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Repeated Pain Assessment in Alzheimer's Disease

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Key Words
Alzheimer's disease · Pain affect · Pain intensity · Visual analogue scales · Analgesics

Abstract
In previous studies, patients with probable Alzheimer's disease (AD) have indicated that they experienced less pain intensity and affect from their painful conditions than nondemented elderly persons. However, in those studies, pain assessment occurred only once. Therefore, it may be possible that pain which had occurred, for example, a day earlier, could have been forgotten. Therefore, in the present study, AD patients' pain was assessed daily, i.e. once a day and even three times a day, during a longer period. The results parallel those of earlier studies, i.e. compared to elderly persons without dementia, AD patients appear to perceive less pain intensity and pain affect. These findings support the hypothesis that AD is characterized by an alteration in pain experience.

An increasing number of studies underscore the problem of pain assessment in cognitively impaired elderly persons [1–3]. It has been observed that 83% of cognitively impaired patients could complete at least one out of seven pain scales [4]. Also, self-reports could be validly used in assessing pain in cognitively impaired patients [5]. Parmelee et al. [5] observed that the more people become cognitively impaired, the less they report pain. Since in both studies [4, 5] the precise diagnosis of the participating subjects was unclear, the observed relationship between cognition and pain remains obscure.

Alzheimer's disease (AD) is characterized by atrophy in the limbic areas, e.g. the septohippocampal region, the amygdala, the hypothalamus, and the intralaminar nuclei of the thalamus [6, 7]; areas which are involved in the experience of pain [8–10]. In several studies, we therefore assessed pain experience exclusively in patients with AD. In a first study, the use of analgesics (nonsteroidal anti-inflammatory drugs, NSAIDs, and other analgesic medications) of 70 nondemented elderly persons was compared with the use of these substances in AD patients at either a mild (n = 14), a moderate (n = 25) or a severe stage (n = 27) of the disease [11]. The results showed that although the number of chronic, painful conditions did not differ between the groups, the nondemented elderly persons used significantly more NSAIDs and other

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analgesic medications than the AD patients, irrespective of the stage of the disease. Subsequently, specific parts of three verbal pain questionnaires, in which memory played the less important role, were completed by 19 AD patients and 18 nondemented elderly persons [12]. The results showed that AD patients indicated that they experienced less intense pain and less pain affect than the nondemented elderly persons, despite the fact that both groups were matched for the presence of chronic painful conditions and the use of analgesics did not differ between both groups. The question arose whether these results reflected an alteration in pain experience in AD or whether they were due to a decline in the patients' ability to communicate about their pain. In order to enhance communication about pain, several simple visual analogue scales which are used in pediatrics were applied to 20 AD patients at a relatively early stage, 20 AD patients at midstage and 20 elderly persons without dementia [13]. Only the subjects who comprehended the concept of the scale were included in the data analyses. The results of that study showed that elderly persons without dementia reported experiencing more intense pain and pain affect from their own painful conditions than the early and midstage AD group. The latter two groups did not differ as far as reporting pain affect was concerned. Eliminating the influence of communicative disorders on pain assessment strengthens the hypothesis that one of the clinical symptoms in AD could be an alteration in pain experience.

It is noteworthy that in the above-mentioned studies pain assessment took place only once, and one cannot, thus, exclude the possibility that the AD patient who had suffered pain, e.g. a day or several hours before the assessment took place, just could not remember it. The septohippocampal region and the amygdala play a well-known role in memory processes as well [14–16]. One of the greatest confounding variables in pain assessment in demented people is the influence of a decline in memory for pain on pain assessment [10]. In the present study AD patients and nondemented elderly persons underwent repeated pain assessment. One condition was that the subject's pain was assessed once a day during 4 weeks and, 2 months later, again for a period of 5 days. After careful verification that the daily visits of the researcher did not upset the subjects (e.g., the doctor visits me every day so I am probably very ill), a second condition was included in which pain assessment took place at three different moments of the day, for 5 days.

Methods

Condition 1

Pain was assessed once a day, during 4 weeks and 2 months later for a period of 5 days.

