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Dissecting the Effect of Aging on the Neural Substrates of Memory: Deterioration, Preservation or Functional Reorganization?

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SYNOPSIS

One of the most common deficits observed during late adulthood is a loss in the ability to learn and remember new information. This cognitive ability depends mainly on the integrity of the hippocampal formation and the prefrontal cortex, which are especially susceptible to the effects of age. Here we provide a selective review of the literature gathered from studies carried out in humans and animals, examining the effect of aging on the functional anatomy of memory. We discuss some of the methodological and theoretical difficulties associated with the current approach to the study of aging and, in turn, a series of strategies that may be implemented to ensure the most accurate interpretation of the data. Altogether, the evidence discussed in this review supports the idea that there is no general age-related deterioration of the neural substrates of memory, but rather a differential effect in which some brain areas may be adversely affected while others may compensate for the neurobiological deterioration associated with age.

KEY WORDS

aging, memory, animal, human, electrophysiology, neuroimaging

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INTRODUCTION

In addition to pervasive physical deterioration, aging entails cognitive decline. Yet, not all cognitive faculties are similarly affected by age. One of the most common deficits observed during late adulthood is a loss in the ability to learn and remember new information. Individuals who exhibit age-related deficits are often impaired at retrieving memories from personally experienced events /19,20,30/, that is, episodic memories /90/. Older humans and animals also show difficulties in working memory tasks in which they are required to hold and/or manipulate stimuli 'in mind' for relatively brief periods of time /17,21/, and in spatial memory tasks /2,3,67,91/. In contrast, other cognitive abilities, such as perception, procedural memory, semantic memory, priming and short-term memory, remain relatively spared throughout the life span /30/.

During the past 40 years, a significant effort has been made to fully characterize these memory deficits behaviorally. Nevertheless, the understanding of the neurobiological deficits underlying cognitive decline in older individuals has only recently begun to be explored. The first hints on the putative brain structures compromised by age came from the neuropsychological literature. The resemblance between memory impairments associated with aging and those produced by direct damage to the hippocampus and prefrontal cortex, suggested that memory decline in old age was linked to the deterioration of these cortices /53,57,83,93/. More recently, the use of high-resolution neuroanatomical and electrophysiological techniques confirmed this hypothesis. Despite some discrepancy encountered in the available reports, there is evidence that the prefrontal cortex (PFC) is most vulnerable to the effects of age /70,71/. Although there is consistent evidence supporting gray matter

volume reduction in older adults, this is not always correlated with cognitive decline /38/. Moreover, although a reduction in neuronal size has been observed in some areas of PFC, there are no conclusive reports indicting an age-related reduction in the number of neurons /56,60,88/. Together with recent studies supporting the existence of white matter lesions /23/, myelin reduction /26,65/, and dendritic regression /22/, the available evidence suggests that age-related memory decline may be partly related to changes in the connectivity of the PFC. In regard to the hippocampal formation, neuroanatomical studies carried out in rats, monkeys and humans have shown very little or no changes in cell number and size, but there is a significant reduction in the number of cortical and subcortical afferents to the hippocampal formation /6,56,68,69,81,84/. Moreover, electrophysiological studies in rats have shown that hippocampal pyramidal cells of older rats are deficient in maintaining synaptic long-term potentiation (LTP) /3/, a putative physiological mechanism underlying learning in several species /45/.

In addition to the neurobiological decay, recent reports suggest that in some cases, the older nervous system may functionally compensate for loss of function /4,24,28,34,54/. Extensive experimental evidence from humans and animals indicates that the functional organization of the adult mammalian nervous system is plastic /10,37, 40/. For example, it has been shown that the topography of primary motor and sensory cortices can undergo restructuring as a result of long-term training /41/ or deafferentation, as occurred after brain lesions or nerve transection /18,51,77/. Given that age-related deterioration entails a reduction in hippocampal and prefrontal connections, it is probable that, like the damaged brain, the functional organization of the aging brain is modified as neurobiological decay progresses. Such modification would be highly adaptive in that it could lead to the preservation of cognitive abilities over extended periods of time.

Despite the growing research aimed at identifying molecular, anatomical and physiological correlates of memory decline, the impact of late ontogenetic changes on information processing at different organizational levels of the brain (neuron, neuronal ensemble, neural network) has remained largely unknown. Nevertheless, recent electrophysiological and neuroimaging investigations have made considerable progress towards understanding the functional organization of the hippocampus and related memory cortices in the elderly. The aim of the present paper is to discuss this literature in depth. Although this review is mainly dedicated to neuroimaging studies in humans, we consider a number of animal studies whose findings have made valuable contributions towards illuminating the physiological basis of age-related memory decline. Given that neuroimaging techniques rely on indirect measures of neuronal populations, the findings from electrophysiological studies appear to be a necessary complement to establish a thorough cognitive neuroscience account of aging. This review is structured as follows: in the first two sections we discuss the results from physiological and neuroimaging studies suggesting that information processing by the PFC, hippocampal formation, and related areas is altered by age. In the next section, we describe current data supporting the hypothesis that functional reorganization of corticolimbic circuits may partly account for spared performance in some older organisms. Finally, we point out some of the most common methodological and theoretical difficulties associated with the current approach to the study of aging and, in turn, discuss a series of strategies that may be implemented to facilitate interpretation of the data.

