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HIGHLIGHTS IN THIS ISSUE:

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- Alpha-1 adrenoceptors augment thermal hyperalgesia in mildly burnt skin
- CCL2 is a key mediator of microglia activation in neuropathic pain states
- Influence of dementia on multiple components of pain

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Influence of dementia on multiple components of pain

Miriam Kunz [a,b,c,*], Veit Mylius [d], Siegfried Scharmann [b], Karsten Schepelman [d], Stefan Lautenbacher [a]

[a] Physiological Psychology, Otto-Friedrich University Bamberg, Markuspl. 3, 96045 Bamberg, Germany
[b] Department of Psychiatry and Psychotherapy, Philipps University Marburg, Germany
[c] Département de stomatologie, Faculté de médecine dentaire, Université de Montréal, Canada
[d] Department of Neurology, Philipps University Marburg, Germany

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ABSTRACT

Experimental findings on the influence of dementia on pain have so far been conflicting. There is evidence for a decreased, an unchanged and even for an increased pain processing in patients with dementia. The present study was conducted to add on the description of the impact of dementia on pain processing by assessing multiple components of pain (subjective, facial, motor reflex and autonomic responses) in parallel in one group of demented patients.

Subjective (rating scale), facial (FACS), motor reflex (NFR) and autonomic (SSR, heart rate) responses to noxious electrical stimulation were assessed in 35 demented patients and 46 aged-matched healthy controls. Stimulus intensities were tailored to the individual NFR threshold.

Demented patients rated the stimuli similarly painful as healthy controls did; however, the ability to provide these self-report ratings was markedly diminished in demented patients. Facial responses to noxious stimulation were significantly increased in demented patients. In line with this the NFR threshold was markedly decreased in the patient group. Autonomic responses on the other hand tended to be diminished in patients with dementia.

In conclusion, dementia tends to affect different pain components in different ways. Therefore, the assessment of pain in patients with dementia should be based on the measurement of multiple components of pain and not solely on subjective self-report ratings. Furthermore, taking into account our findings on facial responses and the NFR, we think that there is sufficient evidence suggesting a rather intensified processing of noxious stimulation in this patient group.

1. Introduction

Pain in dementia has recently become a topic of great interest. Based on clinical findings of reduced pain report and diminished prescription of analgesics in demented patients (Marzinski, 1991; Scherder, 2000; Mantyselka et al., 2004), the question has arisen of whether pain processing might be changed in this patient group. So far, several experimental studies have been conducted that aimed at answering this question. Based on self-report ratings, most studies found that ratings of stimulus intensities around pain threshold were not changed in demented patients (Porter et al., 1996; Benedetti et al., 1999; Rainero et al., 2000; Gibson et al., 2001; Kunz et al., 2007; Lautenbacher et al., 2007), whereas pain tolerance was significantly increased (Benedetti et al., 1999). These findings have given rise to the hypothesis that the sensory pain

dimension might be preserved in demented patients (strictly speaking in Alzheimer patients), while the affective dimension might be changed resulting into a blunted response (e.g. Scherder et al., 2005). However, this conclusion might be unsubstantiated, given that it is mainly based on self-report ratings and that it is known that the cognitive capacity to provide self-report is diminished in demented patients (Smith, 2005; Helme, 2006; Herr et al., 2006). Therefore, in order to validly assess the impact of dementia on pain, it seems essential to focus not only on self-report ratings but also on other indicators of pain (e.g. cerebral, autonomic, facial responses).

A few attempts have already been made to assess alternative indicators of pain in demented patients and interestingly, the findings are much more heterogeneous. Whereas autonomic responses (ECG, blood pressure) to noxious stimulation tended to be diminished in Alzheimer patients compared to healthy controls (this again was interpreted as an indicator of a reduced pain affect, Porter et al., 1996; Benedetti et al., 1999, 2004; Rainero et al., 2000), cerebral responses where either unchanged (evoked potential EEG, Gibson et al., 2001) or even significantly increased in Alzhei-

* Corresponding author. Address: Physiological Psychology, Otto-Friedrich University Bamberg, Markuspl. 3, 96045 Bamberg, Germany. Tel.: +49 951 8631850; fax: +49 951 8631976.
E-mail address: miriam.kunz@uni-bamberg.de (M. Kunz).

mer patients (fMRI, Cole et al., 2006). Surprisingly, this increase in cerebral activation was found in regions being associated with the medial pain system (e.g. aMCC), which rather suggests an increased pain affect. In line with this, it was also observed that facial responses to noxious stimulation were significantly increased in demented patients (Kunz et al., 2007; Lautenbacher et al., 2007).

Thus, experimental findings so far have not been convergent concerning the influence of dementia on pain. Although it is by all means possible that different pain components are differently affected by dementia, the heterogeneous findings might also be due to purely methodological differences between studies, like pain induction methods, severity of dementia, sample size, etc. In order to control for this possibility, it seems advisable to assess multiple pain components in parallel in one group of demented patients, which was the goal of the present study. We aimed at adding on the description of the impact of dementia on pain processing by assessing concurrently multiple pain components (self-report, nociceptive flexion reflex, facial and autonomic responses) during noxious electrical stimulation.

