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Effect of aging on the cerebral processing of thermal pain in the human brain

Ming-Tsung Tseng [a,b,c], Ming-Chang Chiang [d,*], Kong Yazhuo [c], Chi-Chao Chao [a], Wen-Yih I. Tseng [e,f], Sung-Tsang Hsieh [a,g,h,*]

[a] Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
[b] Section of Neurology, Department of Medicine, Far-Eastern Memorial Hospital, Taipei, Taiwan
[c] Center for Functional Magnetic Resonance Imaging of the Brain, Nuffield Department of Clinical Neurosciences, Nuffield Division of Anaesthetics, University of Oxford, Oxford, UK
[d] Department of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan
[e] Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan
[f] Center for Optoelectronic Biomedicine, National Taiwan University College of Medicine, Taipei, Taiwan
[g] Department of Anatomy and Cell Biology, National Taiwan University College of Medicine, Taipei, Taiwan
[h] Graduate Institute of Brain and Mind Sciences, National Taiwan University College of Medicine, Taipei, Taiwan

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ABSTRACT

The perception of pain changes as people age. However, how aging affects the quality of pain and whether specific pain-processing brain regions mediate this effect is unclear. We hypothesized that specific structures in the cerebral nociceptive system mediate the effect of aging on the variation in different pain psychophysical measures. We examined the relationships between painful heat stimulation to the foot and both functional magnetic resonance imaging signals and gray matter volume in 23 healthy subjects (aged 25∼71 years). Increased age was related to decreased subjective ratings of overall pain intensity and the "sharp" quality of pain. Group activation maps of multiple linear regression analyses revealed that age predicted responses in the middle insular cortex (IC) and primary somatosensory cortex (S1) to pain stimuli after controlling for their gray matter volumes. Blood oxygenation level-dependent signals in the contralateral middle IC and S1 were related to ratings of "sharpness," but not any affective descriptors of pain. Importantly, activity in the contralateral middle IC specifically mediated the effect of age on overall pain perception, whereas activity in the contralateral S1 mediated the relationship between age and sharp sensation to pain. The analyses of gray matter volume revealed that key nociceptive cerebral regions did not undergo significant age-related gray matter loss. However, the volume of the cingulate cortex covaried with pain perception after adjusting for corresponding neural activity to pain. These results suggest that age-related functional alterations in pain-processing regions are responsible for changes in pain perception during normal aging.

1. Introduction

Pain perception changes during normal aging [25], but its neural substrate remains unclear. The aging process is accompanied by structural and functional changes in peripheral nociceptors [9,58,81], but the functional and structural alterations that occur in pain-processing brain regions remains elusive. In humans, electrophysiological studies have shown that brain responses to pain decline with advancing age [11,28,77], suggesting alterations in the central processing of pain in normal aging. Given that brain hemodynamic responses of other sensations, including vision [38], audition [39], and olfaction [85] decrease during aging, we hypothesize that a similar decline in pain processing also occurs.

The experience of pain is multidimensional and contains diverse qualities [52]. Functional changes in different pain-related brain regions have been associated with different aspects of pain [76]. For example, the somatosensory cortices and insula have been associated with the sensory quality of pain [36,60], and the cingulate cortex with the affective aspects [68]. However, these cerebral structures receive similar projections from peripheral

* Corresponding authors. Addresses: Department of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan. Tel.: +886 2 28267110; fax: +886 2 28210847 (M.-C. Chiang), Department of Neurology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 10002, Taiwan. Tel.: +886 2 23123456x8182; fax: +886 2 23915292 (S.-T. Hsieh).

E-mail addresses: mcchiang@ym.edu.tw (M.-C. Chiang), shsieh@ntu.edu.tw (S.-T. Hsieh).

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nerve fibers. Given that there are age-related alterations in peripheral nociceptors, it would be important to explore how the experienced quality of pain is affected by age. Surprisingly, only a limited number of behavioral studies have investigated this issue [34], and it is not yet known whether aging is accompanied by changes in the cerebral activity that is related to specific qualities of pain. The present study examined whether the influence of age on distinct pain psychophysics is mediated by specific structures in the central nociceptive system.

In addition to functional changes, aging-related structural changes in cerebral areas that are related to pain processing are not well characterized. Normal aging is accompanied with a gradual loss of brain tissue [44,53,69], including cortical areas related to pain, such as the insula [29], cingulate [74], and somatosensory cortices [69]. Despite accumulated studies describing the relationship between chronic pain and volumetric changes in pain-associated regions [2,26,44,53], limited research has investigated gray matter correlates of acute physiological pain [20,31]. Whether the morphologic changes of pain-associated regions independently contribute to the altered experience of pain in normal aging is unknown. In addition, structural changes potentially confound the evaluation of neural responses to pain [66]. Thus, adjustment of the measured blood oxygen level-dependent (BOLD) responses for the regional volume will help to depict the full picture of age-related functional alterations to pain. Similarly, the relationship between structural changes and pain may be better elucidated by correcting for age-related signal changes in the same region.

