approaches, and attempt to account for the large number of factors influence the aging process and that vary from individual to individual, including genetics and life experiences.

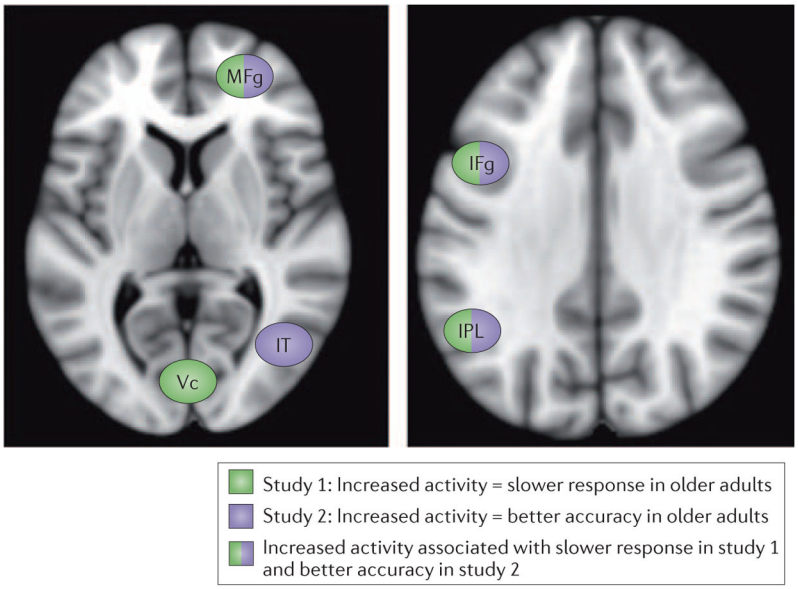

Figure 1. Increased brain activity in older adults may be associated with better or worse task performance

This figure summarizes the results of two studies that differ in how increased brain activity in older adults was associated with task performance. In one of these studies, several brain regions (indicated in blue) showed a correlation between more activity and more accurate performance on an task requiring inhibition of responses in a go/no-go task[45]. In the other study the regions shown in green showed a correlation between more activity and slower reaction times on perceptual and working memory tasks[57]. Note that some regions (colored blue and green) showed an association with better performance in Study 1 and the opposite effect in Study 2. This discrepancy highlights the complexity of trying to relate brain activity in older adults to their behaviour, and indicates that the specific relationships between regional brain activity and task performance in older adults depend on the task demands or on the behavioral measure that is assessed (or both). Abbreviations: MFg, middle frontal gyrus; IFg, inferior frontal gyrus; IPL, inferior parietal lobe; IT, inferior temporal cortex; Vc, visual cortex.

