Age-Related Changes in the Structure and Function of Brain Regions Involved in Pain Processing

Michael J. Farrell, PhD

Florey Neuroscience Institutes, University of Melbourne, Parkville, Victoria, Australia

Reprint requests to: Michael J. Farrell, PhD, Florey Neuroscience Institutes, University of Melbourne, Level 2, 161 Barry Street, Parkville, Vic. 3010, Australia. Tel: +61-3-8344-1941; Fax: +61-3-9347-0446; E-mail: michael.farrell@florey.edu.au.

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Abstract

Objective. This review summarizes the scientific literature addressing the effects of aging on pain processing in the brain.

Design. A literature search was undertaken using PubMed and search terms including pain, aging, and brain.

Settings and Patients. Studies including healthy older people and older people with painful disorders were reviewed.

Measures. Publications reporting the outcomes of neuroimaging techniques including positron emission tomography, structural and functional magnetic resonance imaging, and electroencephalography in samples incorporating older people were reviewed.

Results. Age-related decreases in regional brain volume occur in structures implicated in pain processing, and are most pronounced in the prefrontal cortex and hippocampus, whereas age-related atrophy in brainstem regions involved in pain modulation is less pronounced. Functional brain imaging has revealed decreased pain activation in the putamen and insula among older people during extrinsic stimuli, but any effects of aging on the processing of clinical pain are yet to be reported.

Conclusions. The network of brain regions involved in pain processing are subject to age-related changes in structure, but that the functional implications of these changes are yet to be determined.

Key Words. Older Adults; Magnetic Resonance Imaging (MRI)

Introduction

This review will examine the proposition that age-related changes in the brain are likely to impact on pain processing by briefly discussing the neuroanatomy of pain processing, by summarizing the literature of aging effects on brain structure and function, and through reference to applied studies of pain, aging, and brain structure and function.

The effect of aging on the pain experience cannot be encapsulated simply as an increase, a decrease, or no change in sensitivity because all three situations have been identified in cross-sectional studies of pain and aging. Psychophysical tests have shown that older age is generally associated with an increase in pain threshold, a decrease in pain tolerance, and an increase in the duration of hyperalgesia after tissue injury [1]. Persistent pain is more common in older people, reflecting the epidemiology of many painful chronic disorders such as arthritis and neuropathic pain states [2], although age-related differences in pain processing could provide a partial explanation for the increased vulnerability of older people to ongoing pain. However, some clinical conditions are associated with a decreased risk of pain with increasing age, most notably disorders of the viscera [2]. The variability of aging effects on pain clearly reflects a processing system incorporating multiple components that do not age uniformly. Pain is a function of the brain and the brain is subject to age-related change so it is likely that interactions between brain aging and pain processing contribute to the experience of pain in older people. The focus of this review will be on the extent to which brain aging could provide an explanation for the range of age-related changes in pain experience.

Pain Processing in the Brain

Age-related changes in structure and function occur differentially across brain regions and so it is likely that aging impacts on different pain processing regions to greater or lesser degrees. Understanding the likely impact of aging on pain processing would be facilitated by first apprehending the functional roles of the brain regions in the pain network.
Farrell

The functional roles of regions within the pain network have been inferred from existing knowledge of functional neuroanatomy and tested with functional brain imaging techniques such as electroencephalography (EEG), positron emission tomography, and functional magnetic resonance imaging (fMRI). The literature of functional brain imaging of pain is dominated by studies involving extrinsic stimuli applied to healthy people. Experimental pain in healthy people is represented in a distributed brain network that reflects the multidimensional nature of the experience [3]. Regional brain activation during experimental pain is influenced by many factors that are known to shape the experience of pain, including stimulus attributes [4,5], concurrent mood state [6], and thoughts about pain as well as distracting thoughts [7,8]. Irrespective of the circumstances that shape the experience, there are core brain regions that are commonly activated during experimental pain. These regions include the primary and secondary somatosensory cortices, the insula, anterior cingulate cortex, thalamus, prefrontal cortex, and posterior parietal cortex [9].

