

Effects of Age and Mild Cognitive Impairment on the Pain Response System

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Key Words

Mild cognitive impairment · Pain processing · Facial responses · Autonomic responses · RIII reflex

Abstract

Background: Both age and dementia have been shown to have an effect on nociception and pain processing. The question arises whether mild cognitive impairment (MCI), which is thought to be a transitional stage between normal ageing and dementia, is also associated with alterations in pain processing. **Objective:** The aim of the present study was to answer this question by investigating the impact of age and MCI on the pain response system. **Methods:** Forty young subjects, 45 cognitively unimpaired elderly subjects and 42 subjects with MCI were investigated by use of an experimental multi-method approach. The subjects were tested for their subjective (pain ratings), motor (RIII reflex), facial (Facial Action Coding System) and their autonomic (sympathetic skin response and evoked heart rate response) responses to noxious electrical stimulation of the nervus suralis. **Results:** We found significant group differences in the autonomic responses to noxious stimulation. The sympathetic skin response amplitude was significantly reduced in the cognitively unimpaired elderly subjects compared to younger subjects and to an even greater degree in subjects with MCI. The evoked heart rate response was reduced to a similar degree in both groups of aged subjects. Regression analyses within the two groups of the elderly subjects re-

vealed that age and, in the MCI group, cognitive status were significant predictors of the decrease in autonomic responsiveness to noxious stimulation. Except for the autonomic parameters, no other pain parameter differed between the three groups. **Conclusion:** The pain response system appeared to be quite unaltered in MCI patients compared to cognitively unimpaired individuals of the same age. Only the sympathetic responsiveness qualified as an indicator of early aging effects as well as of pathophysiology associated with MCI, which both seemed to affect the pain system independently from each other.

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Introduction

There is ample empirical evidence that age has an effect on pain processing. However, the effects vary substantially depending on the dimension of pain sensitivity under investigation as well as on the methods applied [for reviews, see 1, 2]. To study the effects of age on pain processing, cross-sectional designs have most often been used, mainly comparing healthy, pain-free young and elderly individuals. A more recent trend in these realms of experimental pain research is the investigation of nociception and pain processing in patients with dementia [3]. Dementia is a group of neurological disorders characterized by an irreversible decline of cognitive abilities which is strongly correlated with age. The incentive for

these research activities was at first a clinical one. It was observed that elderly individuals with dementia have difficulties to verbally communicate the distress of pain and might thus be undertreated for pain [4]. Even for this reason alone, a basic understanding of the impact of dementia on the pain system is crucial [for reviews of recent experimental findings, see 3, 5–7]. However, findings so far have been conflicting, suggesting increased as well as decreased pain processing in patients with dementia. Studies focusing on the impact of dementia on pain processing investigated ‘pain-free’ patients with dementia and compared their responses to pain-free cognitively unimpaired elderly subjects.

Accordingly, in both types of investigation – either dealing with the effect of age or with the effect of dementia on pain sensitivity – pain-free and cognitively unimpaired elderly individuals were studied to deliver the frame of reference. Although the reasoning behind this selection is obvious, since cross-sectional designs benefit from clear-cut definitions of cases, the inclusion of ‘super-normals’ may in fact increase internal but decrease external validity. It has to be acknowledged that a sizeable number of nondemented aged individuals suffer from mild cognitive impairments [for example 8]. Mild cognitive impairment (MCI) is thought to be a prodromal phase of dementia and individuals with MCI are by definition neither cognitively healthy nor demented [8, 9]. Given the relatively high prevalence of MCI in the elderly population, representative samples of nondemented subjects would naturally contain a high percentage of these individuals. Therefore, the scientific logic forces to pose the question of what age or dementia-related changes would have been observed if more representative samples of elderly subjects, including those with mild cognitive impairments, had been used for comparisons. Besides these internal/external validity concerns, it is a critical question in its own right to ask which alterations in pain sensitivity already manifest themselves in persons with mild cognitive impairments.