2. Materials and methods

2.1. Subjects

Thirty-five patients with dementia and 46 healthy control subjects over the age of 65 participated in this study. Sample size calculation was based (1) on previous findings on the impact of dementia on pain and (2) on our interest in effects, which are to be classified at least as "medium" and thus, signal clinical relevance. Since we assessed several responses to noxious stimulation (subjective, facial, motor reflex and autonomic responses), power calculations were conducted separately for each variable. Furthermore, sample size calculations were conducted for 80% power and a 0.05 level of significance. Since recruitment of demented patients who are relatively healthy besides the diagnosis of dementia (see our description of inclusion criteria) is very challenging, we decided to have a greater sample size in the group of healthy controls compared to the group of demented patients in order to guarantee enough statistical power as well as realistic recruitment goals. The mean age in the two groups was 75.7 ± 6.9 years (patients with dementia; ♀: 17, ♂: 18) and 73.7 ± 5.6 years (healthy controls; ♀: 36, ♂: 10), respectively. We age-matched both groups by predefining three age-categories (65–74; 75–84 and above 85 years) and trying to fill these categories in demented patients and in healthy controls to equal proportions.

Control subjects were recruited amongst students of the Senior University at the University of Marburg. Patients with dementia were recruited amongst inpatients from the Department of Neurology and the Department of Psychiatry and Psychotherapy of the University of Marburg. None had taken any analgesic medication for at least 24 h prior to the test session. Participants with any condition – other than dementia in the case of the patients – 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. Moreover, a neuropsychological examination was conducted to evaluate the cognitive status of the subjects. Amongst others, the Mini Mental State Examination test (MMSE), according to Folstein et al. (1975) was used to assess the cognitive status. Patients with dementia had a mean MMSE-score of 16.4 (±5.3SD) and healthy controls had a mean score of 29.5 (±0.8SD).

Furthermore, patients with putative dementia were examined by a neurologist or psychiatrist and diagnosed according to the criteria specified by the ICD-10, NINCDS-ADRDA (McKhann et al., 1984) and NINDS-AIREN (Roman et al., 1993). According to these diagnostic guidelines, analyses of cerebrospinal fluid, blood chemistry analysis, EEG, CT or MRT and ECG-analyses were conducted besides clinical assessment. Thirteen patients met the NINCDS-ADRDA criteria for the clinical diagnosis of probable Alzheimer's disease (AD), 14 patients met the NINDS-AIREN criteria for the clinical diagnosis of probable vascular dementia (VD) and eight patients were diagnosed as suffering from Mixed Dementia (MD).[1] These patients were partly already examined for their subjective and facial responses to pressure pain (Kunz et al., 2007).

The study protocol was approved by the ethics committee of the medical faculty of the University of Marburg. We took care that only patients with dementia were included in the study who still had legal capacity. After being informed in a slow and simple fashion, which was adjusted to the individual intellectual capacities, subjects gave written informed consent. We also provided instructions during testing as simple as possible and monitored the patients continuously for any signs of undue discomfort (verbally or non-verbally), in which case we stopped testing immediately. Healthy subjects were paid for participation to compensate them for their transportation expenses.

2.2. Materials and procedure

All testing was conducted during the hours of 3.00 p.m.–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, the results have been reported elsewhere, Kunz et al., 2007), a short break (10 min) and the assessment of multiple pain components activated by electrical stimulation (30 min). In order to help building up a non-threatening atmosphere for the subjects, we decided to always start with pressure stimulation, since this protocol (for a detailed description see Kunz et al., 2007) offered apparently more control over stimulation and induced natural qualities of pain experience.

The assessment of multiple pain components included the assessment of the nociceptive flexion reflex (NFR) (threshold as well as latency, amplitude and area under the curve of suprathreshold responses), self-report ratings, facial responses and autonomic responses (heart rate and the sympathetic skin response (SSR)). Stimulus intensities of electrical stimulation were tailored to the individual NFR threshold.

2.3. Electrical stimulation and the nociceptive flexion reflex (NFR)

Since electrical stimulation was optimized for assessment of the NFR, we describe electrical stimulation and the NFR assessment together (for a more detailed description of our NFR procedure see Mylius et al., 2005).

Electrical stimulation and the NFR assessment (EMG recording) were performed using a standard electro-diagnostic 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 nerve.[2] This individualized procedure – in contrast to

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[1] Other forms of dementia were deliberately excluded.
[2] Sural neurography was performed during the neurological examination preceding the testing in order to exclude patients with sensory polyneuropathy and in order to localize the sural nerve for NFR stimulation.

standardized retromalleolar stimulation in previous studies (for review see Sandrini et al., 1993) – allows exact stimulation of the sural nerve as determined during prior sural neurography. 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. We inspected, cleaned and abraded skin before to avoid electrode contact with skin abnormalities and to keep the impedance at the lowest level possible.

A time window of 80–150 ms was selected for the onset of the reflex in order to exclude early RII responses and voluntary limb movements according to the results of previous studies (Willer, 1977; Garcia-Larrea et al., 1993; France et al., 2002). Furthermore, amplitude of at least 40 μV 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 (Sandrini et al., 1993; Schepelmann et al., 1998; Mylius et al., 2005). Between each stimulus a variable interval from 20 to 30 s was used in order to avoid habituation.

The *NFR threshold* was assessed using the up–down staircase method (France et al., 2002). Stimulation intensity was increased in 3 mA increments until the flexion reflex RIII component was detected the first time or a maximum stimulus intensity of 40 mA was reached. 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.

Thereafter, *NFR 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 (Willer, 1983). In case of an unstable or elevated baseline before the time window of the RIII component, the voltage level just at reflex onset was defined as baseline for calculation of amplitude and area under the reflex curve.

2.4. 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). The verbal categories were charted on a large cardboard (16.5 × 23.4 in.) and shown to the subjects after each stimulus application. Before the start of the testing procedures, the scale was introduced to the subjects, who were trained to use it by rating different intensities of noxious pressure (part 1 of the study, see also Kunz et al., 2007). This type of verbal category scale has been found to be the scale of choice for assessing pain among older adults, including those with mild to moderate cognitive impairment (Basler et al., 2001; Herr et al., 2004; Taylor et al., 2005).