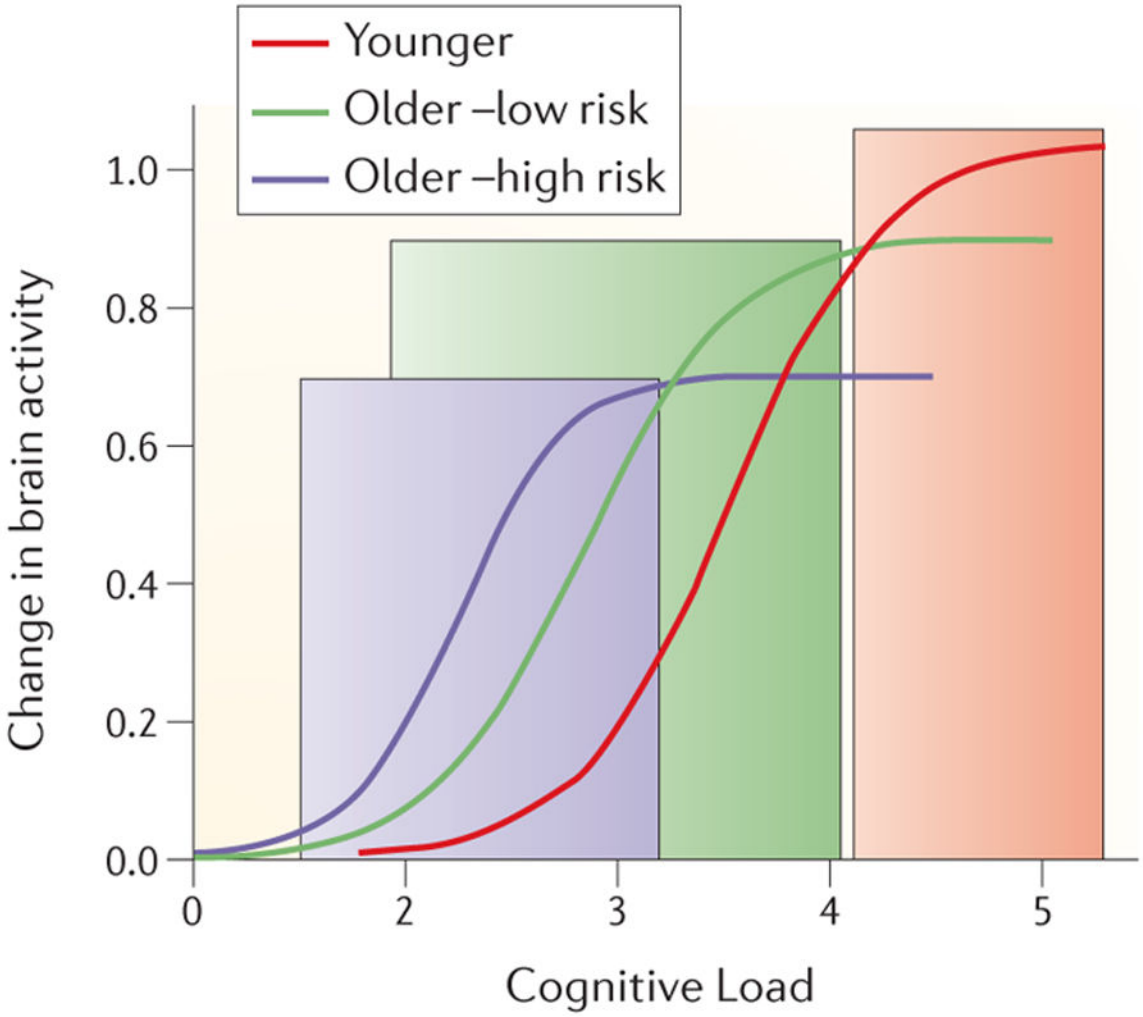

Figure 2. 'Compensation-Related Utilization of Neural Circuits hypothesis'

The function relating the change in brain activity (measured by fMRI during a task of interest) to levels of cognitive load is shown for young adults, old adults with a low risk of developing AD and old adults with high risk of developing dementia. The function in low risk older adults would be shifted to the left relative to that seen in younger adults. At relatively low levels of cognitive load this shift would result in higher activity in older relative to younger adults (green shaded area). However, activity in older adults would reach its peak and level off while younger adults' activity is still increasing, so that at higher load levels there would be no age difference in activity or younger adults would have higher activity (gray shaded area). A similar effect would be seen when high-risk older adults are compared to low-risk older adults – higher activity in high risk groups relative to low risk at low levels of cognitive load (blue shaded area), with the reverse seen at higher levels of load. This hypothesized set of load-dependent functions could explain why studies have reported both under- and over-recruitment in older adults compared to young adults, and in high-risk older adults compared to low- risk older adults.