The aim of the present study was to look at the impact of age as well as of MCI on the pain response system. Given that previous findings on the impact of age and of dementia on pain processing varied immensely depending on the experimental pain methods applied, a multi-method approach seems to be the first choice to address this issue. So far, there is no theoretical or empirical basis, which would allow to select certain methods and to drop others. In fact, we could demonstrate in a series of studies that some experimental pain measures are sensitive to age effects, whereas others are to the impact of dementia

[for example 10–14]. For these reasons, we studied the impact of age as well as of MCI on the pain response system using a multi-method approach, which targets various components of the pain system (self-report, nociceptive flexion reflex, facial and autonomic responses) during noxious electrical stimulation. Since this study is the first of its kind, directed hypotheses can hardly be put forward.

Materials and Methods

Subjects

Forty young subjects¹ between the ages of 20 and 38 years (mean age 24.1 ± 3.2 years; 20 females, 20 males) and 87 elderly subjects over the age of 65 (mean age 73.3 ± 6.3 years; 64 females, 23 males) participated in the study². Young subjects were recruited via advertisements posted in the university buildings, whereas the elderly subjects were recruited amongst students of the Senior University at the University of Marburg as well as amongst students of a local adult education center (Volkshochschule). None had taken any analgesic medication for at least 24 h prior to the test session. Participants who suffered from any condition that could affect pain perception and pain report such as diabetes, hypertension, peripheral and central neuropathy, neurological and psychiatric disorders were excluded from the study. Prior to the experiment, a thorough neurological examination (including examination of the sensory system, testing of deep tendon reflexes, autonomic testing, sural neurography, etc.) was conducted in order to identify persons who met the exclusion criteria. To evaluate the cognitive status of the elderly individuals, subjects underwent neuropsychological assessment using the Structured Interview for the Diagnosis of Alzheimer Disease, Multi-Infarct Dementia and Dementias of other Etiology according to ICD-10 and DSM-IV (SIDAM) [15, 16], the Mini-Mental State Examination (MMSE) [17] as well as a modified Zahlenverbindungstest for geriatric patients – this is an adaptation of the Trail Making Test Part A. ICD-10 diagnoses were made in consensus between neuropsychologists and neurologists and MCI was diagnosed according to the criteria of Petersen et al. [18]. Based on these procedures, 45 elderly individuals were categorized as being cognitively unimpaired (mean age 73.2 ± 5.9 years; 36 females, 9 males¹), whereas 42 subjects were diagnosed as individuals with MCI (mean age 74.2 ± 7.0 years; 28 females, 14 males). Elderly subjects that were categorized as having MCI had a mean MMSE score of 26.4 ± 2.1 (SD) and healthy cognitively unimpaired subjects had a mean score of 29.8 ± 0.4 ($p < 0.001$). As expected, those two groups also differed with regard to the other neuropsychological markers (SIDAM: Healthy Elderly: mean = 53.8 ± 1.0 , MCI: mean = 45.5 ± 4.2 , $p < 0.001$; Zahlenverbindungstest: Healthy Elderly: mean = 21.0 ± 6.2 s, MCI: mean = 30.7 ± 10.3 s, $p < 0.001$).

¹ These subjects were partly already examined for their subjective, facial and motor responses to pressure and electrical stimulation [11, 14].

² Sample size calculation was based on (1) previous findings on the impact of age or dementia on pain and (2) our interest in ‘medium’ effects that might be of clinical relevance.

The study protocol was approved by the ethics committee of the medical faculty of the University of Marburg. After being informed in a slow and simple fashion, which was adjusted to the individual intellectual capacities, subjects gave written informed consent. All subjects were paid for participation.

Materials and Procedure

All testing was conducted during the hours of 3.00 p.m. to 6.30 p.m. and lasted for approximately 2 h. The testing procedure included an examination of potential exclusion criteria (neurological and neuropsychological examination, lasting approximately 1 h), subjective and facial responses to pressure stimulation (20 min, parts of these results have been reported elsewhere [11]), a short break (10 min) and the multi-method approach reported here (30 min). The latter consisted of measuring the subjective component (pain ratings), the motor component (RIII reflex), the facial component (Facial Acting Coding System) and the autonomic component (evoked heart rate response, EHRR, and the sympathetic skin response, SSR) of the pain response system. The pain response system was activated by electrical stimulation of the nervus suralis, with stimulus intensities being tailored to the individual threshold of the RIII reflex.