2.5. Facial expression of pain

Facial responses were assessed and analyzed according to procedures described in detail previously (Kunz et al., 2004, 2008). In short, the face of the subject was videotaped throughout the en-

tire session and facial responses were later analyzed using the Facial Action Coding System (FACS) (Ekman and Friesen, 1978). The FACS is based on anatomical analysis of facial muscle movements and distinguishes 44 different action units (AUs). The intensity for each action unit was rated on a 5-point scale. A FACS coder (qualified by passing an examination given by the developers of the system) identified frequency and intensity of all facial responses. A special software designed for analysis of observational data (the Observer Video-Pro (Noldus Information Technology)) was used to segment the videos and to enter the FACS codes into a time-related data-base.

Time segments of 5 s after stimulus application were selected for scoring. In total, 14 segments of electrical stimulation (trials within the staircase procedure: the last two stimuli just below the NFR threshold, the last two stimuli just above the NFR threshold; trials of the supra-threshold series: 10 stimuli 5 mA above the threshold) were analyzed.

For purpose of necessary data reduction, we combined those AUs that represent facial movements of the same muscle as has been done in preceding studies without any loss of information (e.g. Prkachin, 1992; Kunz et al., 2004, 2006). 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 segments[3] recorded. We did this separately for demented patients and healthy controls (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 dependant groups) for these differences. The values of these effect sizes are also listed in Table 1. For further analysis only those Action Units that reached an effect size $\geqslant 0.5$ (medium effect) in both groups (these AUs are shaded in grey in Table 1) were used to form composite scores of pain-relevant facial responses.

(3a) Prior to computing composite scores, the frequency values of all Action Units had to be given weights. This was necessary because the frequency of AU 45 (blinking of the eye) is disproportionally higher than those of the other AUs. In order to reduce this numerical distortion, we decided to compute weighted frequency values for all AUs. This was done by dividing the frequency of each AU at each stimulus intensity by the mean frequency of the given AU across all stimulus intensities.

(3b) Composite scores of pain-relevant facial responses were formed by calculating mean scores of those AUs that proved to be pain-relevant (shaded in grey in Table 1) separately for each stimulus intensity and separately for FACS frequency and FACS intensity.

2.6. Autonomic responses

Sympathetic skin responses and heart rate responses to electrical stimuli at an intensity of 5 mA above NFR threshold were assessed by use of the Suempathy100 (SUESS Medizin-Technik, Germany). Both biosignals were sampled at a rate of 512 Hz.

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[3] All trials above NFR threshold.

Table 1
Facial action units (AUs) with a critical occurrence of more than 5% in noxious segments in healthy controls and in demented patients (see text for further explanations)

Action Unit	Description	Healthy controls		Demented patients	
		Percent[a]	Effect size (Cohen's d)	Percent[a]	Effect size (Cohen's d)
AU1/2	brow raiser	13.9	d=0.19	18.3	d=0.34
AU4	brow lower	18.8	d=0.076	37.5	d=0.49
AU6/7	orbit tightening	**49.2**	**d=0.51**	**78.8**	**d=0.72**
AU9/10	levator contraction	**10.0**	**d=2.08**	**32.9**	**d=0.77**
AU17	chin raise	14.5	d=0.00	8.8	d=0.36
AU25/26/27	mouth opening	22.2	d=0.11	87.4	d=0.32
AU45[b]	blink	**321.9**	**d=0.54**	**283.8**	**d=0.51**

Relative frequency of occurrence and effect sizes for frequency differences between "noxious" and "non-noxious" segments are given.
Medium and strong effect sizes ($d \geqslant 0.5$) are marked in bold; AUs shaded in grey represent AUs that were consistently more frequent ($d \geqslant 0.5$) during noxious segments in both groups. [a] Percent denotes the 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.

2.6.1. Sympathetic skin response (SSR)

For recording 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 (Drory and Korczyn, 1993; Watanabe et al., 2003). 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 five valid SSR responses were required for computing mean values) SSR responses elicited by stimulation at 5 mA above NFR threshold were selected for further computations.

2.6.2. Heart rate response

The electrocardiogram (ECG) was recorded using a standard 3 leads montage (one on each wrist and the third on the left ankle). Heart rate was computed on the basis of the R–R intervals (HR = (1000 ms/R–R interval ms) × 60). Recording artifacts resulting into unphysiological high and low heart rates were identified and substituted by estimates obtained by interpolation. For further analyses we averaged heart rate responses to electrical stimulation over the 10 stimuli at an intensity of 5 mA above NFR threshold. Following a procedure by Möltner et al. (1990) we carried out a temporal differentiation of heart rate responses by separate analy-

sis in three fixed time windows, from 0 to 3 s, 3 to 6 s, and 6 to 9 s after stimulation.

2.7. Statistical analysis

Multiple analyses of variance with one between-subject factor "group" (demented patients and healthy controls) were conducted to evaluate the influence of dementia on *supra-threshold NFR parameters* (latency, amplitude and area) as well as on *SSR responses* (latency and amplitude). Analyses of variance with repeated measurements were computed to evaluate the influence of dementia (between-subject factor "group" (demented patients and healthy controls)) on *self-report ratings* (one within-subject factor "stimulus intensity" (below, above, 5 mA above NFR threshold)) and on *heart rate responses* (with one within-subject factors "time" (0–3, 3–6, 6–9 s)). To evaluate the influence of dementia on *facial responses*, we computed multiple analyses of variance (frequency and intensity of facial responses) with repeated measurements with one within-subject factors "stimulus intensity" (below, above, 5 mA above NFR threshold) and one between-subject factor "group" (demented patients and healthy controls). In case of significant group difference, univariate analyses of variance or *T*-tests were computed for single comparisons. *T*-tests were also computed to evaluate group differences in *NFR threshold*.

