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Experimental Approaches in the Study of Pain in the Elderly

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Abstract

The present review summarizes experimental data on age-related changes in pain processing. These data suggest an increase in pain threshold and a decrease in tolerance threshold, which both are dependent on the physical nature of the stressor, as well as a developing deficiency in endogenous pain inhibition, which might be paralleled by an enhanced disposition to central sensitization (stronger temporal summation). These findings are arranged in a model that allows for explaining the two seemingly divergent perspectives: age both dulls the pain sense and increases the prevalence of pain complaints. This model is based on the assumption that both excitatory and inhibitory processes are dampened with age but that the later processes age at a faster rate, leading to increasingly unbalanced pain excitation.

Key Words. Pain; Experimental Approaches; Elderly

Introduction

Participants in experimental studies on pain in the elderly have rarely included very old individuals, which are also called "oldest olds." The beginning of this particular age category has been put close to 80–85 years [1]. This exclusion of those individuals, who belong to the most rapidly growing groups in the Western societies, indicates a definite shortcoming of experimental pain geriatrics. Typically, individuals under study are 60–80 years of age, which allows calling them by and large elderly people. The category "elderly" has been used with lower age margins between 65 and 75 years [2]. As all available data have been from cross-sectional studies, comparing young and elderly individuals, true aging has not been assessed in this design because age effects are always confounded by cohort effects.

Experimental approaches in pain research should be able to elucidate two opposing perspectives on age-related changes in pain processing. First, pain can be seen in part as a sensory function, alarming the individual when physical threat to bodily integrity appears. There is no good reason to think that pain as a sensory modality should be spared from the general trend of sensory deterioration over the lifespan. Hence, it would be surprising if there were no "presbyalgos" to accompany the visual and auditory declines, "presbyopia" and "presbyacusis" [3].

A loss of exteroceptive pain sensitivity has important clinical relevance as it might render seniors more vulnerable to injuries. However, the increase in clinical pain complaints known to be associated with advanced age cannot be fully explained by this higher risk of physical damage. It appears that either the aged body produces more or stronger noxious events or that these noxious events are broadcast via interoceptive increasingly unfiltered pathways, thus increasing the frequency of pain complaints in the elderly. The potential change in filtering mechanisms with age is of interest in the present context and provides a second challenge to experimental approaches in the study of pain reactivity. This article aims to summarize findings relating to these two perspectives and to integrate them into a model of age changes in the pain system.

Age-Related Changes in Pain and Tolerance Thresholds

There are many reviews on the subject of age-related changes in pain and tolerance thresholds (e.g., [4–6]), but only a few attempt to meta-analyze the available literature (e.g., [4]). An analysis conducted by our research group [7] is used here to arrange the review of the literature. Literature up to the year 2006 was screened using the search machines relevant for psychophysical pain studies (Pubmed, Psyndex, Google Scholar and Psychinfo). The reference lists of the most recent reviews were used as additional source of primary literature. The search resulted in 52 primary studies. On these studies a series of strict criteria was applied: the use of experimental design and methodology, assessment of pain or tolerance thresholds, chronological definition of age, the presence of at least two age groups, investigation of at least 20 subjects, no indication of major heterogeneity in relevant variables within groups, inclusion of only healthy individuals (no

Table 1 Primary studies included in the meta-analysis

Authors	Type of Threshold	Type of Stressor	Number of Subjects
Bek et al., 2002 [20]	Pain, tolerance	Pressure	100
Chakour et al., 1996 [15]	Pain	Laser	30
Chapman & Jones, 1944 [21]	Pain	Radiation	200
Clark & Mehl, 1971 [22]	Pain	Radiation	64
Edwards et al., 2001 [23]	Pain, tolerance	Contact thermal	68
Edwards & Fillingim, 2001 [24]	Pain, tolerance	Contact thermal	68
Edwards et al., 2003 [25]	Pain, tolerance	Contact thermal	93
Harkins & Chapman, 1976 [26]	Pain	Electrical current	20
Harkins & Chapman, 1977 [27]	Pain	Electrical current	20
Helme et al., 2004 [28]	Pain	Electrical current, contact thermal	30
Jensen et al., 1992 [29]	Pain	Pressure	322
Kenshalo, 1986 [30]	Pain	Contact thermal	48
Lagier et al., 1999 [31]	Pain	Rectal distension	24
Lasch et al., 1997 [32]	Pain	Esophageal distension	27
Lautenbacher & Strian, 1991 [33]	Pain	Contact thermal	64
Lautenbacher et al., 2005 [34]	Pain	Contact thermal, pressure	40
Liou et al., 1999 [35]	Pain	Contact thermal	54
Neri & Agazzani, 1984 [36]	Pain, tolerance	Electrical current	100
Pickering et al., 2002 [37]	Pain, tolerance	Contact thermal, pressure	48
Procacci et al., 1970 [38]	Pain	Radiation	525
Sherman & Robillard, 1960 [39]	Pain	Radiation	120
Sherman & Robillard, 1964 [40]	Pain	Radiation	30
Washington et al., 2000 [41]	Pain	Laser, electrical current	30
Woodrow et al., 1972 [42]	Tolerance	Pressure	11,435
Zheng et al., 2000 [43]	Pain	Pressure	20

