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

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BACKGROUND: Pain perception is known to depend on integrated cognitive processing. Alzheimer's disease affects 5% to 10% of older adults, but the impact of this disease on pain sensitivity and report has yet to be fully investigated.
AIM OF INVESTIGATION: The present study examined pain threshold, the reliability of pain report and the central nervous system processing of noxious input, as indexed by cerebral event-related potentials (CERP).
METHODS: Carbon dioxide laser detection and heat pain thresholds were determined on the hand dorsum of 15 healthy older adults (Mini-Mental State Examination [MMSE] score 29.9±0.3) and 15 persons with cognitive impairment (MMSE score 12.7±6.1). Using an array of 15 silver/silver chloride scalp electrodes, the CERP and subjective rating of stimulus intensity were recorded after fixed intensity, 25 W laser stimuli.
RESULTS: Compared with age-matched controls, the detection threshold for just noticeable sensation was significantly increased in elderly adults suffering from Alzheimer's disease. There was no difference in pain threshold intensity between persons with cognitive impairment and controls, although the former group was less reliable in reporting detection and pain threshold sensations. The subjective rating of a 25 W stimulus was virtually identical in both groups, and the amplitude of the major CERP component (P400) was similar; however, cognitively impaired adults exhibited a significant increase in the latency of the P400 response.

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CONCLUSIONS: The present findings indicate that pain perception in response to an acute heat pain stimulus is not diminished in older persons with cognitive impairment. Patients with Alzheimer's disease may be slightly less reliable in threshold pain report, although the subjective rating of evoked pain and the level of poststimulus cortical activation following noxious stimulation were found to be similar to those of controls. A longer latency of the CERP may suggest slower cortical processing of nociceptive input by persons with Alzheimer's disease.

Key Words: *Alzheimer's disease; Carbon dioxide laser; Cerebral event-related potentials*

Perception de la douleur et potentiels évoqués cognitifs après stimulation au laser à gaz carbonique chez des patients atteints de la maladie d'Alzheimer et des témoins volontaires appariés selon l'âge

CONTEXTE : On sait que la perception de la douleur dépend d'un processus cognitif intégré. La maladie d'Alzheimer (MA) touche de 5 à 10 % des personnes âgées, mais on ne connaît pas vraiment l'incidence de la maladie sur la sensibilité à la douleur et sur son indication.
OBJECTIF : L'étude visait à analyser les seuils de douleur, la fiabilité de son indication et le processus de traitement d'un stimulus nuisible par le système nerveux central, mesuré selon les potentiels évoqués cognitifs (PEC).
MÉTHODE : La détection du laser à gaz carbonique et les seuils de douleur à la chaleur ont été mesurés sur le dos de la main chez 15 adultes âgés en bonne santé (mini-examen de l'état mental [MMSE] : 29,9±0,3) et chez 15 personnes présentant des troubles cognitifs (MMSE : 12,7±6,1). Après avoir posé 15 électrodes de surface en argent et au chlorure d'argent et appliqué des stimulus d'intensité constante (25 W) au laser, nous avons noté les PEC et l'évaluation subjective de l'intensité qu'en faisaient les sujets.
RÉSULTATS : Le seuil de détection des sensations à peine perceptibles était significativement plus élevé chez les adultes atteints de la MA que chez les témoins appariés selon l'âge. Par contre, nous n'avons pas observé de différence quant à l'intensité du seuil de douleur entre les sujets témoins et les personnes présentant des troubles cognitifs, bien que l'indication de la détection du laser et des seuils de douleur par ces dernières était moins fiable. L'évaluation subjective du stimulus de 25 W était à peu près la même dans les deux groupes ainsi que l'amplitude du principal élément des PEC (P400); toutefois, nous avons remarqué une augmentation significative de la latence du P400 chez les adultes atteints de troubles cognitifs.
CONCLUSIONS : Les résultats indiquent que la perception de la douleur en réaction à un stimulus douloureux aigu causé par la chaleur n'est pas diminuée chez les personnes présentant des troubles cognitifs. Même si l'indication du seuil de douleur peut être un peu moins fiable chez les patients atteints de la MA, l'évaluation subjective de la douleur évoquée et le degré d'activation corticale après le stimulus nuisible se sont avérés semblables dans les deux groupes. La latence prolongée des PEC peut être révélatrice d'un ralentissement de l'activité corticale pour traiter le stimulus nociceptif chez les personnes souffrant de la MA.