Furthermore, we conducted correlation analysis to evaluate the extent to which dementia interferes with the *capacity to provide self-report ratings*. Therefore, we computed for each subject the percentage of stimuli that the subject responded to with scorable self-report ratings. Self-report ratings were classified as nonscor-

Table 2
Effect sizes (Cohen's *d*) for differences in multiple pain components during electrical stimulation between patients with dementia and healthy control subjects

Pain component	Effect size (Cohen's *d*)
NFR	
Threshold	1.34
Latency	0.48
Amplitude	0.31
Area under the curve	0.05
Self-report ratings	
Below threshold	0.26
Above threshold	0.47
5 mA above threshold	0.46
Facial responses	
Frequency	
Below threshold	0.46
Above threshold	0.73
5 mA above threshold	0.96
Intensity	
Below threshold	0.52
Above threshold	0.64
5 mA above threshold	0.38
SSR	
Latency	0.21
Amplitude	0.63
Heart rate response	
0–3 s	0.05
3–6 s	0.48
6–9 s	0.62

Fig. 1. Thresholds of the nociceptive flexion reflex in demented patients and in healthy controls (Mean values (±SD)) ($^{**}p \leqslant 0.01$).

able when subjects did not respond at all when asked to rate their stimulus perception or when their response did not fit to any of the categories of the verbal rating scale (e.g. "That was something!"). These percentages of scorable self-report ratings were then correlated with the degree of cognitive impairment (MMSE-score).

In addition, we computed effect-sizes to guide selection of AUs (see Table 1) and to indicate the diagnostic relevance of our findings (see Table 2).

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

3. Results

3.1. Influence of dementia on the NFR

Dementia had a significant impact on the *NFR threshold* ($T(79) = 4.10$; $p \leqslant 0.001$). As can be seen in Fig. 1 the NFR threshold was markedly diminished (strong effect, see Table 2) in patients with dementia compared to healthy controls. In regard to *supra-threshold NFR responses* (that were tailored to the individual NFR threshold), we found no significant group differences ($F(3,76) = 1.78$, $p = 0.158$). Neither latency (controls: $100.4 ± 22.4$ ms/patients: $93.3 ± 12.2$ ms) ($F(1,78) = 2.81$, $p = 0.098$) nor amplitude (controls: $51.7 ± 46.1$ µV/patients: $64.7 ± 69.5$ µV) ($F(1,78) = 1.02$, $p = 0.317$) nor area under the curve (controls: $1830.4 ± 1778.4$ µV ms/patients: $1909.4 ± 2766.4$ µV ms) ($F(1,78) = 0.02$, $p = 0.877$) of the supra-threshold NFR response differed between demented patients and healthy controls. As can be seen in Table 2 the effect sizes for the supra-threshold responses varied between trivial and small effects. The decreased NFR threshold and the relatively unchanged supra-threshold NFR responses in patients with dementia suggests that the whole working range of the NFR was shifted to higher sensitivity but that the supra-threshold sensitivity was not additionally affected.

3.2. Influence of dementia on self-report ratings

Dementia had a strong impact on the *capacity of the subjects to provide self-report ratings*. Whereas healthy controls were able to continuously provide self-report ratings (100%), the percentage of stimuli that demented patients responded to by scorable self-report ratings varied between 0% and 100% (mean value 79%). Furthermore, we found a highly significant correlation between the degree of cognitive impairment and the percentage of scorable self-report ratings. With a decrease in cognitive functioning (MMSE-score) the frequency of scorable self-report ratings declined in demented patients ($r = 0.692$, $p < 0.001$). For further analyses on self-report ratings, we decided to exclude all those subjects were the percentage of scorable self-report ratings was lower than 60% ($N = 7$).

As can be seen in Fig. 2 demented patients rated the stimuli (being on average of moderate pain intensity) similarly painful as healthy individuals did ($F(1,70) = 2.164$, $p = 0.146$). In line with this, the effect sizes indicated only small group effects (see Table 2). Furthermore, the factor "group" did not interact significantly with the factor "intensity" ($F(2,140) = 1.562$, $p = 0.213$). This indicates that the rate of increase in pain intensity ratings, which was significant over stimulus intensities ($F(2,140) = 21.778$, $p < 0.001$), did not differ between the two groups of patients with dementia and elderly subjects without cognitive impairments.
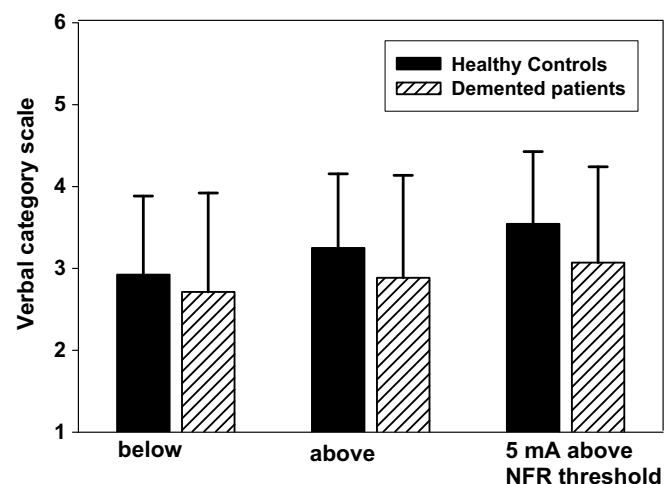

Fig. 2. Self-report ratings of pain intensity in demented patients and in healthy controls (mean values (±SD)) to electrical stimulation.