Electrical Stimulation and the RIII Reflex

Since electrical stimulation was optimized for assessment of the RIII reflex, we describe electrical stimulation and the RIII reflex assessment together [for a more detailed description of our RIII reflex procedure, see 19].

Electrical stimulation and the RIII reflex assessment (EMG recording) were performed using a standard electrodiagnostic device (Viking IV D, VIASYS Healthcare) with modified software. During electrical stimulation, the subjects were seated upright in a comfortable armchair with knees flexed at 130°. The stimulating electrode (bar electrode) was attached on the left calf over the pathway of the sural nerve³. For recording, the differential surface electrode was attached ipsilaterally over the short head of the biceps femoris muscle with the reference electrode fixed near the tendon of the biceps femoris muscle at the head of the fibula bone. A time window of 80–150 ms was selected for the onset of the reflex and an amplitude of at least 40 μ V within 100 ms after the reflex onset was required to reliably distinguish reflex responses from baseline fluctuations. A train of five impulses with 1 ms duration at a frequency of 250 Hz was used for stimulation [14, 19, 20]. Between each stimulus, a variable interval from 20 to 30 s was used in order to avoid habituation.

The RIII reflex threshold was assessed using the up-down staircase method [21]. Stimulation intensity was increased in 3-mA increments until the flexion reflex RIII component was detected the first time. Next, we lowered stimulus intensity in 2-mA steps until the reflex disappeared. After that, steps of 1 mA were used, and the procedure was repeated until the reflex appeared and subsided two more times. Mean values of three peaks (current intensity that just elicited a reflex) and three troughs (current intensity that just no longer elicited a reflex) determined the reflex threshold.

³ Sural neurography was performed during the neurological examination preceding the testing in order to exclude subjects with sensory polyneuropathy and in order to localize the sural nerve for RIII reflex stimulation.

Thereafter, RIII reflex recording using supra-threshold stimulation was performed. An increase of 5 mA above threshold was chosen to definitely reach noxious stimulation levels. Ten supra-threshold stimuli were applied. The evoked motor responses were rectified and averaged. Reflex latency was measured from stimulation onset to the onset of the RIII component within the time window of 80–150 ms; amplitude and area under the reflex curve were measured within 100 ms from onset of the reflex [22].

Self-Report

Right after each stimulus application, subjects were asked to give self-report ratings regarding the peak sensation felt. Self-report was assessed via a 6-point verbal category scale (no pain, mild pain, moderate pain, strong pain, very strong pain, extremely strong pain).

Autonomic Responses

As autonomic responses, we assessed SSRs and the evoked heart rate responses (EHRRs) to the electrical stimuli at an intensity of 5 mA above RIII reflex threshold (supra-threshold stimulation). Both biosignals were assessed by use of the Suempathy100 (SUESS Medizin-Technik, Germany) at a sample rate of 512 Hz.

For recording of the SSR, the differential surface electrode was fixed at the palm of the left hand with the reference electrode fixed on the proximal third of the left forearm. We measured the SSR at the upper extremities, because these responses have been shown to be more reliable than those of the lower extremities, particularly in the elderly [23, 24]. Amplitude and latency of the SSR were measured. Amplitude was defined as voltage difference between the initial negative and the positive peak of the biphasic response. Latency was defined as time from stimulation to the onset of the negative deflection. Trials with initial positive deflection and responses with latencies below 600 ms were not considered for further evaluation. The mean values of amplitude and latency of the 10 (at least 5 valid SSR responses were required for computing mean values) SSR responses elicited by stimulation at 5 mA above RIII reflex threshold were selected for further computations.