Subjects. The sample consisted of two groups: 14 AD patients (12 females, 2 males) at a relatively early stage, i.e. stage 5 of the Global Deterioration Scale [17], and 17 elderly persons without dementia (14 females, 3 males). Gender ($\chi^2 = 0.06$, d.f. = 1, NS) and age (Mann-Whitney U: Z = 0.28, NS) of the two groups did not differ. The AD patients had a mean age of 87.93 (range 78–99), whereas the mean age of the nondemented elderly persons was 87.41 (range 78–97). The AD group and the nondemented group showed no significant difference in education (Mann-Whitney U: Z = 0.13, NS; five categories: elementary school not finished: score = 1; elementary school finished: score = 2; lower secondary school: score = 3; higher secondary school: score = 4; higher vocational training for 18+/university: score = 5): M = 2.36 (range 2–4) and M = 2.41 (range 2–4), respectively.

All AD patients met the NINCDS-ADRDA criteria for the clinical diagnosis of probable AD [18]. Subjects were excluded from participation in this study if they had problems with vision, a history of psychiatric disorder (e.g. depression), alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, disturbances of consciousness, or focal brain disorders.

The level of cognitive functioning was assessed by using a shortened 12-item version [19] of the Mini-Mental State Examination (MMSE) [20]. The 12-item version (maximum score: 12) evaluates orientation to time and place, registration, recall, attention, and calculation, language and praxis, and visuoconstructive abilities [19]. A score of 7–10, which is comparable to a score of 18–24 of the 20-item MMSE version (maximum score 30) [19], indicates mild cognitive deterioration. The mean score of the control group and the AD group appeared to be 10.18 (range 7–12) and 7.43 (range 6–9), respectively, resulting in a significant difference (Mann-Whitney U: Z = 4.04; $p < 0.000$).

Characteristics of Painful Conditions. The two groups were matched for chronic painful conditions, i.e. painful conditions with a duration of at least 6 months. Separate conditions which might cause pain for those with and without dementia were collected by one of the authors (E.J.A.S.) by reviewing their former general practitioner's records and those held by the present nursing home physician. These medical records included the subjects' medical history and their present mental and physical status. Reports from the neurologist, orthopedist, psychiatrist, and neuropsychologist were added. The following three categories of painful conditions emerged: (1) arthritis/arthrosis; (2) recent fractures (within the last year), and (3) miscellaneous (e.g. tendinitis and diabetes neuropathia). These painful conditions are similar to those generally observed in nursing home residents [1]. In the present study, the AD group and nondemented group had either one (85.7 and 82.4%, respectively) or two painful conditions (14.3 and 17.6%, respectively). The AD group and the nondemented group did not appear to differ as far as the number of chronic painful conditions was concerned (Mann-Whitney U: Z = 0.25; NS). The AD group and the nondemented group did not differ in the prevalence of arthritis (85.7 and 94.1%, respectively; $\chi^2 = 0.62$, d.f. = 1, NS), recent fractures (14.3 and 5.9%, respectively; $\chi^2 = 0.62$, d.f. = 1, NS) and miscellaneous (14.3 and 17.6%, respectively; $\chi^2 = 0.06$, d.f. = 1, NS).

Comorbidity. The prevalence of specific categories of illness in demented and nondemented subjects was ascertained to assess

whether the patients in the latter group have diseases which might contribute to their pain experience. Specific categories of illness included congestive heart failure, peripheral vascular disease, chronic pulmonary disease, diabetes mellitus, chronic renal failure, tumors, ulcers, anemia, hyper-hypothyroidism, cholecystectomy, hearing and vision problems, urology, hypertension, Dupuytren's disease, migraine, diverticulosis, esophagitis, liver disturbances, prostatism, strumectomy, and dizziness. For each separate category of illness, comparisons were made between the two groups, using χ^2 tests. Only cholecystectomy occurred with a significantly higher frequency in the nondemented group (30%) as compared to the AD group (0%; $\chi^2 = 4.91$, d.f. = 1, $p < 0.03$). Subsequently, the number of disorders was compared between the two groups. The results revealed that the number of illnesses did not differ between the two groups (Mann-Whitney U: Z = 1.73; NS).