3.3. Influence of dementia on facial responses

The factor "group" had a significant main effect on the frequency and intensity of pain-relevant facial responses to electrical stimulation ($F(2,76) = 3.430$, $p = 0.037$). As can be seen in Fig. 3, the frequency and intensity of facial responses were markedly increased in demented patients compared to healthy controls. Single comparisons (T-tests) revealed that group differences were not evident during non-noxious stimulation (below NFR threshold (AU frequency: $p = 0.151$, AU intensity: $p = 0.103$)) but only during stimulation above NFR threshold (AU frequency: $p = 0.022$, AU intensity: $p = 0.046$) and 5 mA above NFR threshold (AU frequency: $p = 0.003$, AU intensity: $p = 0.239$). This tendency becomes also evident when considering the effect sizes, with strongest effects occurring during noxious stimulation (see Table 2).

Furthermore, we found a significant main effect for "stimulus intensity" ($F(4,308) = 17.365$, $p < 0.001$) with facial responses increasing across stimulus intensities (see Fig. 3). This increase in frequency and intensity of facial responses did not differ between demented patients and healthy controls as indicated by a non-significant interaction between "group" and "stimulus intensity" ($F(4,308) = 2.285$, $p = 0.060$).

We also tested, whether the increase in facial responsiveness was correlated to the cognitive decline (MMSE-score) in the group of demented patients. Correlation analyses between MMSE-score and facial responses of patients with dementia yielded non-significant results (FACS frequency: $r = -0.06$, $p = 0.74$; FACS intensity: $r = -0.05$, $p = 0.76$), thus indicating, that facial responses to pain did not increase across cognitive decline.

3.4. Influence of dementia on autonomic responses

Dementia had a significant influence on *SSR responses* ($F(2,75) = 3.874$, $p = 0.025$). As can be seen in Fig. 4a this group difference was mainly due to reduced SSR amplitudes in patients with dementia ($F(1,76) = 7.841$, $p = 0.006$; moderate effect (see Table 2)), whereas the latency of SSR responses did not differ between groups ($F(1,76) = 0.399$, $p = 0.529$).

With regard to *heart rate responses*, no significant group differences were found ($F(1,76) = 1.751$, $p = 0.190$). Furthermore, heart rate responses did not differ between the three time windows ($F(2,152) = 0.640$, $p = 0.529$). However, as can be seen in Fig. 4b, heart rate responses of demented patients had a tendency to decrease over time, whereas heart rate responses of healthy controls rather increased. This interaction between "group" and "time" though missed level of significance slightly ($F(2,152) = 2.760$, $p = 0.067$). However, when looking at the effect sizes, the suggested group differences during late phases of the heart rate response were corroborated by a moderate effect for heart rate responses 6–9 s after stimulus onset.

4. Discussion

Our major finding was that different pain components were not all affected in the same way by dementia. Whereas the NFR threshold was reduced and facial responses to noxious electrical stimulation were increased in demented patients (suggesting intensified pain processing) compared to healthy controls, autonomic responses tended to be decreased (suggesting reduced pain processing). In regard to self-report ratings, both groups rated the stimuli as similarly painful, however, demented patients were less able to provide scorable self-report ratings. We discuss our findings sepa-
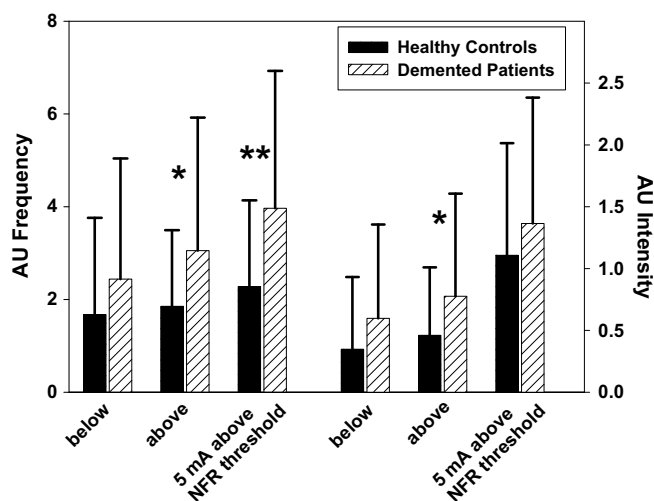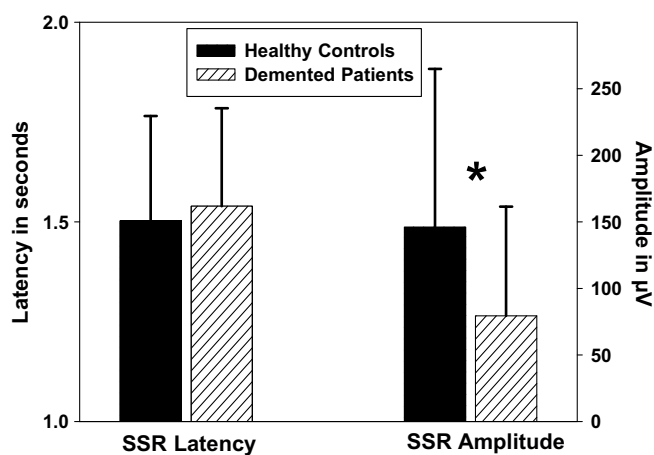