Pain is a complex perceptual experience. The context in which noxious information is processed, the beliefs of the individual and the meaning attributed to noxious sensation are recognized as important factors in shaping the overall pain experience (1,2). As a consequence, any disease that affects cognitive function might be expected to alter pain perception and report. Alzheimer's disease affects 5% to 10% of older adults, and is known to cause gross disturbances in intellectual and cognitive abilities (3). A significant proportion of older adults with dementia have comorbid medical complaints and are expected to suffer from associated pain and discomfort. However, current knowledge on the interaction between pain and dementia is rather limited, and the extent to which cognitive impairment might alter the perceptual experience of pain remains largely unknown (4).

Previous studies have shown that elderly adults with cognitive impairment complain of less frequent and severe procedural pain, such as arthroplasty or postlumbar puncture headache (5,6). Complaints of joint pain also appear to be reduced in patients with Alzheimer's disease compared with age-matched, cognitively intact individuals with similar levels of comorbidity (7,8). Finally, there has been one report of no difference in self-rated pain following venepuncture, although physiological responses (eg, heart rate) were blunted and facial expressions of discomfort were increased in adults with diminished cognitive function (9).

The findings of less intense pain in older adults with dementia may reflect problems with the communication or recall of pain symptoms, although it has also been suggested that dementia may interfere with the perceptual processing of nociceptive information, per se (4,10,11). Unfortunately, it is difficult to compare perceptual experiences and changes in pain sensitivity when examining clinical pain states because the strength of noxious input is seldom known. Psychophysical studies using experimentally controlled levels of noxious stimulation are needed to anchor the subjective experience against a known physical stimulus. To date, only one study has examined the intensity of noxious stimulation required for threshold pain report or pain tolerance in communicative older persons of varying cognitive status (12). They found no difference in electrical pain threshold, but a significant increase in the tolerance to tourniquet-induced ischemic pain in those with dementia compared with healthy, age-matched controls.

The extent to which dementia might alter the transmission and integration of nociceptive information has also received some investigation, although results are inconclusive. A study of 48 patients with senile dementia demonstrated no change in the spinally mediated flexion withdrawal reflex (13). Cornu (10) showed no change in the alpha rhythm of the electroencephalogram as well as no change in the galvanic skin response to noxious electrical stimulation in patients with dementia. In contrast, a recent study by Benedetti et al (12) revealed a significant correlation between pain sensitivity and changes in alpha/delta power spectra of the electroencephalogram associated with cognitive decline. Given this apparent conflict, further study

of central nervous system (CNS) nociceptive processing seems desirable. An examination of the cerebral event-related potential (CERP), which follows noxious input, such as carbon dioxide laser stimulation, may be particularly useful in this regard. The CERP represents a stimulus-induced change in the electroencephalogram and can be divided into early and late components that are denoted by their polarity and latency after stimulus onset (14). Previous research has shown that the amplitude of late components (particularly P400) is strongly correlated with the intensity of noxious carbon dioxide laser stimulation and subjective pain ratings (14-16). However, in common with measures of subjective appraisal, peak amplitude of the CERP is known to be influenced by factors other than nociceptive input, including levels of anxiety, attention and arousal (14,17). On the basis of these attributes, several authors have suggested that CERP might represent a useful physiological correlate of the integrated CNS processing that underlies the perceptual experience of pain (18-20). In adults with dementia, long latency CERPs in response to other sensory modalities (eg, auditory, touch) are reduced in amplitude and increased in latency, suggesting some disruption in the CNS integration of sensory information (21-24). Whether similar changes occur in pain-related CERPs is unknown.

The aims of the current study were to compare subjective ratings of noxious carbon dioxide laser stimulation, to determine the intensity of stimulation required to elicit a threshold report of pain and to examine the integrated CNS processing of noxious input using the CERP, in cognitively intact older adults and persons with Alzheimer's disease. Based on previous literature, the expectation was that patients with Alzheimer's disease would display a reduced amplitude and increased latency of CERP in response to noxious laser stimulation, but that the pain threshold would be similar to that of controls.