patients of any kind), and clear description of statistics. This selection procedure reduced the number of studies to be analyzed to 25, of which 24 included measures of pain threshold and 7 included measures of tolerance threshold (see Table 1). The precision weighted effect size and its standard deviation were computed and are reported here (see Table 2).

Pain Threshold

The effect sizes are—independent of the method used for induction of experimental pain—all positive, which means that an increase in pain threshold over the lifespan is the rule. Such increases appear highest when radiant heat was applied. However, this pain induction method also produced the largest variations between studies and was used mainly in early investigations. The use of contact thermal stimulation, which is prominent in contemporary studies, strongly reduced the effect sizes. Comparable effect sizes were also reported from studies in which electrical and mechanical stimuli were used. Too few studies involved laser stimulation or stimulation of visceral organs to permit reliable insights for those modalities.

On the average, the age-related increase in pain thresholds appears slightly stronger in women than in men. Not

Table 2 Results of meta-analysis: mean, standard deviation (SD), and confidence interval (95% CI) of precision weighted effect sizes

Category	Mean	SD	95% CI
Pain threshold			
Radiation	3.14	0.75	1.44–4.83
Contact thermal	0.23	0.10	0.04–0.42
Electrical current	0.45	0.13	0.20–0.71
Pressure	0.33	0.15	0.04–0.62
Laser	1.20	0.29	0.64–1.76
Visceral distension	2.17	0.37	1.43–2.90
Women	0.31	0.20	–0.09–0.71
Men	0.19	0.19	–0.18–0.56
Age difference small*	0.28	0.09	0.01–0.46
Age difference large*	0.49	0.11	0.27–0.71
Tolerance Threshold			
Contact thermal	0.13	0.15	–0.15–0.41
Electrical	0.08	0.14	–0.20–0.36
Pressure	–0.42	0.14	–0.69–0.15
Women	–0.60	0.03	–0.67–0.54
Men	–0.53	0.20	–0.93–0.13

* All studies were divided by median split into those with small and large age differences.

surprisingly, larger age differences between groups were associated with larger effect sizes.

Tolerance Threshold

When considering the effect of age on pain tolerance thresholds, a very different pattern of results emerges (see Table 2). There seems to be either no age-related changes at all (thermal and electrical tolerance thresholds) or even a decrease (pressure tolerance threshold) over the lifespan. The decrease in pain tolerance does not seem to differ between the two sexes.

Basically, our meta-analysis, in which more conservative criteria for inclusion were used, corroborated the earlier meta-analysis computed by Gibson [4]. The two analyses and earlier narrative reviews suggest a tendency toward increases in pain thresholds and a tendency toward decreases in tolerance thresholds with increasing age. This pattern confirms an early observation by Harkins et al. [8] that older adults underrate low and overrate higher intensities of pain stimuli compared with younger adults.

This might mean that the pain range becomes more limited with increasing age. However, such an interpretation is based on a one-dimensional conceptualization of pain. Alternatively, it might be assumed that the sensory component indicated by the pain threshold is dampened in older adults, whereas the emotional-motivational component indicated by tolerance threshold is enhanced. A third interpretation might be that the prolonged stimulation necessary for assessing pain tolerance activates excitatory processes more than concurrent inhibitory ones, revealing an age-related imbalance between excitatory and inhibitory processes with a preponderance of the excitatory ones. The plausibility of the latter assumption will be considered in the next section on age-related changes in pain inhibition.