ELECTROPHYSIOLOGICAL EVIDENCE FOR IMPAIRED MEMORY PROCESSING IN ANIMALS

Most of the studies discussed in this section are based on electrophysiological recordings of the neural substrates of memory in freely moving rats. Age-related cognitive deficits in rodents are observed for a variety of spatial learning and memory tasks. The fact that rats with lesions of the fimbria-fornix and older rats are impaired at spatial memory tasks suggests that this type of memory relies on hippocampal integrity /3,52,73/. Convergent experimental evidence indicates that in rodents spatial information is coded by hippocampal place cells, pyramidal neurons located in the CA1 area that fire in response to specific

locations in space /61/. The firing pattern of place fields (i.e., firing location) is controlled by the relationship between environmental cues (local and distal cues) and the animal's ongoing behavior /50/. Therefore, during exploratory behavior the population of active place cells represents the position of the animal relative to the environment /61/. The place field of a hippocampal cell is not constant but changes with the environment. Indeed, the entire topography of the active place cell population is modified when the environment changes or in response to task demands (see below). Thus, it is possible that different environments are represented by different maps. Because of its specificity, this coding mechanism has been interpreted by some investigators as a possible neurophysiological basis for the construction of episodic memories /47,62/.

Until recently, it was thought that the spatial information conveyed by hippocampal place cells of aged animals was only slightly altered /46,55/. These results were puzzling because they suggested that the representation of spatial information was not age-sensitive, which contradicted the observed behavioral deficits. Only recently have the findings from a series of influential studies begun to identify where in the process of coding spatial information aged rats are impaired. In one of these studies Tanila and collaborators /85/ examined the ability of old rats to detect changes in the spatial arrangement of a familiar environment, such as those produced by rotating the relative position of distal and/or local cues. The results indicated that young and memory-unimpaired old rats altered their spatial representation with each different condition, whereas memory-impaired old rats maintained a fairly invariant map across all conditions. The authors suggested that hippocampal coding of spatial information is less plastic in older rats. Indeed, this group was associated with the greatest specificity, directionality and reliability of spatial maps. In a different study, Barnes *et al.* /7/ showed that when replaced in exactly the same environment (the north half of a rectangular figure-8 shaped maze, configuration "A"), young rats exhibited highly invariant hippocampal spatial maps, whereas 30% of old rats remapped it. Although the results from these two studies may at first seem incompatible, additional information from this study by Barnes *et al.* /7/ can serve to accommodate both reports with the view that the aged hippocampus is impaired at coding spatial settings efficiently /66/. Between electrophysiological sessions obtained in configuration "A" of the maze, rats were allowed to explore the unfamiliar south half of the maze (configuration "B"). Thus, if the old hippocampus was vulnerable to control by cues that fail to uniquely distinguish a particular spatial setting /66/, it is possible that once replaced in configuration "A", place cell firing may have been driven by the stimuli experienced in configuration "B", thereby recalling the wrong map. Conversely, young rats unambiguously recognized the "A" configuration as familiar. The experimental design used by Tanila *et al.* was orthogonal to this one, i.e., animals were replaced in the same environment (with no intermediate environments during electrophysiological sessions) but the position of the cues was rotated. As in the experiment by Barnes *et al.*, representation of spatial setting by using the wrong cues (those that were constant across conditions) may have led to a failure in recognizing a modification of the environment. These data do not contradict those obtained by Barnes *et al.* /7/, but complement it.

It is important to note that in both cases only a subset of old rats was impaired at processing spatial information efficiently. In fact, both studies showed that some of the old rats performed as well as their young counterparts, and exhibited intact hippocampal representation of space.

Older rats are also impaired at recognizing a familiar environment when the task demands are changed. In a recent study, electrophysiological recordings of place cells were obtained from rats on a plus maze at three times: 1) while on the plus maze ("+" configuration), 2) after having added two arcs to connect opposite pairs of arms ("8" configuration), and 3) after removing the arcs (back to "+" configuration) /62/. Animals were running in both directions of the maze while in the "+" configuration, but were required to perform a working memory task in the "8" configuration. Thus, while the behavioral demands were altered in the "8" configuration, the testing environment remained relatively unchanged. The animals were not removed from the maze at any time. The results

indicated that middle-aged and old rats showed rearrangement of hippocampal spatial maps from the "+" to the "8" configuration, whereas young rats did not. The spatial maps for the first and the last "+" configuration were identical for all groups. The outcomes suggest that whereas young rats recognized the "8" configuration maze as familiar, older rats failed to do so. The authors interpreted this finding as reflecting a change in search strategy or trajectory planning by older animals. In addition, the data support the hypothesis that hippocampal place cells code not only for location, but for location within a reference context.

