

## Original Article

# Vascular changes and brain plasticity: a new approach to neurodegenerative diseases

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**Abstract:** The world's population is aging, which will result in an increasing prevalence of neurodegenerative diseases, such as dementia. Observations from functional brain imaging that older brains can be more active than their younger counterparts challenge stereotypical ideas of aging. In those aging successfully, brain activation is more anterior, less lateralized and more coordinated than in those at risk of, or suffering from, cognitive impairment. Several theories have been proposed to explain these findings. One of the most enticing is the scaffolding theory, which posits that the older brain is a plastic homeostatic organ, able to compensate for its deteriorating structure. However, with aging also come diffuse vascular changes and the resulting white matter damage. This decreases the compensatory capacity, and dementia can ensue. This and alternative hypotheses will be discussed, along with potential methodological problems of this genre of study and with their clinical implications.

**Keywords:** Aging, dementia, imaging, scaffolding, plasticity, compensation

### Functional changes with aging

With an aging population and rising life expectancy, an increasing social and financial burden of neurodegenerative disease is inevitable. The US prevalence of dementia has been reported as 14% in those over 71 years, and the financial cost as over \$170 billion per year [1]. Without a thorough understanding of its pathology, efforts to optimize the prevention and treatment of this disorder may be fruitless.

Aging leads to clinically measurable behavioral changes including decreased processing speed, working, and long-term memory. Structural brain changes can also be observed, for example decreased volume of frontal and parietal regions [2, 3], decreased white matter integrity [4, 5], and neurofibrillary tangles and plaques even in those with normal cognition [6, 7].

Historically, it was believed that normal aging was marked by massive nerve cell loss, less neuronal activation and an absence of the plasticity that facilitates skills acquisition and recovery after injury in the young. However, the appli-

cation of functional brain imaging and stereological principles of cell counting methods has led to some surprising insights. Significant cell loss does not occur during normal aging, and changes in dendritic complexity are subtle and region-specific [8]. Excitingly there is evidence to suggest that older brains are more active than their younger counterparts implying that they may in fact be dynamic, homeostatic organs.

### Normal Aging

Functional brain imaging allows for the dynamic observation of the neural substrates of cognitive processing. It has demonstrated a number of differences in activation patterns in older compared with younger adults: a posterior to anterior shift, a lateralized to bilateral shift, decreased coordination of large scale brain networks and decreased functional connectivity of brain regions.

### Posterior to anterior shift

A posterior to anterior shift in BOLD fMRI activa-

tion pattern can be found with increasing age across task difficulty and response confidence levels, when performance is matched [9]. Increases in frontal activity were correlated with better performance and with occipital decreases. Similarly, increased frontal BOLD signals have been reported during tasks and at rest in older compared with younger subjects [10]. A further study supporting this shift in activation during an encoding task, found weaker correlations between hippocampus and posterior cortices (bilateral medial temporal lobe (MTL), posterior cingulate, right parietal, and inferior temporal (IT) regions) in older adults, whereas correlations with anterior cortices, (including anterior cingulate, bilateral ventrolateral prefrontal cortex (PFC), right dorsolateral PFC, and superior frontal cortex) were stronger [11].

Fourteen younger and thirteen older adults both activated inferior frontal and lateral occipital regions bilaterally during incidental encoding of visual scenes; however, older adults showed less parahippocampal activation than young adults and more activation than young adults in middle frontal cortex [12]. Moreover, there were significant negative correlations between inferior frontal and parahippocampal activity for old, but not young subjects, suggesting that those older adults, who showed the least parahippocampal engagement, activated inferior frontal areas the most.