Age-Related Changes in Endogenous Pain Inhibition

There have been four studies on age-related changes in endogenous pain inhibition tested in a conditioned pain modulation (CPM; formerly called DNIC[1]-like) paradigm, all of which came to similar conclusions (see Table 3). Their findings showed that this kind of pain inhibition is not only functioning poorly in the elderly but sometimes is even reversed into a facilitatory function. In other words, a first pain does not reduce the sensitivity for a second pain in older adults as it does in young individuals but instead enhances it. According to the data presented by Larivière et al. [9], these changes begin already at middle age when the prevalence of chronic pain is starting to peak. This notable convergence of findings makes CPM-testable endogenous pain inhibition a prime candidate for further studies on physiological mechanisms of age-related alteration in the nociceptive system. Complicating our conclusion, it should be noted that cold water, the conditioning stimulus used in all four studies, triggers—besides DNIC mechanisms—also blood pressure changes, which seem to activate another analgesic mechanism [10].

Age-Related Changes in Temporal Summation

Compared with the clarity of findings relating to endogenous pain inhibition, observations of age-related changes in temporal pain summation do not provide unequivocal direction (see Table 4). The common denominator of the findings might be that temporal summation of heat pain is enhanced in the elderly when not assessed at very distal body sites (e.g., lower limb), which might already be affected by age-related axonopathies. Furthermore, the critical frequency needed to start ultra-slow pain summation, claimed to be around 0.33 Hz in young adults [11], seems to be even lower in the elderly, permitting pain stimuli that are temporally fairly distant to sensitize the nociceptive system.

Model of Integration of the Age-Related Changes in the Pain System

Together with the described reduction of pain inhibitory capacities, an enhanced predisposition to sensitization may indicate an age-related shift of the balance between excitatory and inhibitory processes in favor of the former. Considering also the described increases in pain threshold, it is likely that excitatory functions deteriorate with age but—as postulated by the present model—not at the same rate as the inhibitory functions. Figure 1 describes a proposed model based on the concept that both excitatory and inhibitory thresholds increase over the lifespan but at different rates; the relatively higher rate of age-related increase in the inhibitory thresholds produces a growing imbalance in favor of excitatory processes. This

Table 3 Summary of studies on age-related changes in conditioned pain modulation paradigms

Authors	Pain Inhibits Pain	Result
Edwards et al., 2003 [25]	Cold water pain on contact heat pain (concurrent application)	Facilitation
Larivière et al., 2007 [9]	Cold water pain on contact heat pain (concurrent application)	Reduced inhibition
Riley et al., 2010 [44]	Cold water pain on contact heat pain (concurrent application)	Facilitation
Washington et al., 2000 [41]	Cold water pain on electrical or laser pain (application in close succession)	Reduced inhibition

Table 4 Summary of studies on age-related changes in temporal pain summation

Authors	Temporal Summation	Result
Edwards & Fillingim, 2001 [45]	Trains of thermal pulses of 47, 50, or 53°C with a repetition frequency of 0.4 Hz	Temporal summation enhanced in the elderly; degree dependent on the pulse temperature
Farrell & Gibson, 2007 [13]	Trains of electrical pulses with repetition frequencies of 0.2–2.0 Hz	Temporal summation also at very low frequencies in the elderly (ratings); no age difference for the RIII-reflex
Harkins et al., 1996 [16]	Trains of thermal pulses of 51°C of 0.4 Hz for "second pain" summation	Temporal summation similar at the forearm and absent in the elderly at the leg
Lautenbacher et al., 2005 [34]	Trains of thermal and pressure pulses well above pain threshold with repetition frequencies of 0.16 or 0.42 Hz	Temporal thermal pain summation enhanced at both frequencies in the elderly but not pressure pain summation

produces a pain system in the elderly that gets activated a little later (signs of pain insensitivity), but, over time, a relative lack of pain inhibition allows for pain escalation (more prevalent pain symptoms). A second necessary but plausible assumption linking this model to experimental data is that tests that use single brief pain pulses (like in many procedures for pain threshold assessment) predominantly target the excitatory functions, while tests using prolonged or repeated stimulation (as in CPM, temporal summation, and tolerance threshold paradigms) engage inhibitory processes more than excitatory ones.

This assumption permits us to understand that an increase in pain threshold does not contradict the many pain complaints in older adults. An age-related decrease in inhibitory tone is also suggested by the findings of Cole et al. [12], who observed in a functional imaging study a reduction of activity in frontostriatal pathways, which are known for their inhibitory action. While pain inhibition related to basal ganglia and pain inhibition related to the DNIC are different as regards their physiological basis, both sets of findings indicate that the more inhibitory breaks become deficient with advanced age, the less likely pain escalation can be halted.