Altogether, the studies discussed above suggest that old animals are impaired at recognizing whether or not a familiar environment has changed. This hypothesis is supported by the demonstration that spatial representations of a familiar environment by the hippocampus of aged rats are relatively impaired (as compared to their younger counterparts) when changes occur in task demands or environmental cues. These factors may act alone or in combination to reduce the ability of the animal to recognize whether its position relative to the environment remains the same. Among the possible causes underlying deficient recognition is the possibility that older rats are impaired at learning the spatial map. Evidence supporting this hypothesis comes from a study carried out by Shen *et al.* /80/, showing that the hippocampal place field size of older rats (who were impaired at the water maze task), failed to expand as they were trained to learn a spatial task. This inability to learn the spatial map as efficiently as their younger counterparts may have resulted in less accurate population coding of the environment, which may explain the deficits in recognition exhibited by older animals /7,62,85/. The failure of aging hippocampal cells to maintain synaptic long-term potentiation /3/ may be a plausible factor underlying this type of deficit.

NEUROIMAGING EVIDENCE FOR IMPAIRED MEMORY PROCESSING IN HUMANS

Most neuroimaging studies describing age-related changes in the functional neuroanatomy of human memory have explored the integrity of the mechanisms supporting episodic and working memory. In normal young adults, episodic encoding is associated with activation of left PFC, fusiform gyrus, right parahippocampal gyrus and bilateral temporal and entorhinal cortices, whereas episodic retrieval is associated with activation of right PFC, anterior cingulate gyrus, thalamus and the cuneus-precuneus /16,59,89/. This asymmetric pattern of PFC activation, known as the HERA model (hemispheric encoding/retrieval asymmetry), has been reliably replicated by a series of episodic memory studies /15/. In regard to the neural substrates of working memory, the pattern of activations in normal young adults depends on the nature of the stimuli and the type of task. For working memory (WM) tasks requiring short retention intervals with very little or no manipulation of the information, the pattern of activation is asymmetric. Verbal WM is accompanied by activation of left ventrolateral PFC (Broca's area), left premotor, suplementary motor and parietal cortices, whereas spatial WM is accompanied by activation of the corresponding brain areas of the right hemisphere, in addition to BA 47. In contrast, working memory tasks that require information maintenance for longer periods of time or manipulation of that information are supported by activation of dorsolateral PFC /74,76/, which tends to be bilateral.

The majority of human studies investigating the effect of aging on the neural substrates of episodic and working memory have relied on regional analyses to assess group differences. Accordingly, most age-related differences reported in the neuroimaging literature are either increases or decreases in local activity as compared to a younger group. Age-related reductions in local brain activity have often been interpreted as reflecting deficits in neural processing, whereas increases in local brain activity have been interpreted as reflecting a compensatory mechanism for the reduced processing efficiency of other brain areas /31,32,78/. However, more recently some investigators have pointed out that inferences of this kind are not valid unless the relationship between the area(s) of interest and performance is taken into consideration /13,24,30,49/. Other factors such as task difficulty or a different encoding strategy may account for activation differences, and without relating activity

to behavior, it is not possible to distinguish these influences from the functional reorganization of the neural substrates of memory.

Thus, in light of these interpretation difficulties, we have chosen to emphasize in our review those neuroimaging studies that have either controlled for differences in performance across aging groups and/or assessed the relationship of the regions of interest with performance. Given that most reports have pursued the occurrence of age-related changes associated with dysfunction of the hippocampus or the PFC, we divided the literature under these two topics. This distinction is only organizational, and hence it is not meant to reflect any biological compartmentalization of memory processing.

Hippocampal formation

Application of univariate and covariance analysis to neuroimages obtained during episodic memory tasks has shown that both hippocampal brain activity and its network interactions are modified by age. Deficient hippocampal encoding of information was first suggested by the findings of a PET study on episodic memory for faces. In this experiment the right hippocampus of older subjects, who were subsequently impaired at retrieval, was less active than that of their younger counterparts /35/. Age-related reduction in hippocampal activity has also been shown during encoding of pictures, but in this case, both young and older adults exhibited similar levels of performance at recognition /36/. Given that extrastriate visual areas were similarly active in young and old groups, the authors suggested that intact visual processing may have been sufficient to compensate for deficient hippocampal encoding. However, assessment of the correlation between activity in these visual areas and performance would have been necessary to confirm this hypothesis.