For determination of the EHRR, the electrocardiogram was recorded using a standard 3-lead montage with large silver/silver chloride electrodes placed on participants' forearms and the third on the left ankle. Heart rate was extracted offline by measuring the R-R intervals [$HR = (1,000 \text{ ms/R-R interval, ms}) \times 60$]. Recording artifacts resulting into nonphysiological high and low heart rates were visually inspected and corrected by inter- or extrapolation. For further analyses, we averaged heart rate responses to electrical stimulation across the ten stimuli at an intensity of 5 mA above NFR threshold. Changes in heart rate were expressed as changes in heart rate responses compared to heart rate at stimulus onset. Following a procedure by Möltner and colleagues (1990), we carried out a temporal differentiation of the EHRR by separate analyses in three fixed time windows, from 0 to 3 s, 3 to 6 s, and 6 to 9 s after stimulation.

Facial Expression of Pain

Facial responses were assessed and analyzed according to procedures described in detail previously [10, 11, 25]. In short, the face of the subject was videotaped throughout the entire session and facial responses were later analyzed using the Facial Action Coding System (FACS) [26]. A FACS coder (qualified by passing an examination given by the developers of the system) identified

Table 1. Facial AUs with a critical occurrence of more than 5% in noxious segments (see text for further explanations)

AU	Description	Young subjects		Healthy elderly		MCI	
		% ^a	effect size	% ^a	effect size	% ^a	effect size
AU1/2	brow raise	17.9	d = 0.29	13.9	d = 0.19	17.4	d = 0.34
AU4	brow lowering	17.5	d = 0.25	18.8	d = 0.18	26.1	d = 0.49
AU6/7	orbit tightening	49.2	d = 0.61	49.2	d = 0.51	75.0	d = 0.72
AU9/10	levator contraction	19.0	d = 0.52	10.0	d = 2.08	13.7	d = 0.77
AU17	chin raise	19.2	d = 0.47	14.5	d = 0.00	18.8	d = 0.36
AU25/26/27	mouth opening	10.8	d = 0.27	22.2	d = 0.11	38.0	d = 0.32
AU45 ^b	blink	211.9	d = 0.00	321.9	d = 0.54	309.3	d = 0.51

Relative frequency of occurrence and effect sizes for frequency differences between noxious and nonnoxious segments are given. Medium and strong effect sizes ($d \geq 0.5$) are marked in bold; AUs 6/7, 9/10 and 45 were consistently more frequent ($d \geq 0.5$) during noxious segments in both groups.

^a Percentage of occurrence in the entire noxious segments.

^b Blinking of the eye can appear more than once in a time segment of 5 s.

frequency of all facial responses. Time segments of 5 s after stimulus application were selected for scoring.

For purpose of necessary data reduction, we combined those action units (AUs) that represent facial movements of the same muscle as has been done in preceding studies without any loss of information [for example 10, 11, 27]. Therefore, AUs 1 and 2, AUs 6 and 7, AUs 9 and 10 as well as AUs 25, 26 and 27 were combined to form new variables.

To select those AUs that appeared to be pain-relevant in the present experimental context and to summarize these facial responses to composite scores, several steps were necessary.

1 We denominated only those AUs as pain-relevant that occurred in at least 5% of the noxious segments⁴ recorded. We did this separately for young, older and MCI subjects (the results are listed in table 1).

2 To determine which of these AUs listed in table 1 were critically more frequent during noxious segments than during non-noxious segments, we computed effect sizes (Cohen's d for two dependent groups) contrasting these differences (table 1). For further analysis, only those AUs showing an effect size $d \geq 0.5$ (medium effect) in all groups (AUs 6/7, 9/10 and 45; table 1) were selected to form composite scores of pain-relevant facial responses.

3a Prior to computing composite scores, the frequency values of all AUs had to be given weights [see 10, 11]. This was necessary because the frequency of AU 45 (blinking of the eye) is disproportionately higher than those of the other AUs.

3b Composite scores of pain-relevant facial responses were formed by calculating mean scores of those AUs that proved to be pain-relevant (AUs 6/7, 9/10 and 45; table 1), separately for each stimulus intensity.