The ventral posterior thalamus receives input from the spinothalamic tract and projects to the primary and secondary somatosensory cortices. These regions have been ascribed with sensory/discriminative functions such as pain localization and intensity coding [3,4,10]. The anterior cingulate cortex receives inputs from the medial dorsal thalamus and shows levels of activation that are closely related to ratings of pain unpleasantness [11,12]. The insula cortex also has a role in the affective dimension of pain [13], although pain-related function varies between regions within the insula that are also distinguished by differences in cytoarchitecture [14]. Accumulating evidence suggests that the granular, posterior insula is particularly important for the representation of attributes that distinguish pain from other somatic sensations [15–17]. Pain activations in the prefrontal and posterior parietal cortices are likely to represent cognitive processes. Irrespective of the side of painful stimulation, both these regions show right hemisphere predominance [18], which is also observed in studies of brain responses associated with attention to novel stimuli [19].

Activation during experimental pain includes brain regions that are reported less frequently than the core components of the network. These activations can occur in regions that have roles in motor function, including the primary motor cortex, premotor cortex, basal ganglia, and cerebellum. Participants in functional brain imaging experiments are required to remain still during scanning and would consequently need to counteract reflex withdrawal responses and override any conscious desire to escape from painful stimuli, both of which could involve motor responses [20]. Experimental paradigms that involve modulation of pain responses are notable for activation in brain regions that are likely to be involved in the recruitment of descending pathways that modify dorsal horn responses. For instance, the pregenual region of the cingulate cortex and the periaqueductal gray show activation when painful stimuli occur concurrently with placebo analgesia or distracting cognitive tasks [7,21–23]. Recent studies indicate that these cortical and midbrain regions are likely to exert effects on dorsal horn responses via projections from the rostral ventral medulla [24,25].

Extrinsic stimuli have been used in clinical pain groups to identify brain activation associated with experimental pain. Generally, clinical pain patients show similar brain responses to experimental pain when compared with healthy people [9]. However, differences can be apparent when extrinsic stimuli are clinically relevant, such as the application of mechanical stimuli to allodynic skin, although these differences can vary considerably between clinical groups and experimental protocols [26]. What remains to be established is the brain representation of ongoing clinical pain that occurs in the absence of extrinsic stimulation. Progress in clinical pain imaging has been slow because clinical pain does not usually change with a frequency or predictability that is compatible with the standard methods used to measure human brain function. The recent application of a perfusion-based fMRI technique called arterial spin labeling has provided insights into the likely representation of one form of ongoing clinical pain [27]. Contrasts of regional cerebral blood flow between the pre- and postoperative stages of tooth extraction revealed activation in the core components of the pain network and other brain regions. Included among the brain regions activated by ongoing mouth pain were the amygdala, hippocampus, and posterior cingulate cortex, which are rarely activated during experimental pain. The identification of these additional regions is consistent with speculation that clinical pain is likely to involve phylogenetically older pain pathways that project from brainstem nuclei to cortical targets without relay through the thalamus and is consistent with observations made with chronic pain models in animals [28]. Activation in the amygdala and hippocampus during clinical pain could reflect processes involved in emotional responses, memory formation, and the regulation of the hypothalamic pituitary adrenal axis that would evolve as pain persists for longer periods.