METHODS

Participants

Fifteen cognitively intact volunteers over the age of 65 years and 15 elderly patients diagnosed with Alzheimer's disease were recruited into the study. All participants were right handed, did not report any pre-existing pain when asked and were not taking any medications at the time of assessment. In addition, participants had been previously screened for conditions that could potentially affect pain perception, including the presence of peripheral neuropathy, diabetes, hypertension, stroke and psychiatric disorders. Patients with Alzheimer's disease underwent full clinical examination by a neurologist/geriatrician and were classified according to the *Diagnostic & Statistical Manual of Mental Disorders IV* (25), International Classification of Diseases-10, and The National Institute of Neurological and Communicative Disorders and Stroke, as well as the Alzheimer's Disease and Related Disorders Associations criteria, which are the best current research gold standards for dementia diagnosis (26). Patients also completed the Cambridge Mental Disorders of the Elderly Examination questionnaire (27), which monitors various aspects of cognitive function and can assist with differential diagnosis. To comply with the experimental protocol, all selected patients with Alzheimer's disease were verbally communicative and did not suffer from gross behavioural problems.

Measures

After obtaining informed consent, all participants completed a standard battery of psychometric measures, including the Mini-Mental State Examination (MMSE), Spielberger State-Trait Anxiety Inventory-State Form and the Geriatric Depression Scale. In the case of patients with Alzheimer's disease, consent was obtained from the primary caregiver, the treating physician and the next of kin, as well as from the patients themselves. The MMSE (28) provides a global score of cognitive function and examines orientation, verbal reasoning, visual perceptual skills, language and memory. This instrument consists of 11 questions and yields a score from 0 to 30. It has been widely used in screening older adults, shows good agreement with larger test batteries and has been validated against a clinical gold standard (29). A score of 24 or higher is considered normal, while a score of 20 to 23 signifies mild impairment, 10 to 19 moderate impairment and less than 10 marked cognitive impairment (28). The Geriatric Depression Scale was specifically designed for use with older adults and monitors the number of depressive symptoms (30). The instrument contains 30 items that are answered in a yes/no format and scores range from 0 to 30, with a score of 11 or higher suggesting mild depression. The Spielberger Anxiety Inventory was used to monitor levels of anxiety 'right now'. It contains 20 items with a four-point Likert scale and has been validated for use with older persons (31). Scores range from 20 (low anxiety) to 80 (high anxiety).

Procedure

For the assessment of pain threshold and CERP responses, the participant was settled into a comfortable chair in a temperature-controlled room, shielded against electrical and acoustic interference. A carbon dioxide laser (10.6 μm) situated in an adjoining room was used to deliver radiant heat pulses (5 mm diameter, 30 ms duration) onto the dorsal surface of the left hand. All participants were given a minimum of 10 practice trials before testing to familiarize them with the quality of laser sensation, provide some training in the use of pain rating scales (see below) and help reduce any anxiety associated with experimental test procedures. Detection and pain threshold were determined using a double random staircase procedure (32). Threshold was defined as the mean of five consecutive 1 W up-down alternations in the intensity of laser stimulation. If a participant failed to meet these criteria, the staircase was terminated after 60 trials and the last five values were averaged to provide the threshold value. All participants were tested blind to stimulus onset and intensity. To determine the reliability of the threshold determination, a coefficient of variation was com-

puted for each staircase sequence using the following equation:

$$(\text{standard deviation}/\text{mean}) \times 100.$$

Following threshold determination, 24 laser stimuli at 25 W intensity were delivered with a random interstimulus interval (20 to 60 s). Approximately 3 s after the stimulus, participants were instructed to move their hand a few millimetres to minimize the effects of habituation and reduce possible tissue damage. All participants were asked to rate the laser stimulus on an eight-item word descriptor scale (33) and to describe the quality of evoked sensation using a word list developed by Bromm and Treede (14). This list included innocuous sensations (tingle, touch, warm) as well as unpleasant sensations (pricking, stinging, burning). Following each carbon dioxide laser stimulus, 1000 ms of poststimulus electroencephalography was recorded from 15 silver/silver chloride electrodes attached according to the international 10-20 system of placement and referenced to linked ears. Infra- and supraorbital electrodes were used to monitor eye movement, while electrodes placed over the masseter and cervical region of the trapezes were used to record muscle activity. CERP samples were amplified (100 k), filtered with a 0.5 to 70 Hz bandpass, digitized with a sampling rate of 600 Hz and stored on computer for off-line analysis. Artefact-free single trial CERPs were averaged to compute a grand mean CERP for each group. Measures of peak latency and amplitude were calculated using an automated computer program and then checked against visual inspection. Topographic maps and analogue tracing of the grand mean CERP were generated from the same software package.