### *Unilateral-to-bilateral shift*

Prefrontal activity during cognitive performance tends to be less lateralized in older compared with younger adults. The HAROLD model (hemispheric asymmetry reduction in older adults) has support from functional neuroimaging in the domains of episodic, semantic, and working memory, perception, and inhibitory control [13]. Reuter-Lorenz and colleagues [14] used positron emission tomography (PET) to investigate verbal and spatial short term storage in young and older adults. In the young, activation was predominately left lateralized for verbal working memory, and right lateralized for spatial working memory. However, in the older subjects, a global pattern of anterior bilateral activation was seen for both types of memory. Analysis of frontal regions showed bilateral activation in areas associated with rehearsal and laterality in dorsolateral prefrontal sites. In a

second PET study of young and older (low and high performing) adults during the recall and source memory of recently studied words [13], low performing older participants recruited right prefrontal cortex (PFC) regions, as did the young. However, high performing older adults showed bilateral PFC recruitment. Thus, low performing older adults recruited a similar network as younger adults, but appeared to use it inefficiently. Morcom and colleagues [15] found that during a source memory task, older adults' retrieval-related increases in activity were more widespread and of greater magnitude than in the young. Moreover, regions demonstrating retrieval-related decreases in activity were almost absent in the older participants. They concluded that the findings suggested an age-related decline in the efficiency with which neural populations support cognitive function.

Repetitive transcranial magnetic stimulation (rTMS) studies have also lent support to a reduction in hemispheric asymmetry with greater age. rTMS creates a short lasting reversible functional brain lesion in the stimulated brain area. Rossi and colleagues [16] found that in young adults, accuracy of memory retrieval was more affected by left sided than right sided rTMS. In contrast, older adults were equally affected by left and right sided rTMS.

Despite this convincing evidence, a couple of studies have reported results at odds with the HAROLD model by finding bilateral PFC activation in young adults, but only unilateral activation in older adults whilst encoding pairs of concrete-related, concrete-unrelated, and abstract pictures [17]. A second study reported that improved performance of a task was associated with *increased* hemispheric asymmetry in PFC in older adults [18].

### *Less coordination in large scale brain networks/less functional connectivity in healthy and pathological aging*

Although there are no direct approaches to measure connectivity in the living human brain, one indirect approach uses fMRI and examines resting-state functional connectivity with BOLD fluctuations that correlate between functionally connected regions [19]. Some of these, predominantly active at rest, have been described as "default mode networks" (DMN) and are thought to mediate internal states of cognition

e.g. reflection, planning in those with normal cognition [20-22]. The finding that resting-state BOLD correlations are modulated by recent experience has led to the suggestion of a dynamic phenomenon which may be involved in mnemonic processes [23].

Older subjects with normal cognition have reduced and less coherent activity of default mode networks. In an fMRI study of 93 adults, Andrews-Hanna and colleagues reported that anterior to posterior components within the DMN were most severely disrupted with age [24]. Severe reductions in correlation were present even in older adults free from Alzheimer's disease (AD) (diagnosed using *in vivo* amyloid imaging). Reduced correlations were associated with disruptions in white matter integrity (measured using diffusion tensor imaging) and poor cognitive performance (executive function, processing speed and memory). Damoiseaux and colleagues showed decreased activity in older versus younger subjects in two DMN resembling the previously described default network, containing the superior and middle frontal gyrus, posterior cingulate, middle temporal gyrus, and the superior parietal region [25]. Amyloid accumulation is correlated with functional disruption of the default network [26, 27], even in those with normal cognitive performance.

In younger adults, default networks are suppressed during cognitive tasks [28, 29]. This is generally thought to reflect a switch away from "default-mode" processing in the passive condition (thus deactivating regions supporting the default mode), to processing during the task in regions that support task-related processing. Older adults show less suppression of DMN during tasks, and this is correlated with their performance on the task. Patients with mild cognitive impairment show less deactivation than healthy controls, but more than those with Alzheimer's disease [30, 31]. One can hypothesize that older adults, especially those with dementia, have reduced resources to divert to active tasks or difficulties with resource allocation [31, 32]. It has been suggested that increased frontal activity in older adults represents a failure to shift out of the relaxation or default state into more active modes of cognitive processing [33].

### **At risk of pathological aging**

Although a number of changes have been ob-

served in those aging normally, are these relevant to those aging pathologically? Individuals carrying an ApoE4 allele, a well-established genetic risk factor for later onset Alzheimer's disease (AD), provide an opportunity to investigate this further.