In summary, pain in humans is represented in a distributed brain network that incorporates core regions ascribed with sensory/discriminative, affective/motivational, and cognitive/evaluative functions during the application of relatively brief, novel, noxious stimuli. Expansion of the core pain network can include brain regions involved in motor responses and the recruitment of modulating circuits. The representation of clinical pain states in the brain is an outstanding question, but preliminary findings suggest that brain regions receiving spinobulbar projections are likely to further expand the network of responses when pain persists. The distributed nature of pain in the brain means that aging could interact differentially with functional processing depending on the extent to which constituent brain regions are subject to age-related change.
Aging and Brain Structure and Function

Advanced age is associated with decreased brain volume and increased volume of the ventricles. Changes in brain morphology across the lifespan follow varied trajectories. Some brain regions increase in volume early in life and some plateau in middle age, but almost all brain regions show volume loss of varying degrees in the later years of life. The notable exception is the preservation of brainstem volumes into advanced age [29] because the brainstem contains nuclei that are critical for top-down modulation of dorsal horn responses to nociceptive inputs. The literature of aging and brain morphology is yet to reach a firm consensus on regional age-related volume loss but reports of large cross-sectional and longitudinal studies usually identify the hippocampus, prefrontal cortex, inferior temporal cortex, cerebellum, and striatum as regions showing the most pronounced decreases in volume with increasing age in the later part of the lifespan [29,30].

Contrary to conventional wisdom, neuronal loss only contributes to a small degree to age-related changes in brain morphology. Histological evidence has indicated that other factors including shrinking of neurons, loss of synaptic spines, and reduction of synapses are the principle drivers of decreased gray matter volumes in advanced age [31]. Additionally, age-related changes in white matter are likely to contribute substantially to decreased brain volumes [32]. The neurochemistry of the brain is also subject to differential age-related changes, with dopamine [33,34] and serotonin showing substantial age-related decreases [35,36].

Morphological and biochemical changes in the brain measured longitudinally or in different age groups explain variances in behavioral performance that are consistent with knowledge of regional brain function. A growing literature continues to identify age-related changes in brain measures including regional volumes, cortical thicknesses, white matter integrity, and receptor dynamics that show associations with measures of cognitive and behavioral performance. Instances include increased levels of cortical thickness in the inferior temporal lobe and posterior cingulate that are associated with increased performance on tests of fluid intelligence in older people [37], and longitudinal changes in hippocampus volumes that predict episodic memory performance in older people [38]. Of particular note are the observations that training can influence brain morphology and that increases in cortical thickness during training are correlated with improvements in memory performance in older people [39], which suggests that age-related changes in brain structure and function are dynamic.

The dynamic nature of the brain during aging has been amply demonstrated by functional brain imaging experiments. Comparisons between older and younger people of regional patterns of brain activation during cognitive tasks are notable for substantial differences that do not simply conform to the decreases that would be expected on the basis of age-related changes in cognitive performance and brain morphology [40]. For instance, cognitive paradigms that involve lateralized prefrontal cortex activations in younger people are frequently associated with bilateral prefrontal activations in older people [41]. The expansion and distinct nature of distributed networks in older people is also observed for other experimental paradigms, such as motor tasks [42,43]. More importantly, the extension of brain activity in older people would appear to be adaptive because the levels of activation in these additional regions show a positive correlation with task performance [44].

In summary, aging is associated with a loss of brain volume that exhibits regional variability. The ubiquitous nature of age-related changes in brain morphology means that all the regions in the hemispheres that activate during pain are likely to be affected by aging. The components of the broader pain network that show the most pronounced age-related decreases in volume are the prefrontal cortex and the hippocampus. In contradistinction, brainstem regions that project to pain processing regions and that are involved in descending modulation of dorsal horn responses show preservation of volume with aging. However, it is difficult to predict the impact of age-related changes in brain structure on pain processing. This difficulty arises because the aging brain can undergo plastic changes that seemingly compensate for decreases in functional capacity associated with morphological, histological, and biochemical decrements. The dynamic interplay between age-related structural and functional brain changes means that empirical tests of pain and brain aging must adopt a multimodal approach that integrates measures of behavior, brain morphology, and brain function.