Fig. 3. Composite scores of pain-relevant facial responses in demented patients and in healthy controls (mean values (±SD)) to electrical stimulation. ($^{**}p \leqslant 0.01$; ($^{*}p \leqslant 0.05$)).
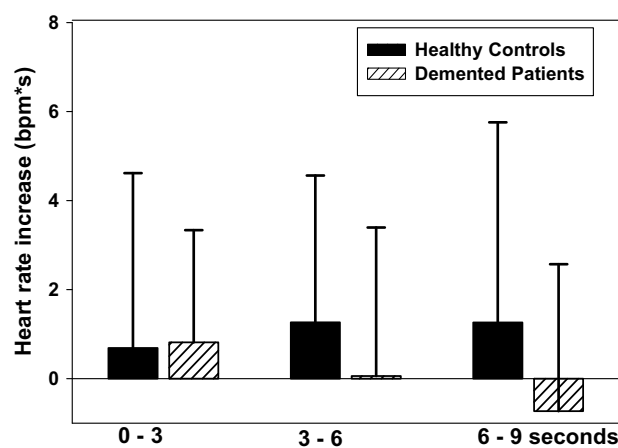
(a) SSR-response

(b) Heart rate response

Fig. 4. Autonomic responses ((SSR; a), (heart rate, b)) in demented patients and in healthy controls (mean values (±SD)) to noxious electrical stimulation with an intensity of 5 mA above NFR threshold. ($^{*}p \leqslant 0.05$).

rately for each pain component first before we try to integrate them.

4.1. Self-report ratings

In accordance with previous studies (Porter et al., 1996; Benedetti et al., 1999; Rainero et al., 2000; Gibson et al., 2001; Kunz et al., 2007) we found that patients with dementia rated the noxious stimuli of moderate intensity similarly painful as healthy control subjects. However, it is open to discussion whether this indicates an unchanged pain experience in patients with dementia because the ability of demented patients to provide self-report ratings was markedly diminished. 46% of our 35 patients with dementia were not able to provide scorable self-report ratings continuously although our pain rating scale was cognitively non-demanding. This inability was strongly related to the degree of cognitive impairment, which has also been reported before (Parmelee, 1996; Porter et al., 1996; Scherder and Bouma, 2000).

4.2. Facial responses

Pain-relevant facial responses to noxious electrical stimulation were significantly enhanced in demented patients compared to healthy controls. This finding again is in accordance with results obtained in previous studies (Porter et al., 1996; Hadjistavropoulos et al., 2000; Kunz et al., 2007). Given that in all studies different pain induction methods (e.g. painful physical exercise, venipuncture, experimental pressure stimulation) were used, the enhancement of facial responses to potentially noxious stimulation in demented patients seems to be a very robust finding. As we could demonstrate earlier (Kunz et al., 2007), this enhancement is not due to an unspecific overall increase of facial responses but to a specific increase of pain-relevant muscle movements.

It is possible that facial responses to noxious stimulation are increased simply because the cognitive ability to control behavioral impulses by learnt display rules is impaired in patients with dementia (Kunz et al., 2007). However, it seems equally likely that the enhanced facial responses are a result of an intensified pain processing in demented patients. This interpretation would also fit well with our findings regarding the NFR response.

4.3. Nocifensive flexion reflex (NFR)

To our knowledge this is the first time that the NFR has been systematically investigated in patients with dementia. Since it has been shown that electrical pain thresholds are not altered in demented patients (Cornu, 1975; Benedetti et al., 1999; Rainero et al., 2000; Gibson et al., 2001) and since pain and NFR thresholds have been found to be correlated (Sandrini et al., 2005), one could expect that the NFR threshold would not differ between the two groups, either. However, we did find the NFR threshold to be markedly decreased in demented patients. The discrepancy between our findings on the NFR threshold and previous findings on pain thresholds might be due to the reduced validity of subjective pain ratings in demented patients. However, there is also increasing evidence that dissociation between reflex activity and pain sensation can occur (Gracely, 2005), and this might also be the case in patients with dementia.

Supra-threshold NFR responses (latency, amplitude, area under the curve) did not differ between demented patients and healthy controls. This finding together with our evidence for a decreased NFR threshold means that the whole working range of the NFR was shifted to higher sensitivity but that the supra-threshold sensitivity was not additionally affected.

But what are the reasons for the reduced NFR threshold in patients with dementia? At the spinal level the peripheral input for the NFR is processed and subject to segmental and descending control in a polysynaptic pathway before it triggers the motor response (Ellrich et al., 1998). It might be that neurodegeneration affects brain structures that are involved in descending inhibition of spinal nociceptive transmission. One brain structure of interest might be the raphe nucleus, which is believed to be involved in supra-spinal modulation of the NFR (e.g. Skljarevski and Ramadan, 2002) and has also been found to be affected by neurodegeneration in dementia (Aletrino et al., 1992; Hendricksen et al., 2004; Lyness et al., 2003).

4.4. Autonomic responses

In accordance with previous studies (Rainero et al., 2000; Benedetti et al., 2004) we found that autonomic responses to noxious stimulation being of mild to moderate pain intensities tended to be diminished in demented patients. At least SSR responses to noxious electrical stimulation were significantly reduced in demented patients compared to healthy controls. And although no significant group differences were found for heart rate responses, heart rate responses of demented patients had a tendency to decrease over time whereas heart rate responses of healthy controls rather increased (see also the effect sizes). These decreased autonomic responses to noxious stimulation have been interpreted as an indication of a reduced pain affect in patients with dementia (Rainero et al., 2000; Benedetti et al., 2004). However, this interpretation does not consider that the association between autonomic responses and ratings of pain affect can be very weak and subject to great inter-individual variability (Donaldson et al., 2003; Tousignant-Laflamme et al., 2005). Furthermore, the reduced autonomic responses to noxious stimulation in demented patients might simply be due to altered function of the autonomic nervous system in patients with dementia, which has been reported before (e.g. Allan et al., 2007); and thus not be pain specific.