In contrast to these two studies, more recent reports have shown that deficient encoding in the elderly is not always associated with a reduction of hippocampal activity. Grady and collaborators further investigated the effect of using different strategies to encode faces /29/. Although activation of left PFC and temporal cortices differed across groups, other brain areas including the right hippocampus were similarly active during encoding even though older adults were impaired at recognizing unfamiliar faces. Subsequent examination of brain-behavior correlations indicated that hippocampal activity was a good predictor of successful performance in the young but not in the old. Likewise, in a functional magnetic resonance imaging (fMRI) study, Iidaka *et al.* showed similar hippocampal activation for young and old subjects during picture encoding, for which old subjects were impaired at recognition /39/. Here too, hippocampal activity was highly correlated with successful performance in the young but was uncorrelated in the old. These findings indicate that hippocampal activity *per se* may not be a good indicator of its functional integrity, even though behavioral performance is similar across groups. To get a more complete appreciation of age-related changes in hippocampal function, activity during encoding should be assessed in relation to the overall level of performance, ideally through the direct correlation of performance and hippocampal activity.

Most of the experimental evidence discussed above described age-related changes in regional brain activity. However, given the extensive anatomical connectivity of the brain, it is likely that local changes in anatomy and physiology in one area impact on functionally related brain areas. Support for this idea has been shown by the presence of age-related changes in the functional connectivity of the hippocampus as assessed with positron emission tomography (PET). Functional connectivity refers to the level of association between two brain areas during a certain task, and can be determined by computing the correlation between activity in the two areas /27/. Grady and collaborators /35/ first showed that the right hippocampus was not only less active in old than in young subjects during episodic encoding of faces, but also had different functional connectivity. Hippocampal activity was strongly correlated with activity in the anterior cingulate gyrus in the young, but with the left parahippocampal gyrus in the old. Similarly, Esposito *et al.* /25/ reported age-related differences in the connectivity between the right parahippocampal gyrus/hippocampus and the left dorsolateral PFC, which in turn varied depending

on the memory task. Specifically, these two regions were highly correlated during performance on the Raven's progressive matrices task in the old subjects but not in the young, whereas they were highly correlated in the young subjects, but not in the old, during performance on the Wisconsin Card Sorting task.

Taken together, the experimental evidence discussed above suggests that hippocampal processing of information during encoding is impaired in older adults. The impact of aging is not only reflected in local changes of hippocampal activity, but in its interaction with functionally connected areas. These findings support those obtained from electrophysiological studies, indicating deficient hippocampal coding of information with age, and further suggest that examining hippocampal activity in relation to memory performance may provide a more comprehensive picture towards understanding the extent and functional significance of age-related deficits.

Prefrontal cortex

Neuroimaging findings obtained from older adults performing memory tasks confirm the neuroanatomical evidence suggesting that the function of the PFC is altered by age. A relatively consistent effect observed in older adults is the bilateral activation of PFC during the retrieval phase of episodic and low-demanding working memory tasks. This apparent 'loss' of symmetry occurring in older individuals has been recently conceptualized by Cabeza /11/ into the HAROLD model (hemispheric asymmetry reduction in the old), an adaptation of the HERA model to older adults. Bilateral activation of PFC (BA 47) during episodic memory retrieval was first reported by Cabeza *et al.* /13/ during recall of word pairs, and has been confirmed recently for item recognition /12/. Given that in both tasks, memory performance was comparable across groups, the authors suggested that activation of left PFC may have functionally compensated for deficient information processing by the right PFC. Correlating the activity of PFC with performance would have been necessary to confirm this hypothesis but the small variability of memory scores made this difficult. Bilateral activation of PFC has also been reported for recognition of words /44/ and faces /29/ in older adults who were impaired at memory retrieval. However, in these studies, further correlational analysis suggested that activation of the left PFC was not necessarily compensatory. Indeed, whereas activity of the left PFC was a good predictor of successful performance across groups in the study of Grady *et al.* /29/, it was not a good predictor in that of Madden *et al.* /44/. Conversely, in the latter study, activity of the right PFC predicted memory retrieval equally well for both groups, whereas in the former study activity in the right PFC predicted successful performance at retrieval in the old but not in the young.

Bilateral activation of the ventrolateral PFC has also been reported during a low-demanding (or infracapacity) working memory task, encompassing short-term information storage. In a recent PET study, Reuter-Lorenz *et al.* have shown that the asymmetric pattern of PFC activation typically observed when comparing verbal (VWM) versus spatial (SWM) short-term working memory tasks was not maintained in older adults /72/. Age-related differences in memory performance were only significant for the VWM. Univariate analysis of the PET images indicated that young adults had greater left frontal activity during VWM and right frontal activation during SWM, whereas older adults showed bilateral frontal activity in both tasks. Based on these results, the authors interpreted the recruitment of the contralateral PFC as possibly reflecting a compensatory mechanism. Indeed, activation of the right hemisphere homolog of Broca's area has been shown in patients who have recovered language function after damage to Broca's area /9,92/. Given that the connectivity of the PFC is modified by age, the development of an analogous plastic mechanism compensating for deficient processing in the elderly seems conceivable. However, the fact that performance during VWM was impaired in the elderly, plus the results of a correlational analysis showing no significant correlation between the right ventrolateral PFC and successful performance in the old adults, casts some doubt on this interpretation.