Use of NSAIDs and Other Analgesic Medication

The researcher (E.J.A.S.) who reviewed the records was not informed about the subjects' medication status. The nursing home pharmacist, who did not know the purpose of the study, selected the most frequently prescribed NSAIDs (ibuprofen, Voltaren, Arthrotec, diclofenac, naproxyn) and other analgesic medication (paracetamol, tramadol, caffeine and codeine), and summarized the type and number of these drugs used by each subject over a period of 8 months. For overall drug use, the difference between the number of nondemented subjects (82.4%) and the number of AD patients (50%) showed a trend ($\chi^2 = 3.68$, d.f. = 1, $p < 0.06$). More specifically, with respect to the use of NSAIDs, the number of AD persons (7.1%) and the number of nondemented elderly persons (23.5%) did not significantly differ ($\chi^2 = 1.52$, d.f. = 1, NS). However, the number of AD patients (42.9%) using other analgesic medication was significantly lower than the number of nondemented elderly persons (76.5%; $\chi^2 = 3.66$, d.f. = 1, $p < 0.03$).

Condition 2

Two months after condition 1, pain was assessed three times a day, during 5 days.

Subjects. In the 2 months following condition 1, the number of subjects in each group was considerably reduced, due to death and noncompliance. From the original 14 AD patients, 11 patients (9 women, 2 men) could be included (3 persons died), and from the original 17 nondemented elderly persons, only 9 subjects (7 women, 2 men) could still participate (3 subjects died, 5 subjects had to be excluded for noncompliance).

Data analyses revealed that the AD and nondemented group in condition 2 did not differ in gender ($\chi^2 = 0.06$, d.f. = 1, NS), age (M = 87.45 and 87.78, respectively; Mann-Whitney U: Z = 0.12; NS) and education (M = 2.36 and 2.56, respectively; Mann-Whitney U: Z = 0.43; NS). The AD and nondemented group showed a significant difference in MMSE scores (M = 7.64 and 10, respectively; Mann-Whitney U: Z = 3.13; $p < 0.001$).

Characteristics of Painful Conditions. The subjects of the AD group and the control group had either one (81.8 and 88.9%, respectively) or two painful conditions (18.2 and 11.1%, respectively). The data showed no significant differences between the AD group and the nondemented elderly group for the total number of pain areas ($\chi^2 = 0.19$, d.f. = 1, NS), prevalence of arthritis (90.9 and 100%, respectively; $\chi^2 = 0.86$, d.f. = 1, NS), recent fractures (9.1 and 11.1%, respectively; $\chi^2 = 0.02$, d.f. = 1, NS) and the category miscellaneous (0 and 18.2%, respectively; $\chi^2 = 1.82$, d.f. = 1, NS).

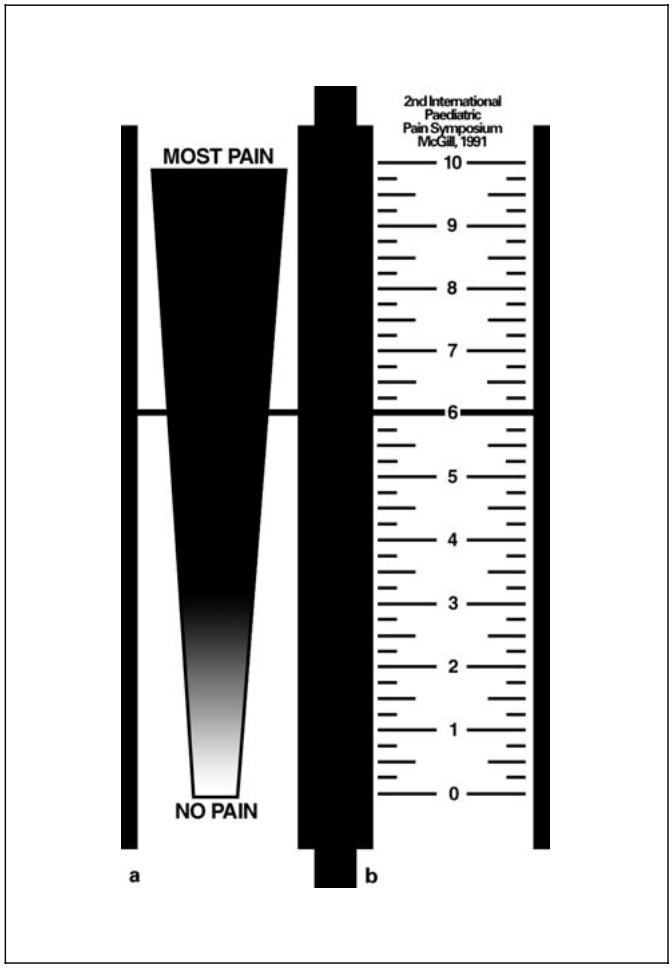

Fig. 1. CAS to rate pain intensity. **a** Front of the CAS as seen by the subjects. **b** Back of the CAS which shows the numerical value of the rating shown on the CAS. Reprinted from McGrath et al. [21] with permission from Elsevier Science.