4.5. General conclusions

We found that dementia affects different pain components in different ways. At first glance it might seem striking that the two pain indicators, which suggest an increased processing of noxious stimulation in demented patients, are both motor responses. Therefore, one explanation for our findings could simply be a general disinhibition of motor responses during the course of dementia. However, this interpretation seems unlikely, since findings for non-painful motor responses in demented patients do not suggest a general disinhibition of motor responses in this patients group (e.g. no augmentation of the blink reflex (Ueki et al., 2006); no augmentation of the Hoffmann reflex (Lamour et al., 1987)). Moreover, the increased facial responses to noxious stimulation in patients with dementia were pain specific and were not accompanied by an overall increase in facial responsiveness (Kunz et al., 2007).

Alternatively, our findings might prove an intensified processing of noxious stimulation in patients with dementia, possibly due an impaired endogenous pain inhibition. The perspective of intensified processing of noxious stimulation was also given by a recent study on cerebral responses (fMRI) to noxious stimulation in demented patients (Cole et al., 2006). Cole et al. reported that pain-related cerebral activations were significantly greater in demented patients compared to healthy controls. Thus, one can find indices for intensified processing of noxious stimulation in patients with dementia not only when looking at facial responses and the NFR but also when assessing cerebral activation.

A more neuropsychological interpretation of our findings refers to the lacking capacity of pain anticipation and situational evaluation in patients with dementia (Porter et al., 1996; Benedetti et al., 2004). Even repeated pains might be new and surprising; prepara-

tory actions are missing. All this could have led to greater anxiety, increased distress as well as increased startle responses in the group of demented patients, which might have been the causal factors for the enhanced facial responses and the decreased NFR threshold in demented patients.

So far, however, we can only conclude that dementia tends to affect different pain components in patients with dementia in different ways. Nevertheless, taking into account the reduced validity of self-report ratings and the questionable pain-specificity of autonomic responses, our data rather suggest an increased responsiveness to noxious stimulation in demented patients.

4.6. Limitations and future directions

Due to the number of different pain components that we assessed, multiple statistical testing could not be avoided; thus increasing the risk of committing alpha errors. However, our positive findings of differences are well in line with previous findings and, by that, do not appear spurious. Another limitation of the study regards the unequal sex-distribution amongst the group of healthy controls and patients with dementia. Analyses computed separately for males and females did not change results and thus refute sex as being a confounding factor.

The aim of the present study was to assess multiple pain components in parallel in one group of demented patients in order to describe more comprehensively the impact dementia exerts on pain processing. Future research, however, should focus more on investigating possible mechanisms of action underlying altered pain processing in demented patients. A promising approach might be to investigate, whether a deficiency of the diffuse noxious inhibitory control system (DNIC) as a part of the descending inhibitory system might contribute to the altered pain responses in demented patients. Knowing more about these mechanisms of action will be crucial in order to provide adequate pain treatment in this fragile patient group.

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References

Aletrino MA, Vogels OJ, Van Domburg PH, Ten Donkelaar HJ. Cell loss in the nucleus raphes dorsalis in Alzheimer's disease. Neurobiol Aging 1992;13:461–8.

Allan LM, Ballard CG, Allen J, Murray A, Davidson AW, McKeith IG, et al. Autonomic dysfunction in dementia. J Neurol Neurosurg Psychiatry 2007;78(7):671–7.

Basler HD, Bloem R, Casser HR, Gerbershagen HU, Griessinger N, Hankemeier U, et al. A structured pain interview for geriatric patients. Schmerz 2001;15:164–71.

Benedetti F, Vighetti S, Ricco C, Lagna E, Bergamasco B, Pinessi L, et al. Pain threshold and tolerance in Alzheimer's disease. Pain 1999;80:377–82.

Benedetti F, Arduino C, Vighetti S, Asteggiano G, Tarenzi L, Rainero I. Pain reactivity in Alzheimer patients with different degrees of cognitive impairment and brain electrical activity deterioration. Pain 2004;111:22–9.

Cole LJ, Farrell MJ, Duff EP, Barber JB, Egan GF, Gibson SJ. Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease. Brain 2006;129:2957–65.

Cornu F. Pertubations de la perception de la douleur chez les dements degeneratifs. J Psychol 1975;4:461–72.

Donaldson GW, Chapman CR, Nakamura Y, Bradshaw DH, Jacobson RC, Chapman CN. Pain and the defense response: structural equation modeling reveals a coordinated psychophysiological response to increasing painful stimulation. Pain 2003;102:97–108.

Drory VE, Korczyn AD. Sympathetic skin response: age effect. Neurology 1993;43:1818–20.

Ekman PE, Friesen WV. Facial Action Coding System. Palo Alto (CA): Consulting Psychologists Press; 1978.

Ellrich J, Andersen OK, Treede RD, Arendt-Nielsen L. Convergence of nociceptive and non-nociceptive input onto the medullary dorsal horn in man. Neuroreport 1998;9:3213–7.

Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the state of patients for the clinician. J Psychiat Res 1975;12:189–98.

France CR, France JL, al'Absi M, Ring C, McIntyre D. Catastrophizing is related to pain ratings, but not nociceptive flexion reflex threshold. Pain 2002;99:459–63.

Garcia-Larrea L, Charles N, Sindou M, Mauguiere F. Flexion reflexes following anterolateral cordotomy in man: dissociation between pain sensation and nociceptive reflex RIII. Pain 1993;55:139–49.

Gibson SJ, Voukelatos X, Ames D, Flicker L, Helme RD. An examination of pain perception and cerebral event-related potentials following carbon dioxide laser stimulation in patients with Alzheimer's disease and age-matched control volunteers. Pain Res Manage 2001;6:126–32.

Gracely RH. Studies of pain in human subjects. In: McMahon SB, Koltzenburg M, editors. Wall and Melzack's textbook of pain. 5th ed. Edinburgh: Churchill Livingstone (Elsevier); 2005. p. 267–89.