Statistical Analysis

To evaluate group differences in facial responses and in self-report ratings, we computed univariate analyses of variance with

⁴ All trials above NFR threshold.

repeated measurements with one within-subject factor stimulus intensity (below, above, 5 mA above NFR threshold) and one between-subject factor group (young subjects, healthy elderly and MCI). Group differences (young subjects, healthy elderly and MCI) in the RIII reflex were analyzed either with a univariate analysis of variance (RIII reflex threshold) or with a multiple analysis of variance (latency, amplitude, area under the reflex curve). To analyze group differences in SSR, a multiple analysis of variance (latency, amplitude) with one between-subject factor group (young subjects, healthy elderly and MCI) was conducted. With regard to group differences in EHRR, a univariate analysis of variance with repeated measurements (within-subject factor time; 0–3, 3–6, 6–9 s) was computed (between-subject factor group (young subjects, healthy elderly and MCI). In case of significant group differences, univariate analyses of variance or T tests were computed for single comparisons.

Moreover, in case of significant group differences, we were also interested to analyze whether the impact of age and of cognitive decline do not only manifest themselves when comparing groups of subjects but also within the groups of healthy elderly and MCI subjects. Therefore, regression analyses were conducted to analyze the association between age (within the group of healthy elderly) or age as well as cognitive status (within the group of MCI) on the one hand and the pain parameters under investigation on the other.

Findings were always considered to be statistically significant at $\alpha < 0.05$.

Results

Effects of Age and MCI on the Different Pain Components – Analyses of Group Differences

Self-report ratings did not differ significantly between the three groups. As can be seen in table 2, young sub-

Table 2. Descriptive statistics (mean \pm SD) and group differences (analyses of variance) for subjective, facial and motor reflex responses to electrical stimulation in young subjects as well as in healthy elderly and MCI elderly subjects

	Descriptive statistics			Analyses of variance		
	below NFR threshold	above NFR threshold	5 mA above threshold	F	d.f.	p
Self-report				0.531	2,124	0.590
Young	2.90 \pm 0.88	3.19 \pm 0.86	3.54 \pm 0.92			
Healthy elderly	2.96 \pm 0.95	3.24 \pm 0.89	3.59 \pm 0.89			
MCI	3.16 \pm 0.95	3.19 \pm 0.99	3.84 \pm 0.96			
Facial response				0.389	2,124	0.679
Young	0.27 \pm 0.40	0.39 \pm 0.53	1.55 \pm 2.28			
Healthy elderly	0.28 \pm 0.39	0.29 \pm 0.29	1.33 \pm 1.64			
MCI	0.29 \pm 0.33	0.48 \pm 0.69	1.61 \pm 2.03			
NFR threshold				0.418	2,124	0.659
Young	18.88 \pm 9.54					
Healthy elderly	20.78 \pm 9.65					
MCI	19.77 \pm 9.60					
	Latency	Amplitude	Area under the curve			
NFR reflex curve				2.058	6,248	0.059
Young	98.72 \pm 18.35	46.08 \pm 44.08	2,233.92 \pm 1,425.36			
Healthy elderly	99.39 \pm 21.21	57.22 \pm 46.41	2,224.53 \pm 2,266.09			
MCI	92.99 \pm 16.53	54.99 \pm 48.42	1,593.21 \pm 1,203.94			

jects, healthy elderly without MCI and elderly subjects with MCI rated the electrical stimuli as equally painful. We found a significant main effect for stimulus intensity [F(2, 248) = 78.167; $p < 0.001$], with self-report ratings increasing across stimulus intensities. This increase did not differ between groups as indicated by a nonsignificant interaction effect [F(4, 248) = 1.989; $p = 0.097$].

Similarly, no significant group effect was found for facial responses to electrical stimulation (table 2). We again found a significant main effect for stimulus intensities [F(2, 248) = 54.726; $p < 0.001$]. As can be seen in table 2, facial responses increased significantly across stimulus intensities. This increase in facial responses did not differ between young subjects and elderly subjects with or without MCI, as indicated by a non-significant interaction effect [F(4, 248) = 0.216; $p = 0.929$].