An alternative interpretation is that increased activation of the PFC in the elderly may be related

to the higher degree of difficulty experienced by older adults in performing demanding memory tasks. This hypothesis is supported by neuroimaging studies showing that in young subjects, increasing task difficulty or memory load is accompanied by augmented activity of prefrontal cortices. For example, increasing activity of the left ventrolateral PFC (BA 10) has been reported in young adults during episodic memory retrieval with increasing task difficulty /58/. Likewise, increased activation of DLPFC (BA 9/46) has also been reported for working memory tasks in which either the memory load /8,74/ or the delay interval between stimuli /33/ were increased. Examples of age-related increases in PFC associated with difficulty can be found in two recent PET studies and one fMRI study describing the effect of age on highly demanding working memory tasks. Unlike the asymmetry associated with episodic or low-demanding working memory tasks, performance on demanding working memory tasks is associated with bilateral activation of the PFC in the young /74,76/. Grady *et al.* /33/ showed that the typical bilateral activation of ventrolateral PFC observed during working memory for faces was also present in older adults who performed slightly worse than their younger counterparts. In addition, old subjects also exhibited higher activity in DLPFC with increasing delay. Given that activity in this area was positively correlated with reaction time (RT), it is likely that its activation in older subjects reflected difficulty. Age-related increases in left DLPFC have also been observed in older subjects while performing the Operation Span task, a demanding working memory task in which subjects perform a memory task while verifying simple equations /82/. Overall, young and old subjects exhibited similar levels of accuracy when performance in the Operation Span task was compared to mathematical and memory tasks alone. However, the high variability of the brain data for the young group revealed the existence of good and poor performers in the experimental sample. The result from re-grouping the sample was striking: whereas poor young performers and old subjects showed increased activity in left DLPFC for the Operation Span task, the good young performers did not. Thus, it is likely that recruitment of the left DLPFC by the old reflected difficulty in complying with the task demands.

These results are similar to those of a recent fMRI study encompassing the effect of aging on three different working memory tasks requiring supracapacity information maintenance /75/. Subjects had to encode high or low memory load stimuli presented in a memory set (letters in experiment 1 and 2; objects and locations in experiment 3), retain them for either 8 or 12 seconds, and then determine whether a single stimulus was presented in the memory set or not. Accuracy was similar for both groups, although latency was higher for older adults. Univariate analysis of the fMRI images yielded an overall significant increase in activity of bilateral DLPFC (but not ventrolateral PFC) in younger adults for the high load condition. However, subsequent correlational analysis with RT indicated that activation of DLPFC was negatively correlated with performance in the young, but positively correlated with performance in the old. Thus, whereas good young performers exhibited lower activity in DLPFC than the poorer young performers, good old performers exhibited higher activity in DLPFC than the poorer old performers. These findings confirm the results obtained by Smith *et al.* using different working memory tasks, i.e., that low performing young and high performing old adults require a higher level of activation of DLPFC to achieve optimal performance.

In addition to the literature based on local changes in brain activity, a couple of multivariate analyses have been carried out to investigate the effect of aging on the functional connectivity of PFC during memory performance. Using path analysis, Cabeza *et al.* /14/ constructed a model to investigate the neural interactions leading to age-related recruitment of left BA 47 during episodic retrieval of word pairs /13/. In accordance with the HERA model, the neural interactions between left area 47 and related cortical areas, such as medial frontal gyrus and anterior cingulate, were positive during encoding in young adults, whereas the neural interactions between right area 47 and related cortical areas on the right hemisphere were positive during retrieval. This asymmetric pattern was not seen in older adults. Rather, although frontal interactions were not clearly lateralized

during encoding, they were bilaterally positive during retrieval.

The effect of aging on the functional connectivity of the PFC has also been investigated during associative learning. Using a combination of univariate and multivariate analyses, Shreurs *et al.* /79/ scanned young and old subjects during eyeblink conditioning by PET. Old subjects exhibited significantly lower levels of conditioning. Initial analysis indicated that whereas both groups showed learning-related changes in the cerebellum, inferior right PFC and cingulate, only young subjects exhibited higher activity levels in the inferior left PFC. Subsequent partial least squares (PLS) analysis using the inferior left PFC to identify functionally related regions, showed that this area was highly associated with cerebellum, hippocampus, thalamus and temporal cortex during eyeblink conditioning in the young, but not in the old. These findings are consistent with a previous study on associative learning showing that young subjects who showed low neural interactions with left prefrontal cortex did not learn the association /48/. These findings suggest that assessing the connectivity of key neural structures of memory is necessary to understand the broad impact of aging on memory decline.