### **Apo E4**

Interestingly, patterns of activation during memory tasks differ depending on the genetic risk of AD, even in the absence of clinical features of the disease. Bookheimer and colleagues [34] determined fMRI activation patterns in 30 neurologically normal subjects (aged 47-82 years), during tasks (memorize and recall unrelated word pairs) and at rest. Sixteen of the subjects were carriers of Apo E4, and 14 were homozygous for Apo E3. Memory was reassessed in 14 after 2 years. The magnitude and extent of brain activation in left hippocampal, parietal, and prefrontal regions was greater in carriers of E4 compared with E3. The degree of base-line brain activation correlated with the severity of memory decline at 2 years. In another study, picture learning was completed in nondemented subjects with and without the Apo E4 allele [35]. Those with ApoE4 showed a greater magnitude and extent of BOLD response in bilateral fusiform gyri, right superior parietal lobe, left middle frontal gyrus, and the medial frontal gyrus. Han and colleagues [36] reported that Apo E4 carriers had greater activity in right hemisphere regions compared with non-carriers during a verbal paired-associate task. Differential BOLD response occurred in the presence of equivalent behavioral and neuropsychological performances as well as comparable hippocampal and overall structural segmentation volumes between groups. No differences between genetic groups in activation patterns have been found during digit span tests. This may suggest that additional cognitive effort in Apo E4 carriers is specific to memory tasks [37].

Functional imaging may also help in the prediction of cognitive decline in those at risk. Older  $\epsilon 4$ -carriers show reduced cerebral blood flow relative to older non-carriers despite preserved grey matter volume [10]. Woodard and colleagues [38] found that greater fMRI activation in those with Apo E4 carriers was associated with a lower probability of decline over 18 months. In summary, those at genetic risk of Alzheimer's disease demonstrate over-activation of certain brain regions compared to

those not at risk. This may be an attempt to compensate for deteriorating brain structure earlier, or to a greater extent than in normal controls.

### *Other genes associated with AD*

One study has reported an apparent compensatory recruitment in a 20-year-old, largely asymptomatic carrier of the presenilin I gene [39], a gene which leads to certain development of AD at a relatively young age. More work is needed to determine whether this is a robust finding, and whether carriers of presenilin II and APP genes show similar patterns.

### **Pathological aging**

#### *Mild cognitive impairment*

Mild cognitive impairment (MCI) is a clinical diagnosis and probably describes a group of heterogeneous causative pathologies. Patients have objective memory problems but without impairment in activities of daily living. The annual rate of conversion to dementia has been estimated to be 10-12% [40-42], and hence they represent an informative population to study in the investigation of dementia. Structurally, the brains of those with MCI have reduced entorhinal cortex neurons [43], reduced hippocampal volumes [44], and reduced white matter integrity [45].

Dickerson and colleagues [46] report on fMRI in 32 elderly volunteers with MCI. They performed a visual encoding task and were tested for recognition of stimuli afterwards. Greater extent of activation within the hippocampal formation and parahippocampal gyrus (PHG) correlated with better memory performance. A paradoxical relationship was found between the extent of activation and clinical status at baseline and follow up (2.5 years). Those with more impairment recruited a larger extent of right PHG during encoding. MCI patients exhibit increased fMRI responses in left anterior hippocampal, parahippocampal and fusiform regions [47, 48]. Hippocampal volume and parahippocampal activation appear to be correlated negatively in MCI but not in controls or those with AD.

### **Theories of normal aging**

Several theories have been proposed to explain the processes behind the differing patterns of

activation found in aging. These will be summarized below.

#### *Cognitive reserve*

This theory attempts to explain the finding that factors associated with cognitive deterioration do not necessarily predict performance [49, 50]. The cognitive reserve theory suggests that decline is mitigated by compensatory activity or other factors such as education or intelligence [51]. Amyloid deposition is associated with lower cognitive performance both in AD patients and in the normal elderly, but the association is modified by cognitive reserve, which can be estimated by education and American National Adult Reading Test intelligence quotient as proxies [52]. At progressively higher levels of cognitive reserve, increased amyloid deposition was less or not at all associated with poorer neuropsychological performance.

#### *Scaffolding*

The Scaffolding Theory of Aging (STAC, [33]) assumes that frontal activation increasing with age is a marker of an adaptive brain. Compensatory scaffolding is seen as a response to challenges posed by declining neural structures and function. It involves the use and development of complementary, alternative neural circuits to achieve a cognitive goal. Synaptogenesis and neurogenesis, processes previously believed to be absent in the elderly brain, are thought to mediate this. Differences in resilience to aging may result from differences in the brain's ability to scaffold. According to this hypothesis, clinical cognitive impairment is evident once the need for scaffolding exceeds the brain's capacity for plasticity and reorganization.