Comorbidity. The participating AD patients and the nondemented elderly persons did not show significant differences, either in the total number of illnesses ($\chi^2 = 9.03$, d.f. = 6, NS), or in the separate categories of illnesses, except for cholecystectomy (0 and 44.4%, respectively; $\chi^2 = 6.11$, d.f. = 1, $p < 0.02$).

Use of NSAIDs and Other Analgesic Medication. Condition 2 occurred 2 months later; during this period no changes in medication occurred. The difference between the number of AD patients (45.5%) and the number of nondemented elderly persons using drugs (88.9%) appeared to be significant ($\chi^2 = 4.10$, d.f. = 1, $p < 0.05$). With respect to the use of NSAIDs, no significant difference was observed between the number of AD patients (9.1%) and the number of elderly persons without dementia (11.1%; $\chi^2 = 0.02$, d.f. = 1, NS). Furthermore, the number of AD patients using other analgesic medication (36.4%) significantly differed from the number of nondemented elderly people taking these drugs (88.9%; $\chi^2 = 5.69$, d.f. = 1, $p < 0.01$).

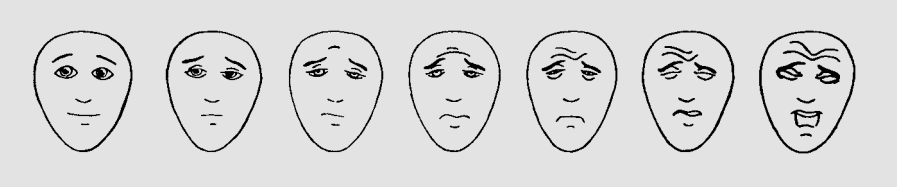

Fig. 2. The FPS. Reprinted from Bieri et al. [22] with permission from Elsevier Science.

Materials and Procedure

To assess pain intensity and pain affect, three visual analogue scales, one verbal pain questionnaire and one observation scale were used.

Visual Analogue Scales. The results of a former study indicated that visual analogue scales which were originally developed for young children can be reliably administered to AD patients [13]. Therefore, in the present study, the following scales were used: (i) *the Coloured Analogue Scale for the assessment of pain intensity* (CAS) [21] (fig. 1), (ii) *the CAS for the assessment of pain affect and* (iii) *the Faces Pain Scale (FPS)* (fig. 2). The CAS is designed to assess, in a nonverbal manner, the intensity of pain which subjects experience. The CAS looks like a thermometer (a triangular shape); the different scale positions are marked by different colors and areas which facilitate the subject's selection of a scale position which best reflects the intensity of his/her pain [21]. Selecting the appropriate scale position is done by sliding a horizontal marker from the bottom (no pain) to the top (maximum pain). The subject's score is the numerical value on the back of the scale which matches the selected scale position (range 0–100). This scale appears to be suitable to AD patients, since in a former study all early-stage AD patients and all nondemented elderly persons fully comprehended the concept of the CAS [13].

In the present study, the CAS [21] (fig. 1) was also used to assess pain affect, i.e. the extent of suffering from the subject's own painful condition(s). The label 'no pain' at the bottom was replaced by the label 'no suffering' and the label 'maximum pain' at the top by the label 'a great deal of suffering'. Similar to the original CAS, each scale position referred to a number (a numerical value) which was on the back of the scale. The subject's scores ranged from 0 to 100.

The FPS (fig. 2) primarily measures the severity of pain and possibly, to a lesser extent, its affective components [22]. The FPS consists of line drawings of seven faces, i.e. one neutral face and six faces that express increasing feelings of pain. Each face is 6 cm high. The faces are rank ordered from 0 to 6, from left to right. Subjects could rank their feelings from 'no pain' (score 0, the neutral face, at the extreme left side), to the most severe pain (score 6, the face expressing the most feelings of pain, at the extreme right side). The subject's score is identical to the scale number, i.e. ranging from 0 to 6. In the former study, all nondemented elderly persons and 60% of the AD patients at an early stage fully comprehended the concept of the scale [13].