Most imaging studies of pain in the healthy population involve participants with a narrow range of age, making the impact of age impossible to fully explore. We recruited a group of healthy participants with a large age range to elucidate age-related functional and structural changes in pain-processing brain regions. We hypothesized that aging would accompany a change in the psychophysical measure of the distinct quality of pain, which would be mediated by neural activity in the cerebral nociceptive system.

2. Materials and methods

2.1. Subjects

Twenty-three healthy right-handed normal subjects (9 men and 14 women) between 25 and 71 years of age (mean 45.6 years) participated in the study. Nine females were premenopausal, and they were scanned during days 5∼10 of their menstrual cycle. Each subject's personal history was taken using questionnaires to review neurologic systems in order to exclude latent neurologic disorders. Neurological examinations were performed to exclude any neuropsychiatric disorder or pain symptoms. Because clinically silent cerebrovascular pathology in persons of advanced age may affect neurovascular coupling and BOLD signals [18], subjects with the presence of cerebral infarcts, hemorrhage, or subcortical arteriosclerotic encephalopathy on T2 magnetic resonance imaging (MRI) were not enrolled in the current study. The study protocol was approved by the Ethics Committee of National Taiwan University Hospital, Taipei, Taiwan, and informed consent was obtained from all subjects before the experimental procedures.

2.2. Thermal stimulation

Thermal stimulation was delivered by a contact heat-evoked potential stimulator (PATHWAY sensory evaluation system; Medoc, Ramat Yishai, Israel) via a 27-mm-diameter circular thermofoil (572 mm^2) [11,78]. The thermofoil permitted a very rapid heating rate (up to 70°C/s) and a fast cooling rate (up to 40°C/s). The stimulus temperature in this study was defined as the temperature of thermofoil applied to the skin. Cooling began immediately after the thermode reached its target stimulus temperature.

2.3. Image acquisition

The functional MRI (fMRI) study was performed using a 3T MRI scanner (Trio; Siemens, Erlangen, Germany). The subject's head was comfortably positioned inside a receive-only 8-channel head coil, padded with sponges, and fixed with a strap across the forehead to minimize head motion. Each subject was provided with earplugs to minimize scanner noise. A whole-brain high-resolution T1-weighted image was acquired using 3D acquisition with magnetization-prepared rapid gradient echo sequence (repetition time [TR] = 1380 ms; echo time [TE] = 2.6 ms; time to inversion [TI] = 800 ms; flip angle = 15°; field of view [FOV] = 25 × 25 cm; slice thickness = 1 mm; 192 slices in axial plane; acquisition matrix = 256 × 256; acquired resolution = 0.98 × 0.98 × 1.00 mm). Gradient-echo echo planar imaging was used to acquire BOLD contrast data. The acquisition parameters were TR/TE of 3000/30 ms, a flip angle of 90°, a 64 × 64 matrix, a FOV of 250 × 250 mm, and a slice thickness of 3.9 mm, resulting in a voxel size of 3.9 × 3.9 × 3.9 mm. In total, 35 horizontal slices along the anterior/posterior commissure line were obtained covering the entire brain. The first 4 images were discarded to account for spin saturation effects.

2.4. Experimental protocol

We used a block-designed fMRI protocol similar to our previous designs [78]. One hour before fMRI scanning, subjects were brought to a waiting room where they were familiarized with the instructions for the experiment and the rating procedure. The imaging session consisted of one T2-weighted image, one T1-weighted anatomical scan, and one functional scanning run. The thermode was strapped to the dorsum of the right foot without causing any pressure, and the stimulation site was fixed during the functional scan. The stimulus sequence during the functional scanning run consisted of 5 presentations of the same stimulus that ramped from the baseline 32°C (36 seconds) to 44°C (12 seconds) at 20°C/s and then returned to the baseline temperature at 40°C/s. Immediately before scanning, subjects were instructed to refrain as much as possible from moving throughout the imaging session, to pay attention to the stimuli, and to keep in mind the sensation they felt and report it after each functional scan was completed. Subjects were also instructed to keep their eyes closed during stimulation. After the fMRI scan, subjects were asked to verbally rate the average perception for the 5 stimuli. In order to obtain an overall, rather than unidimensional, measure of pain perception and to minimize errors in the elderly subjects [41], we used a verbal rating scale (VRS) ranging from 0 to 10: with 0 indicating no sensation, 4 just painful, and 10 unbearable pain, which had been adopted in previous studies [45,57,71]. Since one of the aims of this study was to examine age-related changes in pain quality, the Short-Form McGill Pain Questionnaire [51], which has been used to characterize changes in different qualities of pain perception in healthy subjects [42,49], was employed to assess 11 sensory and 4 affective descriptors [71]. Each descriptor was rated on a 4-point scale from no (0) to severe (3) sensation (Table 1).

2.5. Functional image analysis

fMRI image processing and data analysis were performed using SPM8 (www.fil.ion.ucl.ac.uk/spm) [22] implemented in MATLAB (MathWorks, Sherborn, MA, USA). Briefly, the fMRI data series was realigned to the first volume in each scan sequence and re-sliced with sinc interpolation to correct for motion artifacts [23].