The evidence discussed in this section suggests that in addition to changes in hippocampal activity, memory performance in older adults is associated with differential recruitment of prefrontal cortices. Nevertheless, additional recruitment of PFC during memory tasks is not always related to improved memory performance in the elderly. In fact, the experimental evidence gathered above, from episodic and working memory tasks, indicates that age-related increments in the activity of PFC may reflect task difficulty, a change in encoding strategy or functional compensation. Thus the observation of a consistent activation pattern across different memory tasks, such as the bilateral PFC activation described by the HAROLD model, does not necessarily reflect the existence of a unique physiological mechanism and should thus not be used by itself to infer function.

FUNCTIONAL REORGANIZATION OF THE BRAIN - WHAT DO WE KNOW AND WHERE ARE WE GOING?

Most of the experimental evidence discussed in the preceding sections suggests that memory decline in older organisms is associated with deficient hippocampal processing of spatial and non-spatial information. Neuroimaging studies suggest that the functional integrity of prefrontal cortices is also compromised by age. But are these specific changes in brain function always detrimental? Some of the evidence cited above suggested that, in some cases, age-related changes in brain function might be compensatory and thereby facilitate performance. We now turn to evidence that bears directly on the question of compensation in older individuals.

The electrophysiological evidence discussed above appears to suggest that, when they occur, age-related changes in hippocampal processing are in fact disadvantageous /7,63,80,85/. However, a recent study carried out by Mizumori and Kalyani /54/ indicates otherwise. The authors examined the electrophysiological correlates of spatial learning in young and old rats that had become familiarized with a radial maze. Based on their learning performance, old animals were grouped into impaired or unimpaired. In order to assess whether unimpaired rats were using the same or a different neural mechanism than impaired rats to process spatial information, the number of errors made during acquisition was correlated with spatial encoding by hippocampal place cells. The results indicated that as fewer errors were made, CA1 cells of unimpaired old rats showed higher spatial selectivity. In other words, as learning progressed the cell's firing rate became more location and/or directionally tuned. This correlation was not significant for either young or memory-impaired old rats, suggesting that the rearrangement in spatial representation exhibited by the unimpaired old group was not a sign of deficient spatial processing but most likely the result of a compensatory mechanism for age-related deterioration.

Additional electrophysiological evidence supporting the existence of functional compensation in the rat hippocampus comes from a series of *in vitro* experiments carried out by Barnes and McNaughton

/6/. Using extracellular recordings, the authors demonstrated that the reduction in the number of afferent fibers to the granule layer of the hippocampus in old rats was associated with a larger synaptic field potential driven by the remaining synapses of the perforant pathway. Complementary intracellular recordings of granule cells indicated that this functional compensation was paired with a significant reduction in the voltage threshold and the latency of the action potential, suggesting that granule cells may have compensated for loss of synapses by becoming more responsive to electrical stimulation. It is likely that this or a similar adaptive mechanism underlies the change in spatial processing by CA1 cells reported by Mizumori *et al.*. Together with those of Mizumori and Kalyani, these findings seem to challenge the idea discussed above that place cells of old rats are either intact or less plastic than those of young rats. Instead, it appears that there is no general age-related deterioration of hippocampal cells but rather a differential effect in which some cells may be directly affected, some may be preserved and others may compensate for the neurobiological deterioration associated with age. These studies also highlight the importance of evaluating brain changes in the behavioral context.

In addition to the animal literature, several recent neuroimaging studies have provided direct evidence that functional compensation may also exist in humans. This possibility has been investigated in two recent studies aimed at examining the effect of aging on the functional connectivity of the hippocampus /24,34/. It is important to emphasize that by functional connectivity of the hippocampus, we refer to its relationship with other cortical structures, not to its intrinsic connectivity, which could be determined by using electrophysiological techniques. In one of these studies, Della-Maggiore *et al.* PET scanned young and old subjects while they performed a simple delayed-visual-discrimination task that yielded similar levels of performance in both groups. Analysis of task effects in the PET images revealed that whereas the right insula and left medial temporal gyrus were more active in young adults, the left superior frontal gyrus was more active in older adults. Interestingly, although no age-related differences in activity were found for the hippocampus, investigation of its functional connectivity by applying multivariate analysis (PLS) uncovered the existence of two different corticolimbic networks in young and old subjects. Specifically, whereas in older adults the hippocampus was highly associated with the superior and medial frontal gyrus, anterior and middle cingulate gyrus, middle temporal gyrus and caudate, in the young it was highly associated with more posterior areas such as bilateral fusiform gyrus, bilateral posterior cingulate, inferior frontal gyrus and left hippocampus. Interestingly, the corticolimbic regions specific for the old group were highly correlated with performance in the old but not in the young. Conversely, the pattern of regions identified for the young group was highly associated with performance in the young group but not in the old group. These findings support the hypothesis that age-related functional reorganization of corticolimbic networks may support spared visual memory in older adults.