The Number of Words Chosen-Affective (NWC-A; McGill Pain Questionnaire) [23]; Dutch language version [24]. This affective pain scale consists of five items, each of which with three affective adjectives. The items are arranged by increasing intensity (ranking), which allows the subjects to indicate the nature of the pain (e.g. worry, depression). The adjectives of the NWC-A were read aloud by the examiner. By adding the results of this scale, a maximum score of 15 could emerge.

The Feldt Checklist of Nonverbal Pain Indicators (CNPI) [25]. This observation scale is a revised version of the University of Alabama Pain Behavior Scale [26]. The scale includes the following five nonverbal behaviors: (1) nonverbal vocalizations, e.g. moans, groans, grunts, cries; (2) grimacing, e.g. furrowed brow, narrowed eyes, tightened; (3) bracing, e.g. clutching or holding onto side rails, bed; (4) restlessness, e.g. constant or intermittent shifting of position, and (5) rubbing, i.e. massaging the affected area. In addition, the presence/absence of verbal pain indicators were recorded: verbal vocalizations (a verbal descriptor subscale), e.g. 'that hurts', cursing during movement [25]. The interrater reliability ranges from 0.625 to 0.819 for individual items (κ statistics) [25]. A Spearman correlation of the five nonverbal subscales of the CNPI with the verbal descriptor subscale is $r = 0.428$ ($p < 0.0001$) for a nondemented group ($n = 32$) and $r = 0.426$ ($p < 0.009$) for a demented group ($n = 32$) [25]. In the present study, the examiner observed the presence/absence of the pain behavior(s) during standing up, walking and sitting down, with or without an aid. The score on each items is 0 if the behavior is absent and 1 if the score is present. Maximum score is 6.

Administration of Scales

Frequency

Condition 1. First, all scales were administered during 4 weeks in succession, once a day (long-term assessment: LTA-1), 5 days a week, resulting in 20 measurements of pain experience. If the subject was absent during the week, pain was assessed at the weekend. In order to exclude the possibility that pain assessment had taken place in a period which happened to be very painful or not painful at all, pain assessment was repeated after a period of approximately 2 months. However, this second pain assessment period was shorter, i.e. 5 days in succession, once a day (short-term assessment: STA-1). From a practical point of view, shortening the assessment period from 1 month to 1 week made it possible to examine whether the data collected within 1 week were comparable to the data collected within 1 month.

Condition 2. After 2 months, pain assessment took place at three varying, random times a day, again on 5 successive days (STA-3).

Comprehension of the Scales

Each time the scale was administered, subjects were tested for their comprehension of the concept. For the original CAS and for the CAS used for the assessment of pain affect they were asked to indicate at what level the marker should be positioned when a person had the most severe pain/suffered the most (top of the scale) or no pain at all/no suffering (bottom of the scale). For the FPS, they were asked to indicate which face showed the most pain and which face showed the least pain. For the LTA-1, STA-1, and STA-3 the maximum scores on all three scales were 20, 5, and 15, respectively.

Pain Experience

On the CAS the subjects were asked to indicate whether the marker should be if it were to match their own level of pain/suffering, both at the moment of administration and/or on the preceding 3 h. The subjects were then asked to point out, on the FPS, the face which best reflected the pain they experienced at the moment of administration and/or on the preceding 3 h. For the various periods (LTA-1, STA-1 and STA-3), the mean pain scores of only those subjects who comprehended the concept of the scales were calculated.

Data Analyses

The SPSS-PC program [27] was used for statistical analyses, including χ^2 tests and Mann-Whitney U tests. The Bonferroni correction was applied to the significance level of $p < 0.05$, resulting in a critical value of $p < 0.01$.

Results

For each separate scale the data will be presented as follows: (a) comprehension of the scale, i.e. the number of correct and false interpretations of the concept of the scale of the subjects in each group, and (b) report of pain experience. Only those subjects who correctly interpreted the meaning of the scale were included in the analyses.

CAS Intensity

Comprehension of the Scale. During both the LTA-1, the STA-1, and the STA-3 periods, all subjects comprehended the concept of the scale, except for 1 subject in the nondemented group who misinterpreted the concept of the scale on three different occasions during the LTA-1 period.

Report of Pain Experience. The results show that in all three periods the nondemented elderly persons experienced significantly more intense pain than the subjects in the AD group. Noteworthy is that the mean score of the patients in the nondemented group in the STA-1 period is considerably lower compared to the mean scores in the other two assessment periods (table 1). Consequently, using an analysis of repeated measures within subjects, we examined whether the mean scores of the subjects without dementia differed significantly over the three periods. This appeared not to be the case [$F(2,7) = 2.73$; NS].