Structure and Function of Brain Regions Involved in Pain Processing in Older People

Experimental Pain

The literature of pain and aging is replete with physiological studies that generally report an increase in the pain threshold for most stimulus modalities [1]. The reasons for decreased pain sensitivity in older people are likely to be multivariate, but brain processing is certainly a candidate factor. Changes in peripheral neural elements have been implicated in age-related increases of the pain threshold, with evidence supporting an increased contribution of nociceptive C-fibers to pain responses in concert with age-related decreases of Aδ fibers [45]. This relative deafferentation has implications for cortical processing because clinical conditions involving loss of peripheral nerves are associated with shrinking areas of the associated homunculi in the primary somatosensory cortex [46], although this effect has not been examined in the context of age-related change. The implication of peripheral fiber loss in older people for processing of threshold levels of pain has not been tested yet, and there are limited data available for age-related changes in somatosensory responses to innocuous stimu and associated brain function. In one study of aging and two-point discrimination,
dipole analysis of EEG potentials associated with fingertip stimulation showed an expansion of the representation of the fingers in the primary somatosensory cortex in older people that reflected age-related decrements in tactile acuity [47]. If replicated for painful stimuli, this expansion of the homunculus would be in direct contrast to the expected changes on the basis of decreasing peripheral inputs. However, speculations of this nature may be ill-advised. Due to the lack of empirical data, it is impossible to predict how aging actually impacts on the structure and functions of the primary somatosensory cortex in the processing of painful stimuli. Furthermore, a recent experiment involving fMRI measures of brain responses during stimuli at the pain threshold in young people indicated that the posterior insula, and not the primary somatosensory cortex, was the brain region that showed discrimination for pain [17], which elevates the posterior insula for focused attention in future investigations of age-related changes in the pain threshold.

Age-related changes in brain responses during suprathreshold thermal pain stimuli have been reported for EEG evoked potentials and fMRI measures. Brief laser stimuli at twice the pain threshold evoke decreased potentials at increased latency in older people compared with younger people [48], suggesting that aging leads to a decrease and slowing of brain activation during the experience of moderate pain. The brain regions contributing to the evoked potentials recorded in this study were not reported, but were presumably cortical. Brain activation during moderate levels of thermal pain measured with fMRI has identified regional age-related decreases in the anterior insula and supplementary motor area, albeit in a small sample using a region of interest analysis [49]. Replication of this study in a larger sample and a voxelwise analysis would be a welcome test of the veracity of this preliminary outcome.

Pain responses to mechanical stimuli are notable for showing a relationship to aging that is the inverse of other stimulus modalities, in that older people tend to be more sensitive to noxious pressure [1]. Age-related changes in regional brain activation have been investigated during the experience of pressure pain using fMRI and standard whole-brain analyses [50]. The only regions with age-related changes during moderately painful thumbnail pressure were the contralateral putamen and caudate, which both showed a decreased level of activation in the older group. Volumes of the putamen and caudate were decreased in the older group, but this atrophy was in proportion to global brain volumes, and individual levels of atrophy did not account for age-related changes in pain activation. The parsimonious explanation for the age difference in pressure pain activation is that motor responses were altered in the older people, although this proposition was not tested by the experimental design. Differences in pain modulation between the age groups provide another prospective explanation because there is evidence that the basal ganglia is involved in the recruitment of descending pain-modulating circuits (see [51] for review) and aging is associated with decreased efficiency of endogenous analgesia [52,53]. Supporting this interpretation is the observation that the older group required lower levels of stimulation than the younger participants to evoke moderate levels of pain during brain scanning.

Any summary of studies of aging and brain responses to experimental pain must necessarily be circumscribed given the lack of empirical data. The most substantive study to date, involving pressure pain in two age groups [50], reported decreased pain activation in the striatum, but is possibly more notable for an absence of age differences in the core regions of the pain network. At time of writing, there are no empirical data that address age effects on brain responses during experimental pain at levels near tolerance, nor the experience of pain in association with hyperalgesia.

Clinical Pain

Studies of brain structure and function in older people with clinical pain have appeared in the literature, although the majority of these studies do not expressly investigate age-related changes through contrasts with younger people. Musculoskeletal pain has been the most frequent clinical problem among older people participating in studies of pain and the brain, and osteoarthritis is the most common diagnosis for pain in these samples.