With regard to the RIII reflex, we again observed no significant group differences. As can be seen in table 2, neither the RIII reflex threshold nor the supra-threshold RIII reflex differed significantly between young and elderly subjects with or without MCI.

In contrast, we found significant group differences in SSRs [F(4, 248) = 5.413; $p < 0.001$], with significant group

differences in the amplitude of the SSR [F(2, 124) = 11.382; $p < 0.001$]. The SSR latency was unchanged [F(2, 124) = 0.171; $p = 0.843$]. As can be seen in figure 1, the amplitude of the SSR response was significantly decreased in the healthy elderly compared to younger subjects [T(83) = 2.580; $p = 0.012$]. Interestingly, this decrease was even more pronounced in elderly subjects with MCI [compared to younger subjects: T(80) = 4.199, $p < 0.001$; compared to elderly subjects without MCI: T(85) = 2.536, $p = 0.013$].

Furthermore, we also observed significant group differences in EHRRs to noxious stimulation [F(2, 124) = 8.485; $p < 0.001$]. As can be seen in figure 2, the EHRR in elderly subjects was markedly decreased compared to younger subjects, whereas no differences in EHRR were found between the two groups of elderly subjects with or without MCI [F(1, 85) = 1.886; $p = 0.174$]. Although figure 2 seems to suggest that the EHRR in younger subjects increased across the three time windows, whereas heart rate responses in elderly subjects remained stable, we neither found a significant main effect for time [F(2, 248) = 0.602; $p = 0.542$] nor a significant interaction effect between the factors group and time [F(4, 248) = 1.521; $p = 0.197$].

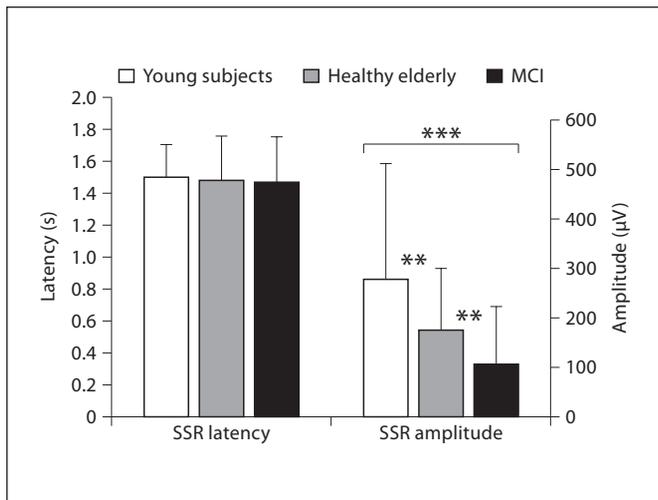


Fig. 1. SSRs (latency and amplitude) in young, healthy elderly and MCI subjects (mean values \pm SD) to noxious electrical stimulation (** $p \leq 0.01$; *** $p \leq 0.001$).

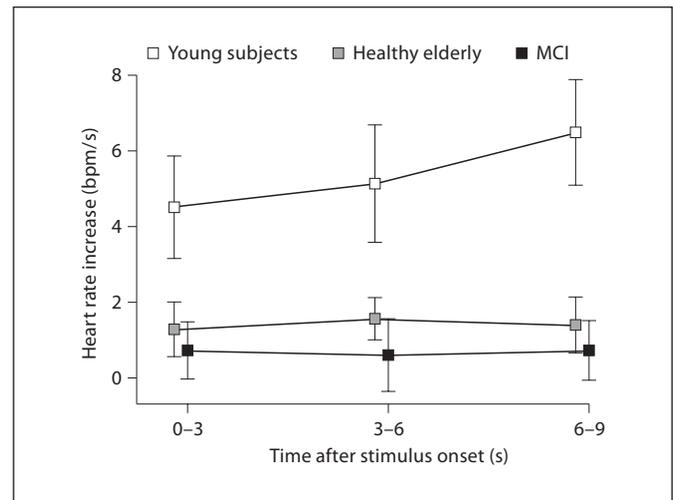


Fig. 2. EHRRs in young, healthy elderly and MCI subjects (mean values \pm SD) to noxious electrical stimulation.