CAS Affect

Comprehension of the Scale. Similar to the CAS intensity scale, the same subject of the nondemented group misinterpreted the meaning of the CAS affect scale during the LTA-1 assessment period.

Report of Pain Experience. Furthermore, the results show that, compared to the AD group, the nondemented elderly persons indicated that they suffered significantly more pain affect, irrespective of the assessment period.

FPS

Comprehension of the Scale. Overall, the results indicated that despite the fact that 3 nondemented elderly persons misinterpreted the meaning of the scale, the FPS was somewhat better understood by the nondemented group than by the AD group. Particularly data from the LTA-1 period showed that the subjects of the nondemented group (M = 19.29; range 12–20) comprehended the scale more than the AD group (M = 16.79, range 11–20; Mann-Whitney U: $Z = 2.33$; $p < 0.05$). The subjects without dementia (M = 4.86; range 4–5) and the AD patients (M = 4.07, range 2–5) showed no significant differences in the STA-1 period (Mann-Whitney U: $Z = 1.52$; NS) or in the STA-3 period (M = 14.89, range 14–15, and M = 13.45, range 6–15, respectively; Mann-Whitney U: $Z = 0.55$; NS).

Report of Pain Experience. Elderly persons without dementia reported experiencing significantly more pain than the AD patients during the three periods (table 1).

NWC-A

The data (table 1) indicate a significant difference between both groups, i.e. the nondemented elderly persons reported that they experienced much more affective components of pain than the AD patients, again in all the three periods LTA-1, STA-1, and STA-3.

CNPI

As indicated in table 1, in both the LTA-1 and STA-3 periods, the nondemented elderly persons showed somewhat more expression of pain than the subjects of the AD group, but the difference between the groups did not appear to be significant.

Discussion

Comprehension of the Scales

The Original CAS for Pain Intensity and the CAS for Pain Affect. The results of the present study show that, irrespective of the duration of the assessment period (LTA-1, LTA-2, STA-3), all AD patients interpreted correctly the meaning of the original CAS for pain intensity and the CAS in assessing pain affect [13].

This finding supports the suggestion that the CAS is a valuable instrument in assessing both quantitative (intensity) and qualitative (affect) components of pain in cogni-

Table 1. Means (M), standard error of the means (SE) and Mann-Whitney U tests of the various pain scales (one tailed)

Pain scales	Nondemented elderly persons			AD patients			Mann-Whitney U tests	
	M	SE	n	M	SE	n	Z	p
Pain experience								
CAS intensity LTA-1	42.54	4.45	17	2.94	1.31	14	4.62	0.000
CAS intensity STA-1	28.21	5.29	14	3.11	1.91	14	4.01	0.000
CAS intensity STA-3	43.59	7.47	9	1.26	1.10	11	3.94	0.000
CAS affect LTA-1	33.33	4.20	17	1.71	0.81	14	4.56	0.000
CAS affect STA-1	26.31	5.27	14	1.67	1.14	14	4.24	0.000
CAS affect STA-3	41.36	6.85	9	0.81	0.66	11	3.94	0.000
FPS LTA-1	2.05	0.33	17	0.27	0.15	14	4.12	0.000
FPS STA-1	1.73	0.38	14	0.18	0.12	14	3.81	0.000
FPS STA-3	2.55	0.29	9	0.01	0.01	11	4.02	0.000
NWC-A LTA-1	2.87	0.56	17	0.20	0.10	14	4.28	0.000
NWC-A STA-1	2.20	0.56	14	0.23	0.19	14	4.07	0.000
NWC-A STA-3	3.88	0.86	9	0.08	0.08	11	3.94	0.000
CNPI LTA-1	0.93	0.09	17	0.82	0.09	14	1.71	0.05
CNPI STA-1	0.89	0.09	14	0.80	0.12	14	0.47	0.36
CNPI STA-3	1.11	0.17	9	0.76	0.13	11	1.87	0.06

LTA-1 = Long-term assessment (1 month, once a day); STA-1 = short-term assessment (5 days, once a day); STA-3 = short-term assessment (5 days, three times a day); CAS = colored analogue scale; FPS = the faces pain scale; NWC-A = number of words chosen – affective; CNPI = the Feldt checklist of nonverbal pain indicators.

tively impaired elderly persons. The same conclusion can be applied to nondemented elderly persons, despite the fact that 1 subject was not able to indicate the correct meaning of the scale in both conditions.

