Influence of dementia on multiple components of pain

Miriam Kunz, Veit Mylius, Siegfried Scharmann, Karsten Schepelman, Stefan Lautenbacher

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.

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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 Alzheimer patients.
mer patients (MRI, Cole et al., 2006). Surprisingly, this increase in cerebral activation was found in regions being associated with the medial pain system (e.g. mACC), 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 predetermining 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 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 (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 more 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 supra-threshold 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.

2.2. 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 (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 more detailed description see Kunz et al., 2007) offered apparently more control over stimulation and induced natural qualities of pain experience.

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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 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 neuropathy 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; García-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; Scheppelmann 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 subside 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 stimulus levels. Ten supra-threshold 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.

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 entire 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 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 dependent 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 of 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 disproportionately 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.
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 analyses 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>
<thead>
<tr>
<th>Action Unit</th>
<th>Description</th>
<th>Healthy controls</th>
<th>Demented patients</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>Percenta</td>
<td>Effect size (Cohen’s d)</td>
</tr>
<tr>
<td>AU1/2</td>
<td>brow raiser</td>
<td>13.9</td>
<td>d=0.19</td>
</tr>
<tr>
<td>AU4</td>
<td>brow lower</td>
<td>18.8</td>
<td>d=0.076</td>
</tr>
<tr>
<td>AU6/7</td>
<td>orbit tightening</td>
<td>49.2</td>
<td>d=0.51</td>
</tr>
<tr>
<td>AU9/10</td>
<td>levator contraction</td>
<td>10.0</td>
<td>d=2.08</td>
</tr>
<tr>
<td>AU17</td>
<td>chin raise</td>
<td>14.5</td>
<td>d=0.00</td>
</tr>
<tr>
<td>AU25/26/27</td>
<td>mouth opening</td>
<td>22.2</td>
<td>d=0.11</td>
</tr>
<tr>
<td>AU45b</td>
<td>blink</td>
<td>321.9</td>
<td>d=0.54</td>
</tr>
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</table>

Relative frequency of occurence and effect sizes for frequency differences between “noxious” and “non-noxious” segments are given. Medium and strong effect sizes (d ≥ 0.5) are marked in bold; AU shaded in grey represent AUs that were consistently more frequent (d ≥ 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.

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)
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 ($F(79) = 4.10; p < 0.001$). 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: $100.4 \pm 22.4$ ms/patients: $93.3 \pm 12.2$ ms) ($F(1,78) = 2.81, p = 0.098$) nor amplitude (controls: $51.7 \pm 46.1 \mu V$/patients: $64.7 \pm 69.5 \mu V$) ($F(1,78) = 1.02, p = 0.317$) nor area under the curve (controls: $1830.4 \pm 1778.4 \mu V$ ms/patients: $1909.4 \pm 2766.4 \mu V$ 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.
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. (∗ $p < 0.01$; (∗∗ $p < 0.05$).](image)

![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. (∗ $p < 0.05$).](image)
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; Hadjistavroupolos 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 (Aletino et al., 1992; Hendriksen 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; Toussignant-Lafllamme 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 automatic 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 thereby support our hypothesis. 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 refuse 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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