Likewise, Grady *et al.* /34/ have recently reported evidence suggesting that functional compensation of corticolimbic networks may also be responsible for spared episodic recognition in older adults. PLS analysis of PET images revealed that during encoding of words and pictures hippocampal activity was highly correlated with that of ventral prefrontal and extrastriate regions in young subjects, but not in old subjects. Activity of these brain areas was also highly correlated with successful performance in the young but not in the old. In turn, hippocampal activity in old subjects was highly correlated with that of dorsolateral prefrontal cortices and parietal regions. Likewise, these regions were highly correlated with successful performance in the old but not in the young.

The recruitment of more dorsal areas of the prefrontal cortex by old subjects in both studies suggests a compensatory role for these regions. This observation is strengthened by the fact that each network was highly related to performance in the corresponding age group but not in the other, suggesting that recruitment of the dorsal regions of the PFC by the old was necessary to maintain behavioral performance. Although the findings of these neuroimaging studies illustrate the existence of age-related changes at a higher level of brain

organization (i.e., networks of neuronal ensembles), they probably reflect physiological changes occurring at a neuronal/neuronal ensemble level of organization, such as those illustrated with the electrophysiological studies. In this regard, it is likely that age-related changes in the anatomical connectivity of the hippocampus have modified its ability to process information efficiently, resulting in functional rearrangement of the large-scale corticolimbic network, thereby engaging more anterior and dorsal brain areas to compensate for deficient hippocampal processing in the old. Thus it may be that age-related changes at the cellular level within a brain region may impact more globally by altering how this region interacts with distal areas at the level of large-scale neural networks.

DIFFICULTIES ASSOCIATED WITH THE CURRENT APPROACH TO THE STUDY OF AGING

The experimental evidence discussed in previous sections indicates that age-related changes can result in deterioration, preservation or functional reorganization of neurobiological substrates. Identifying which of these alternatives underlies age-related changes in brain activity constitutes a major challenge of aging research. In the preceding sections we have presented experimental evidence indicating that changes in regional activity are necessary but not sufficient to infer the effect of aging on the functional neuroanatomy of memory. Therefore, activation may not always reflect compensation and deactivation may not always reflect dysfunction. Neural activity is clearly modulated by a number of different factors in old, as well as young adults, and thus should be interpreted within the experimental context. Among these factors are the behavioral relevance of the region(s) in question, task-related differences, task difficulty, the use of different cognitive strategies, as well as statistical limitations. Several experimental strategies, some of which have been mentioned earlier, can be implemented to control for confounding factors and thus aid in interpreting the aging data. In this section we summarize some of these problems and propose possible solutions to help in dealing with them.

Behavioral relevance

As mentioned repeatedly throughout the preceding sections, a main step in interpreting the effect of aging on a brain region is to examine whether its activation is related to memory performance. Only then can a deficit in information processing be differentiated from a possible compensatory role of the structure. The simpler approach relies on computing the Pearson correlation of each separate region and behavior. According to this approach, an age-related increment in brain activity would be interpreted as compensatory if the area was positively correlated with successful performance in the old but uncorrelated in the young, or as a deficit if it was negatively correlated with performance in the old and positively correlated with performance in the young. Conversely, an age-related reduction in brain activity would be interpreted as reflecting a deficit if it was positively correlated with successful performance in the young but negatively correlated with performance in the old. A more thorough approach would be the application of multivariate statistical analysis to identify brain patterns whose relationship with memory performance varies with age. By applying this technique to PET images obtained from young and old subjects performing a visual memory task, McIntosh *et al.* /49/ were able to identify a pattern of brain regions whose activity was differently associated with memory performance across groups, even though the overall level of performance was similar across groups. This approach of directly assessing brain changes in the context of performance provides the best way to determine the ultimate behavioral significance of brain changes and whether this significance changes with age.