FPS. In contrast to our earlier study in which all nondemented elderly persons comprehended the purpose of the FPS [13], here 3 persons without dementia misinterpreted the meaning of the scale on various occasions during the LTA-1 assessment period. It should be noted, however, that in the former study [13] pain assessment occurred only once, whereas the LTA-1 period in the present study consisted of 20 assessments. In other words, the chance of misinterpretation of the scale was considerably enhanced in the present study. Compared to the nondemented group, a significantly larger number of misinterpretations of the FPS was observed in the AD group during all three assessment intervals. The finding that the FPS is harder to understand for AD patients than for elderly people without dementia is consistent with earlier results [13].

Report of Pain Experience

Independent of the duration of the pain assessment period (LTA-1, STA-1, STA-3) and the frequency with which assessment took place (once or three times a day), the elderly subjects without dementia indicated that they experienced significantly more pain intensity and pain affect of their own painful conditions (CAS intensity, CAS affect, FPS, and NWC-A; table 1) than the AD patients. It is remarkable that the experience of nondemented elderly persons of pain intensity and, to a lesser extent, pain affect varied over the three assessment periods. Such a variation in scores was not observed in the AD group. In view of the fact that arthritis/arthrosis was the most prevalent condition in both groups, one could argue that fluctuations in the inflammatory processes which underly this joint disease [28] might apparently be better perceived by the nondemented group than by the AD group.

Both groups did not significantly differ in their scores on the CNPI [25]. In the present study, participants scored on only two variables of the CNPI, one of which was bracing, e.g. clutching or holding onto side rails and/or bed. However, this variable appeared to be applicable

to almost all subjects of *both* groups because they walked with an aid. The other nonverbal variable of the CNPI was grimacing. Particularly furrowed brows were observed in some of the elderly persons without dementia who also reported high levels of pain intensity and pain affect. This latter finding might explain the trend which was found in the LTA-1 and STA-3 intervals (table 1). Future studies need to examine under which condition people reporting pain will also score on the other four variables of the CNPI.

The clinical evidence for an alteration in pain perception in AD is further supported by studies which examined AD patients' responses to *experimental* pain stimuli. Compared to nondemented elderly persons, heart rate increased less in the preparatory phase but increased more during a standard venipuncture procedure [29]. These findings suggest a blunting of anticipation and physiological response [29]. Benedetti et al. [30] applied electrical stimulation and ischemic pain to one arm of AD patients and nondemented elderly persons. The results showed that the detection of the electrical stimulus and the pain threshold for both the electrical stimulation and the ischemic pain did not differ between the two groups. However, compared to the nondemented elderly persons, AD patients showed a significantly higher pain tolerance. Interestingly, they found that the level of pain tolerance was inversely related to the cognitive functioning of AD patients, i.e. the more severe the cognitive decline, the higher the pain tolerance [30]. Benedetti et al. [30] observed that increase in pain tolerance was reflected in a slowing down of the EEG rhythm. It would be worthwile to examine whether such an EEG pattern is also correlated with a decrease in the *clinical* experience of pain intensity and pain affect, as measured by e.g. visual analogue scales. A positive correlation would further support the reliability of the instruments applied for the assessment of pain in AD.

Finally, although not directly related to pain experience at first sight, a significantly higher prevalence of cholecystectomy was observed in the nondemented group compared with the AD group. Interestingly, gallstone formation appears to be enhanced by the apolipoprotein (apo) E E4 allele [31], a genetically polymorphic protein which is also a known risk factor for AD [32]. Considering the role of the apo E E4 allele in both the formation of gallstones and AD, one might have expected a higher percentage of cholecystectomy in AD patients. The opposite was found here. One explanation might be that the prevalence of this protein in the AD group was low. However, if this assumption is true, one should be careful to generalize from the present findings. It cannot be excluded that the observed alteration in pain experience is associated with a subgroup of AD patients, who do not have the apo E E4 allele. Consequently, a suggestion for future studies on the influence of AD on pain experience is that one should differentiate between AD patients with and without the apo E E4 allele.

Conclusion

The results of the present study strengthen the hypothesis that AD at a relatively early stage may be accompanied by an alteration in actual pain experience. The role of the apo E E4 allele in pain experience needs to be further clarified.

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