Hadjistavropoulos T, LaChapelle DL, MacLeod FK, Snider B, Craig KD. Measuring movement-exacerbated pain in cognitively impaired frail elders. Clin J Pain 2000;16:54–63.

Helme RD. How useful are currently available tools for pain evaluation in elderly people with dementia. Nat Clin Pract Neurol 2006;2:474–5.

Hendricksen M, Thomas AJ, Ferrier IN, Ince P, O'brien JT. Neuropathological study of the dorsal raphe nuclei in late-life depression and Alzheimer's disease with and without depression. Am J Psychiatry 2004;161:1096–102.

Herr KA, Spratt K, Mobily PR, Richardson G. Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. Clin J Pain 2004;20:207–19.

Herr K, Bjoro K, Decker S. Tools for assessment of pain in nonverbal older adults with dementia: a state-of-the-science review. J Pain Symptom Manage 2006;31:170–92.

Kunz M, Mylius V, Schepelmann K, Lautenbacher S. On the relationship between self-report and facial expression of pain. J Pain 2004;5:368–76.

Kunz M, Gruber A, Lautenbacher S. Sex differences in facial encoding of pain. J Pain 2006;7:915–28.

Kunz M, Scharmann S, Schepelmann K, Hemmeter U, Lautenbacher S. The facial expression of pain in dementia. Pain 2007;133:221–8.

Kunz M, Mylius V, Schepelmann K, Lautenbacher S. The impact of age on the facial expression of pain. J Psychosom Res 2008;63:311–8.

Lamour Y, Willer JC, Roudier M, Davous P. The Hoffmann reflex (H-reflex) in senile dementia of the Alzheimer's type – preliminary results. Funct Neurol 1987;2:165–71.

Lautenbacher S, Kunz M, Mylius V, Scharmann S, Hemmeter U, Schepelmann K. Multidimensional pain assessment in patients with dementia. Schmerz 2007;21:529–38.

Lyness SA, Zarow C, Chui HC. Neuron loss in key cholinergic and aminergic nuclei in Alzheimer disease: a meta-analysis. Neurobiol Aging 2003;24:1–23.

Mantyselka P, Hartikainen S, Louhivuori-Laako K, Sulkava R. Effects of dementia on perceived daily pain in home-dwelling elderly people: a population-based study. Age Ageing 2004;33:496–9.

Marzinski LR. The tragedy of dementia: clinically assessing pain in the confused nonverbal elderly. J Gerontol Nurs 1991;17:25–8.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.

Möltner A, Holzl R, Strian F. Heart rate changes as an autonomic component of the pain response. Pain 1990;43:81–9.

Mylius V, Kunz M, Schepelmann K, Lautenbacher S. Sex differences in nociceptive withdrawal reflex and pain perception. Somatosens Motor Res 2005;22:207–11.

Parmelee PA. Pain in cognitively impaired older persons. Clin Geriatr Med 1996;12:473–87.

Porter FL, Malhotra KM, Wolf CM, Morris JC, Miller JP, Smith MC. Dementia and response to pain in the elderly. Pain 1996;68:413–21.

Prkachin KM. The consistency of facial expressions of pain: a comparison across modalities. Pain 1992;51:297–306.

Rainero I, Vighetti S, Bergamasco B, Pinessi L, Benedetti F. Autonomic responses and pain perception in Alzheimers's disease. Eur J Pain 2000;4:267–74.

Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN international workshop. Neurology 1993;43:250–60.

Sandrini G, Arrigo A, Bono G, Nappi G. The nociceptive flexion reflex as a tool for exploring pain control systems in headache and other pain syndromes. Cephalalgia 1993;13:21–7.

Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. Prog Neurobiol 2005;77:353–95.

Schepelmann K, Schugens MM, Loschmann PA, Klockgether T, Dichgans J. The non-competitive N-methyl-D-aspartate-antagonist memantine does not affect segmental mono- and polysynaptic reflexes in man. Neurosci Lett 1998;257:159–61.

Scherder EJ. Low use of analgesics in Alzheimer's disease: possible mechanisms. Psychiatry 2000;63:1–12.

Scherder EJ, Bouma A. Visual analogue scales for pain assessment in Alzheimer's disease. Gerontology 2000;46:47–53.

Scherder E, Oosterman J, Swaab D, Herr K, Ooms M, Ribbe M, et al. Recent developments in pain in dementia. BMJ 2005;330:461–4.

Skljarevski V, Ramadan NM. The nociceptive flexion reflex in humans – review article. Pain 2002;96:3–8.

Smith M. Pain assessment in nonverbal older adults with advanced dementia. Perspect Psychiatr Care 2005;41:99–113.

Taylor LJ, Harris J, Epps CD, Herr K. Psychometric evaluation of selected pain intensity scales for use with cognitively impaired and cognitively intact older adults. Rehabil Nurs 2005;30:55–61.

Tousignant-Laflamme Y, Rainville P, Marchand S. Establishing a link between heart rate and pain in healthy subjects: a gender effect. J Pain 2005;6:341–7.

Ueki A, Goto K, Sato N, Iso H, Morita Y. Prepulse inhibition of acoustic startle response in mild cognitive impairment and mild dementia of Alzheimer type. Psychiatry Clin Neurosci 2006;60:55–62.

Watanabe H, Shindo K, Ida H, Tanaka H, Nagasaka T, Shiozawa Z. Aging effects of sympathetic reflex activities on skin nerves. Gerontology 2003;49:366–73.

Willer JC. Comparative study of perceived pain and nociceptive flexion reflex in man. Pain 1977;3:69–80.

Willer JC. Nociceptive flexion reflexes as a tool for pain research in man. Adv Neurol 1983;39:809–27.