The ability to use this homeostatic mechanism may be strengthened by cognitive engagement, exercise and low levels of default network engagement. A randomized longitudinal dual-task training study showed performance improvements were correlated with an increase in hemispheric asymmetry and a reduction in age differences in ventral and dorsal prefrontal activation. Voss and colleagues found aerobic training improved resting functional efficiency, increased functional connectivity between frontal, post and temporal cortices within default mode and frontal executive networks [53]. Increased functional connectivity was associated with a greater improvement in executive function.

### *CRUNCH*

Another proposal to explain the less lateralized and more anterior activation patterns in older brains is the Compensation-related utilization of neural circuits hypothesis (CRUNCH) [54]. This hypothesizes that decreased neural efficiency in old age leads to increased engagement of neural circuits. More neural resources are engaged by older brains to accomplish computational goals completed with fewer resources by younger brains. Therefore, the elderly are more likely than young adults to show over-activations at lower memory loads, and under-activations at higher memory loads.

In support of this, Cappell and colleagues [55] used event-related fMRI and found age-related over-activation in the right dorsolateral prefrontal cortex with lower memory loads despite equivalent performance accuracy across age groups. In contrast, with the highest memory load, older adults were significantly less accurate and showed less activation compared with their younger counterparts. CRUNCH is compatible with the Scaffolding Theory of Aging and Cognition because compensatory activations may provide scaffolding to support aging cognition.

### *De-differentiation*

Others have suggested that rather than having a specific compensatory function, these activation changes are by-products of aging. This could represent a loss of regional specialization or specificity and a greater engagement of generalized processes. The concept of dedifferentiation originated in behavioral research with older adults [56, 57].

### *Other Theories*

Cabeza and colleagues have proposed that the scaffolding and de-differentiation models may be compatible [58]. Additional interpretations of the changes seen in the aging brain on functional imaging include age related changes in cognitive strategies and task-related neural networking, lateralized connectivity changes [59], and increased neural noise [60, 61].

### **Methodological problems**

Despite the encouraging and exciting findings in

this wealth of functional imaging studies, one must be aware of certain potential limitations when interpreting them. Firstly, functional MRI uses blood flow as a proxy for neural activity; it is not a direct measure of neuronal activity. Secondly, it is unclear whether comparisons in activation can be made between participants that have different task performances. For example, is the decreased activation observed in AD patients a product of neuropathology, poorer task performance, or a combination of both? Finally, using episodic memory tasks in the scanner may present challenges. Episodic memory performance declines as symptoms appear in MCI or AD and hence discrepancies in task performance may confound interpretation of data. These tasks are challenging for the elderly, and resulting frustration and effort may produce increased activation.

### **Conclusions**

White matter changes are prevalent in the aging brain [62]. These may consist of diffuse changes ("white matter hyperintensities") or small infarcts. Vascular compromise, secondary to small vessel disease, is thought to underlie much of this damage to white matter tracts. Hypertension is a key risk factor [63]. Frontal white matter tracts seem to be more vulnerable to such deterioration, as shown on DTI [64]. Non-specific scaffolding may be able to compensate for this damage for a certain time. Once diffuse vascular changes occur, the compensatory capacity declines and clinical deterioration (dementia) ensues [51]. One can hypothesize that those at genetic risk for Alzheimer's disease are more susceptible to vascular compromise and white matter tract damage, and hence need to compensate earlier.

### **Clinical Implications**

If differences in functional imaging patterns in successfully aging adults represent an attempt to compensate for deteriorating brain structure, a deeper understanding of resilience to aging is possible. Early detection and intervention for those at risk, and ultimately preventative strategies may result. There is some indication already that scaffolding may be strengthened by cognitive engagement [65], and exercise [66, 67] and weakened by depression [68]. The establishment of the plasticity potential of the older brain has wider implications beyond

neurodegenerative disease.

## Declaration of Conflicts of interest

The authors declare no conflicts of interest

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