Two studies from independent groups have examined the effects of osteoarthritis of the hips on brain morphology when symptoms are present and after the resolution of pain following arthroplasty in patients with mean ages in the mid- to late 60s [54,55]. One of these studies reported a significant reduction in the volume of the contralateral thalamus in the osteoarthritis patients compared with controls [54]. This observation is consistent with reports from other clinical pain groups [56,57] and resonates with functional measures of the thalamus that indicate a decrease of activation associated with duration of persistent pain [58–60]. Thus, middle-aged people with persistent pain show qualitative changes in the thalamus that match findings in younger people. It remains to be established whether aging leads to different quantitative effects on the thalamus during clinical pain compared with younger people. The other major finding of the osteoarthritis study was that the volume of the thalamus increased after arthroplasty to the degree that differences between patients and controls were no longer apparent [54]. This effect is qualitatively similar to other longitudinal studies in older people that have noted increases in regional brain volumes associated with changes in function, such as increased cortical thickness following cognitive training. The implication of reversed volume loss is that pain-related atrophy is not driven by cell death and that other histological changes are more likely to be in operation [55].

Reports of morphological change in older samples with musculoskeletal pain are not confined to atrophy of the thalamus. However, it is difficult to synthesize the outcomes across studies because results are inconsistent. For instance, in addition to changes in the thalamus,
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Gwilym and colleagues [54] reported volume increases among hip osteoarthritis patients compared with controls in brain regions, including the orbitofrontal cortex, amygdala, insula, and cerebellum that were reported by a second group as showing the opposite effect of a decreased volume in a very similar cohort of hip osteoarthritis patients. Another study of older people (mean age 75 years) with low back pain has shown decreases of volume in the posterior parietal cortex [61], which did not show changes in the two studies of hip osteoarthritis [54,55]. In the oldest cohort reported to date (mean age 82 years), pain intensity and duration were inversely related to hippocampal volumes [62]. To some extent, the variance across studies in the older cohorts replicates a similar diversity among morphological studies in younger people with persistent pain. It is feasible that the diversity reflects a highly variable effect of different pain pathologies on brain morphology, although it is also possible that the low sensitivity of measures of brain morphology necessitates sample sizes that are not typically enrolled into studies of brain volumes in pain patients.

Functional brain imaging studies of ongoing clinical pains have involved groups of knee osteoarthritis patients with mean ages in the range of 56–59 years [63–65]. Unlike the reports of brain morphology in pain patients, the associations with spontaneous osteoarthritis pain have been consistent across studies. The major finding of these studies is that ongoing osteoarthritis pain is primarily represented in medial prefrontal and limbic regions, including the orbitofrontal cortex, hippocampus and amygdala [64,65]. Akin to the samples used to investigate brain morphology in osteoarthritis patients, the functional studies have not included younger participants as a point of contrast, and so, commonalities and differences in clinical pain activation between older and younger cohorts are unknown. However, the distinction between ongoing pain and evoked pain is clearly important with respect to brain processing and, consequently, future investigations of pain and brain aging should avoid interpretations that extrapolate the outcomes from experimental pain imaging to the clinical situation.

Conclusion

The well-established effects of aging on pain experience provide considerable impetus to explore the interaction between brain aging and pain processing. It is very likely that aspects of the pain experience in older people including acuity for noxious stimuli, tolerance, endogenous analgesia, and hyperalgesia are influenced by age-related changes in the brain. Furthermore, processing of clinical pain occurs in regions including the prefrontal cortex and hippocampus that are particularly vulnerable to age-related changes in structure and function, which may provide future explanations for the manifestation of clinical pain in older people. Despite a strong rationale for the investigation of pain and brain aging, progress in this field has been slow. Hopefully, the pace will accelerate in the near future. There are powerful tools available for the investigation of human brain structure and function, and a rich literature of brain aging that will inform future efforts to explore pain processing in older people.

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