Further Experimental Observations

An electrophysiological parameter that is said to parallel pain perception and to represent nociceptive processing at early, primarily spinal stages is the **nocifensive RIII-reflex**. There have been only two investigations on age changes in the RIII-reflex both with negative findings [13,14]. In the standard experimental paradigms, the reflex represents mainly the excitatory spinal echo of very brief electrical pulses. These findings, coupled with the weak age-related increases observed for the electrical pain thresholds, suggest that age does not strongly affect nociceptive Aδ-fibers that are critical for this kind of reflex and for subjective responses to electrical pain. This does not necessarily contradict the observation that Aδ-fiber functions deteriorate somewhat earlier in life than C-fiber functions [15,16].

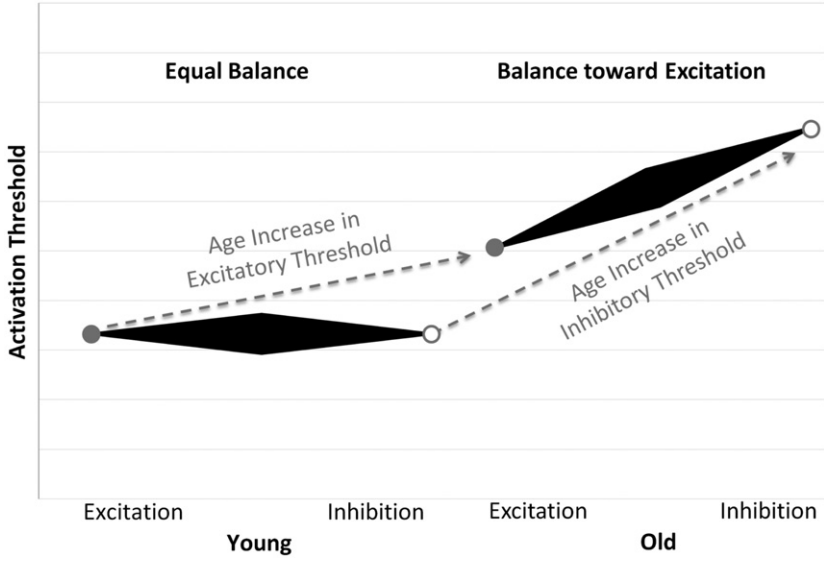

Figure 1 Model of age-related changes in excitatory and inhibitory functions in pain processing.

A behavioral parameter of relevance for the diagnosis of clinical pain is the **facial response to pain**. As assessment of pain in patients with dementia relies more and more on such parameters, knowledge of normal age changes is critical. There is a widely held belief that the elderly become more stoical in their expression of pain, a conviction, which is even shared by seniors themselves [17]. Therefore, it is tempting to assume a decline in facial responses to pain. However, the experimental assessment of facial responses to pain revealed no age-related changes [18,19], corroborating findings of rare age changes in the facial display of emotions. Accordingly, a decline of facial expressivity of emotions cannot be verified, although it is assumed by many and even by the elderly themselves.

Conclusions and Future Challenges

The available experimental data fit well with the assumption that age slightly dulls the pain sense and leads to a weak presbyalgos (exteroceptive pain function). Due to that, external threats may be detected later and seniors may run higher risks of injuries. However, the data on CPM inhibition and on temporal summation suggest a relative preponderance of excitatory processes while inhibitory processes become increasingly difficult to be activated. Consequently, pain complaints become more likely (interoceptive pain function).

Although this model would also allow explaining clinical findings in elderly pain patients, this has to be done with caution because the experimental results have been obtained almost exclusively in pain-free individuals. Nevertheless, the proposed dichotomy between exteroceptive nociception, tested using short stimuli targeting superficially located nociceptors, and interoceptive nociception, tested by using prolonged stimuli targeting deep tissue nociceptors, might form a heuristic framework for the understanding of age changes in pain sensitivity. It appears likely and should be tested in the same individuals that exteroceptive nociception deteriorates as a classical body sense while there is a disinhibition of interoceptive nociception due to a decline in pain inhibitory efficiency.

There are further shortcomings in the literature that necessitate future research. While the reported findings on age changes in temporal pain summation seem robust, age-related changes in pain-correlated brain potentials and in brain imaging of pain are understudied. Moreover, current experimental approaches have not adequately considered individual factors that likely modify aging of the pain system. The first candidate that ought to be examined is sex/gender. Finally, the study of oldest olds (above 85 years of age) must receive more attention as these individuals belong to the most rapidly growing proportion of the population of the Western societies.

Note

1. Diffuse noxious inhibitory controls.

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