Task specificity

It has long been shown that neural activity in response to stimulation is not only determined by the sensory input to the brain, but also by the task demands /1,64/ As suggested by the studies of Della-Maggiore *et al.* /24/ and Grady *et al.* /34/, the functional connectivity of the hippocampus and PFC is likely to be modified by age. This change in functional connectivity of the corticolimbic net-

work would likely alter the response of the nervous system to task demands. Experimental evidence supporting this hypothesis comes from a recent PET study carried out by Esposito *et al.* /25/, in which they examined age-related changes in brain activity associated with two tasks with varying dependency on working memory processing: the Raven's progressive matrices (RPM) and the Wisconsin Card Sorting Test (WCST). Analysis of the brain images indicated that whereas some areas normally recruited during performance on RPM, such as the parahippocampal gyrus, inferior parietal and fusiform cortices, were less active in the old, other areas typically active during performance on WCST, such as the parahippocampal gyrus, cingulate and inferior parietal gyri, were more active in older adults. Thus, although both tasks were problem-solving tasks with a working memory component, the effect of aging on the parahippocampal gyrus differed according to specific cognitive demands. Task-related changes in activation have also been reported for old subjects during recognition and recall of word pairs /13/. The results support the general conclusion that changes in brain activity *per se* do not necessary reflect the neural effect of aging, but, as in young adults, may reflect task modulation of incoming information. Therefore, a thorough examination of age-related effects in brain activity should encompass testing older adults in different tasks, even though they tap similar cognitive processes.

Task difficulty

When confronted with an experimental task, some individuals may find it more demanding than others. As mentioned earlier, individual differences in information processing can result in differential patterns of brain activity. For example, activation of the left PFC during episodic memory tasks increases with difficulty, whereas activation of the DLPFC during working memory increases with memory load and delay interval /33,58,74/. One way of eliminating task difficulty as a possible confound is by selecting memory tasks that can be similarly performed by young and old subjects. However, similar level of performance as assessed by averaging within age groups will not always guarantee the elimination of individual differences in perceiving task difficulty. Indeed, the outcomes discussed earlier from the study of Smith *et al.* /82/ indicate that increased activity in the left DLPFC during working memory was found in poor young performers and older adults, whereas good young performers did not show this pattern. Including experimental conditions with increasing level of difficulty within group (by increasing memory load or interval delay) may help solve this problem by allowing the examination of the effect of task difficulty on an individual basis.

Cognitive strategy

When trying to determine whether certain brain areas or their connections have been functionally reorganized with age, one has to face the possibility that older subjects may be using a different cognitive strategy to solve the task. If efficient, this change in strategy, rather than functional reorganization, may compensate for deficient processing associated with a cognitive ability susceptible to age. A change in sensory processing strategy has been suggested by some studies showing that old animals rely more on local than on distal cues to learn a maze /5,87/. Because this behavior has also been reported after fimbria-fornix lesions, it has been argued that such change in strategy may partly originate in age-related disruption of hippocampal function /86/. Age-related changes in processing strategies have also been reported in humans (e.g., semantic encoding of verbal stimuli) /43/. One way of avoiding the occurrence of alternative strategies is by selecting stimuli that resist alternative encoding. In the case of rats, testing the animals with either the distal or the local cues presented in the maze one at a time would be sufficient to eliminate the use of alternative landmarks. In the case of humans, using abstract stimuli, such as gratings, instead of faces, pictures or words, would reduce the possibility of semantic encoding as a possible confound. Another option would be to use a similar orienting strategy, in which subjects are asked to make the same judgments about stimuli (e.g., word meaning, physical characteristic of stimuli). These strategies should always be complemented with post-experiment debriefing reports, which should add support to the experimental results.

Statistical approach

The use of univariate statistics to assess changes in neural activity assumes that function is localized and brain activity is additive. We have shown evidence supporting the idea that the role of a brain region is not constant, but determined by its interaction with functionally associated regions /14,24, 25,34/. Therefore, it is possible that the functional connectivity of a region is very much affected by age even though the region itself does not show age-related differences in activation /24,42/. This situation can be illustrated with the study carried out by Della-Maggiore *et al.* in which activity of the hippocampus did not differ across age groups. In that particular case, functional reorganization of the corticolimbic network in the elderly would have remained unnoticed had the authors focused the data analysis solely on task-related changes in brain activity. Thus, multivariate techniques present a clear advantage for exploring the functional connectivity of regions regardless of their level of activation, and should be used to complement univariate analysis and fully estimate the impact of aging on the functional neuroanatomy of memory.

CONCLUSIONS

Unlike the once generally accepted concept of global deterioration, aging is associated with specific changes in the anatomy, physiology and molecular biology of selected brain areas. Among the cerebral regions involved in cognition, the hippocampal formation and the prefrontal cortex appear to be the most susceptible to the effects of age. Age-related changes can result in deterioration, preservation, or functional reorganization of the neural substrates of memory. Identifying which of these alternatives underlies age-related changes in brain activity constitutes a major challenge of aging research. Convergent experimental evidence from physiological and neuroimaging studies suggests that understanding the impact of aging on the relationship between brain activity and behavior - as opposed to its impact on brain activity alone - is a necessary step to identify the biological nature of age-related changes. Moreover, the implementation of experimental tools aimed at controlling for factors, such as the use of alternative encoding strategies, that can be confounded with the effect of age is imperative. In this regard, the implementation of tasks with different levels of difficulty should be considered to further tease apart the nature of age-related changes in neural activity.

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