Table 3. Regression analyses between the predictor variables age (within the group of healthy elderly) or age and MMSE (within the group of MCI) and the autonomic responses SSR or EHRR as dependent variables

Dependent variables	Predictor variables							
	healthy elderly		MCI					
	age ^a		age ^a and MMSE ^b		age		MMSE	
	r	p	r	p	r	β	r	β
SSR								
Latency	0.208	0.181	0.523	0.003	0.349	0.018	-0.326	0.026
Amplitude	(-) 0.355	0.019	0.469	0.009	-0.346	0.021	0.264	0.049
EHRR								
1-3 s	(-) 0.055	0.743	0.299	0.244	0.184	0.309	0.278	0.129
3-6 s	(-) 0.058	0.717	0.301	0.240	0.071	0.693	0.308	0.094
6-9 s	(-) 0.181	0.257	0.424	0.050	-0.108	0.527	0.388	0.029

Significant results are marked in bold.

^a Age range in the group of healthy elderly subjects: 65–83 years, and in the group of MCI subjects: 65–87 years.

^b Range of MMSE scores in the group of MCI subjects: 20–29.

Effects of Age and Cognitive Status on Pain Responses within the Two Groups of Elderly Subjects – Regression Analyses

Since the three groups only differed significantly with regard to their autonomic responses to electrical stimulation, regression analyses were only computed for the SSRs and the EHRRs. In the group of healthy, cognitively un-

impaired elderly subjects, only age was entered as a predictor variable, whereas in the group of MCI age and cognitive status (MMSE) were entered as independent predictor variables. As can be seen in table 3, there was a significant relation between age and the amplitude of SSR in the group of healthy elderly subjects, with the SSR amplitude decreasing even further with increasing age. The

heart rate response to noxious stimulation, on the other hand, did not further decrease with age within the group of healthy elderly subjects. Regression analyses within the group of MCI subjects revealed that age as well as cognitive decline significantly affected the autonomic responses in this group (table 3). The latency of the SSR significantly increased with age and with cognitive decline (lower MMSE scores), whereas the amplitude of the SSR response significantly decreased. The heart rate response in individuals with MCI was also significantly affected by the predictor variables. As can be seen in table 3, a decline in cognitive performance (MMSE) was significantly related to a decline in EHRR in the late response window.

In sum, age was a significant predictor of the SSR decrease within the group of healthy elderly subjects. Within the group of MCI subjects, age as well as the score of the MMSE were significantly and independently correlated both with the decrease in the SSR and the diminished EHRR.

Discussion

The present study on the effect of age and MCI on the pain response system produced two major results. (1) The autonomic responses (SSR and EHRR) were significantly reduced in the groups of elderly subjects with and without MCI compared to younger subjects. Moreover, the autonomic components of the pain response were even more declined in individuals with MCI than in age-matched controls. This was especially true for the SSR, which was significantly decreased in the MCI subjects. With regard to all other measures of pain responsiveness (subjective, motor, facial), the groups did not differ from each other. (2) Within the group of elderly individuals with MCI, age and cognitive decline (MMSE) were significantly correlated with the decrease in the SSR and EHRR. Age was also a predictor for the SSR decrease within the group of cognitively unimpaired elderly subjects. These findings corroborate the outstandingly strong influence of age on the autonomic component of pain. Furthermore, they suggest that the cognitive status represents an additional, age-independent factor of influence.

Our data allow for the assumption that pain processing in elderly individuals with MCI is unaltered with respect to most components of the pain response system, with the exception of the autonomic component of pain, which is slightly diminished in individuals with MCI

compared to cognitively unimpaired elderly individuals. These subtle differences might seem surprising when comparing them to those differences observed in demented patients and healthy controls. Demented patients have been found to not only differ in their autonomic responses to noxious stimulation [12, 13, 28] but also in their motor [12], facial [10], subjective [28, 29] as well as in their cerebral responses [30]. Thus, MCI – although thought to be a transitional state between the cognitive changes of normal aging and very early dementia [8] – does not seem to drive the pain response system too strongly towards pathophysiology. Consequently, using more representative samples, which may include individuals with MCI, and not only super-normals for comparisons between young and older individuals as well as between healthy elderly subjects and patients with dementia would presumably not lead to very different results than previous ones. It appears that the dementia-related neuropathology only affects the pain response system after it has passed the threshold of the clinical manifestation of dementia; with one exception, namely the autonomic component of the pain response system.