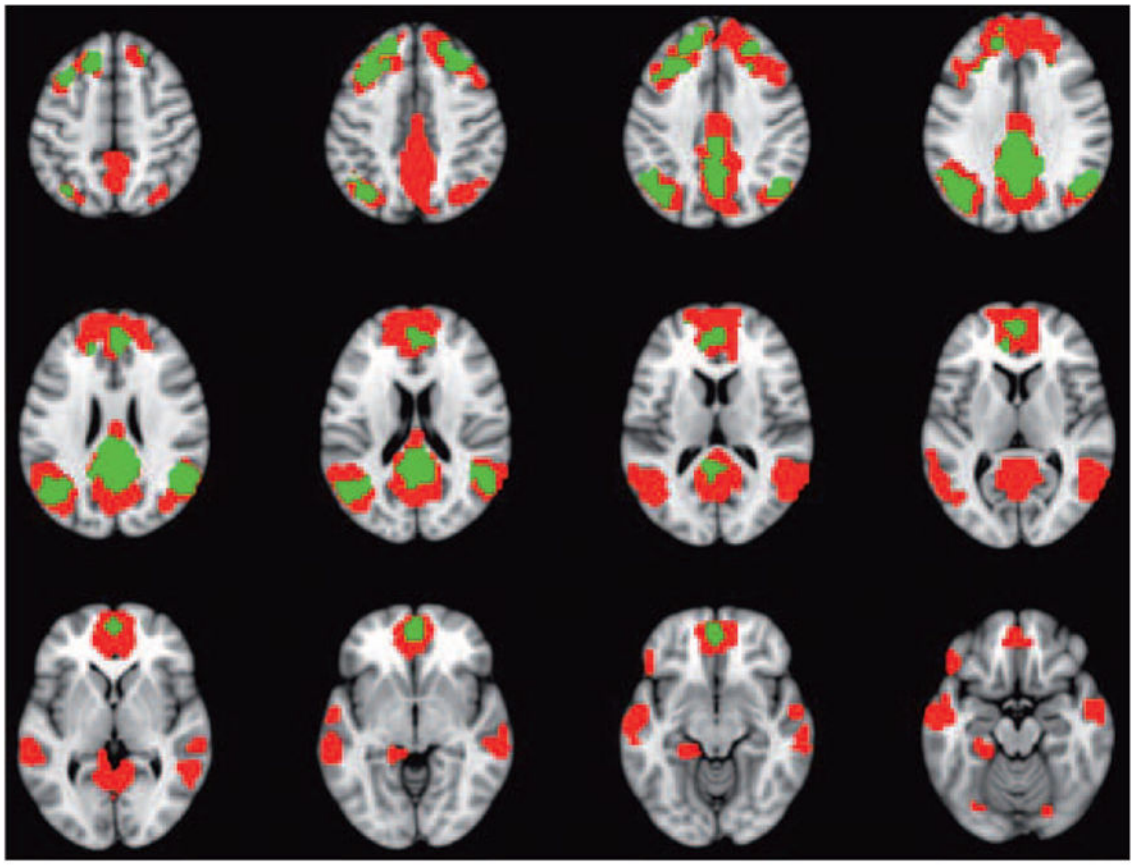

Figure 3. The default network in young and older adults

The regions making up the default network (DN) are shown in this figure (brain areas shown in red). The DN was defined using a multivariate, whole-brain approach[198] that identified regions where activity at rest was correlated with activity in the posterior cingulate cortex (PCC, a major node of the DN). The DN includes lateral inferior parietal regions (IPL), as well as ventromedial prefrontal cortex (vmPFC), superior frontal gyrus (SFG), and the medial temporal lobe (MTL). The green regions represent a subset of DN areas, both medial and lateral, with weaker resting functional connectivity in older compared to young adults (also see Box 1).

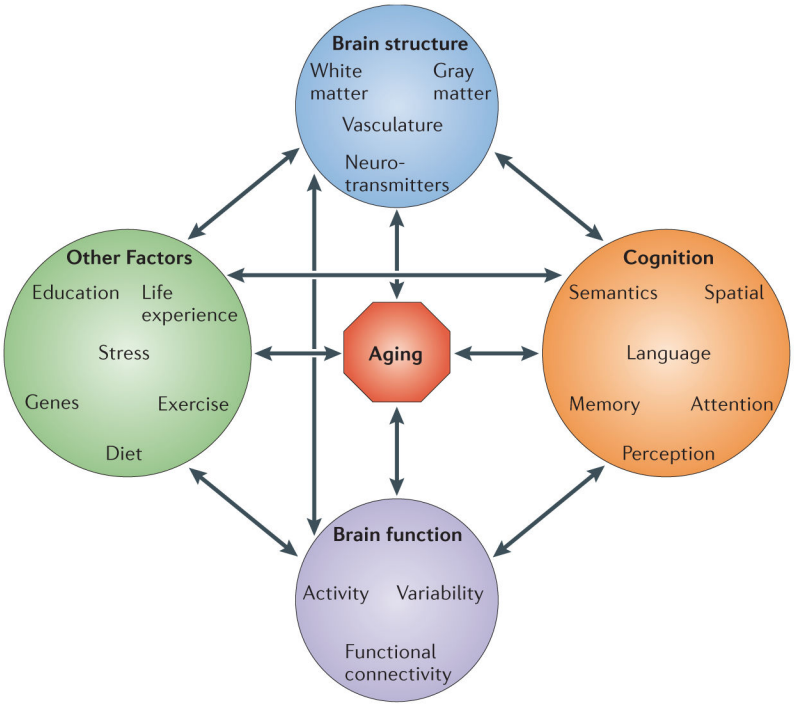

Figure 4. A hypothetical model of the various dimensions that can interact with aging

The model is intended to show the interplay among a wide array of physical and behavioral aspects (some of which are discussed in this review) and the aging process. The arrows are bidirectional to indicate that the influence can potentially arise from these factors on the aging process, or vice versa. For example, genetic factors could influence how an individual ages, and aging can enhance the effects of genes on specific behaviors. There are other factors that could be included here, such as risk factors for vascular disease or dementia, but this incomplete list gives a sense of how complex the study of aging is, and how difficult it would be to comprehensively assess these variables in a single experiment.