Our findings were particularly unequivocal when the SSR, a measure selectively reflecting sympathetic activity, was considered. The SSR did not only differ between young and older subjects but also between elderly individuals with and without MCI. Moreover, within the two groups of elderly subjects, the SSR was significantly correlated with age as well as with cognitive status. Since the SSR is known to habituate across repetitive stimulation [31], one might argue that the significant impact of age and MCI might only be due to group differences in SSR habituation across the ten noxious stimuli, with greater habituation in the elderly subjects. However, analyses of group differences in SSR habituation revealed that this was not the case, but instead that SSR amplitudes habituated to a greater extent in the group of young compared to older subjects (significant interaction between group and habituation; $p = 0.002$). The findings regarding the EHRR, a measure showing the net effect of sympathetic and parasympathetic activity, were not as clear. We found significant differences between young and elderly subjects but not between elderly subjects with and without MCI. Furthermore, within the two groups of elderly subjects, the EHRR was not correlated with age and only partly correlated with the cognitive status. Given that our findings were especially unequivocal regarding the SSR, the nociceptive response of the sympathetic system appeared to be especially vulnerable to age and to cognitive decline. There is some contradictory literature available,

debating whether the sympathetic or the parasympathetic branches of the autonomic nervous system are more sensitive to age changes [32–36]. Unfortunately, we cannot contribute to this discussion because we could only inform that the selective measure SSR was more sensitive to age than the compound measure EHRR.

Although the impact of MCI on the pain system was only moderate, our finding that age and cognitive status are independent predictors of the decline in sympathetic responsiveness to noxious stimulation implies that the neuropathology related to MCI [37, 38] affects the pain system in a way that cannot be fully explained by age in the late phase of life. It is unlikely that the mere decline in cognition (e.g. inability of pain anticipation, different threat expectations) caused the decreased sympathetic responsiveness because according to our observations the MCI individuals should have been able to understand the demands and characteristics of the experimental situation. It seems more likely that neuropathological and neurodegenerational changes related to MCI were responsible for the decrease in sympathetic responsiveness to noxious stimulation. Interestingly, in line with our observation, recent findings have suggested sympathetic and parasympathetic dysfunction also in patients with dementia [39–41]. However, this reasoning about possible mechanisms of action cannot be based on our data and may at best be thought provoking.

The clear discrepancy between the impact of age on the autonomic responses compared to its impact on the other components (subjective, motor, facial) of the pain response system cannot be compared to data from the literature because to our knowledge previous studies did not apply a similar multi-method approach to one and

the same sample. Our findings suggest a relatively early aging of the autonomic component of the pain response system. Further studies will be necessary to replicate this differential grading of age changes in the pain system. Our result of no age changes in the subjective ratings of electrical stimulation fits well with numerous preceding studies, in which psychophysical data were assembled by usage of this type of physical stressor [42–46]. This also gives weight to our new observations because we did not seem to have produced atypical results. Unfortunately, it is not possible to compare our findings on the RIII reflex and the facial responses to previous reports, since we were the first who studied the impact of age on these pain parameters (the sample of the present study partly overlaps with those in the previously conducted studies [11, 14]).

In summary, individuals with MCI appeared similar to age-matched cognitively unimpaired subjects and even to young persons with respect to most of the experimentally assessed components of the pain system. The SSR and the EHRR were the only measures that clearly provided evidence for age-related decline in the pain response system, thus suggesting that the autonomic component of pain might get lost with age. This decline in autonomic responsiveness was additionally affected by MCI. Thus, age and cognitive status seem to affect the pain response system independently from each other.

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