RESULTS

Demographic information on the 15 healthy older control volunteers and the 15 patients with probable Alzheimer's disease is presented in Table 1. Participants were well matched for age, sex distribution, skin temperature of the hand dorsum, and self-rated depressive symptoms and anxiety. Analysis with univariate *t* test or χ^2 analysis revealed no significant difference between the two groups. As expected, the group with Alzheimer's disease displayed significantly poorer performance on the Mini-Mental Test of Cognitive Function ($T_{[28]}$=10.83, P<0.001), with scores ranging from mild to severe levels of impairment.

The mean ± SEM intensity of carbon dioxide laser stimulation required to elicit a report of just noticeable sensation or just noticeable pain for healthy older persons and for patients with Alzheimer's disease is shown in Figure 1. The threshold data (detection, pain) were analyzed using MANOVA, and a significant difference was noted between groups ($F_{[2,27]}$=7.39, P=0.003). Subsequent post hoc univariate ANOVA revealed that patients with Alzheimer's disease exhibited significantly higher detection thresholds ($F_{[1,28]}$=10.41, P=0.003) but no difference in pain threshold intensity ($F_{[1,27]}$=0.85, P=0.364), suggesting a comparable sensitivity to noxious laser stimulation. With regard to the reliability of threshold determination, the mean ± SEM coefficients of variation in healthy aged adults were 5.06±0.52% and 4.3±0.54% for detection and pain threshold, respectively. In contrast, the mean coefficients of variation in the group with Alzheimer's disease were 7.7±1.04 for detection threshold and 8.9±1.4% for pain threshold determination. MANOVA revealed a significant overall difference between groups ($F_{[2.27]}$= 4.9, P=0.015), and subsequent univariate analysis showed that patients with Alzheimer's disease were slightly less reliable in reporting both detection threshold ($F_{[1,28]}$=4.86, P=0.036) and pain threshold sensations ($F_{[1,28]}$=8.44, P=0.007) than healthy adults.

The grand mean CERP in response to a fixed intensity, 25 W laser stimulus, at each of the 15 scalp sites is presented in Figure 2 for the healthy control volunteers and Alzheimer's patients. The CERP response was character-

TABLE 1
Demographic characteristics of patients with Alzheimer's disease and healthy control volunteers

	Healthy elderly (n=15)	Alzheimer's patients (n=15)	P
MMSE score mean (range)	29.73 (29-30)	12.7 (2-19)	<0.001
CAMDEX score (mean ± SEM)	–	4.46±0.46	
Age, years (mean ± SEM)	81.6±1.65	82.4±1.43	0.445
Depression score (mean ± SEM)	5.2±1.1	6.2±0.64	0.465
Anxiety score (mean ± SEM)	26.5±2.53	26.9±2.14	0.906
Sex (male/female)	5/10	3/12	0.509
Skin temperature, °C (mean ± SEM)	31.54±0.39	31.46±0.36	0.801

CAMDEX Cambridge Mental Disorders of the Elderly Examination; MMSE Mini-Mental State Examination

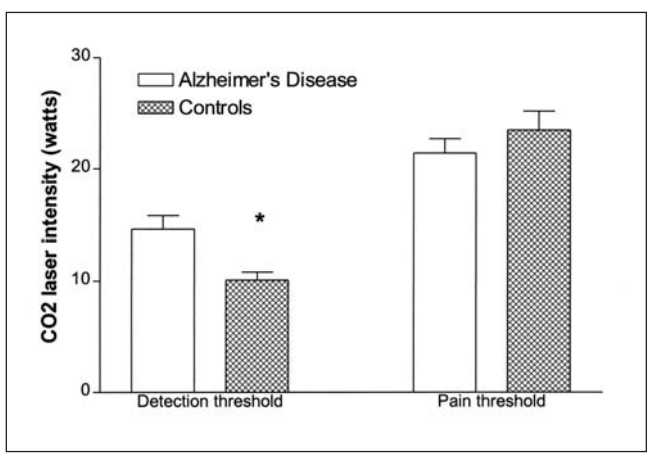

Figure 1) Detection and pain thresholds in response to carbon dioxide laser stimulation in patients with Alzheimer's disease and age-matched, control volunteers. *Significant between-group difference, P<0.05

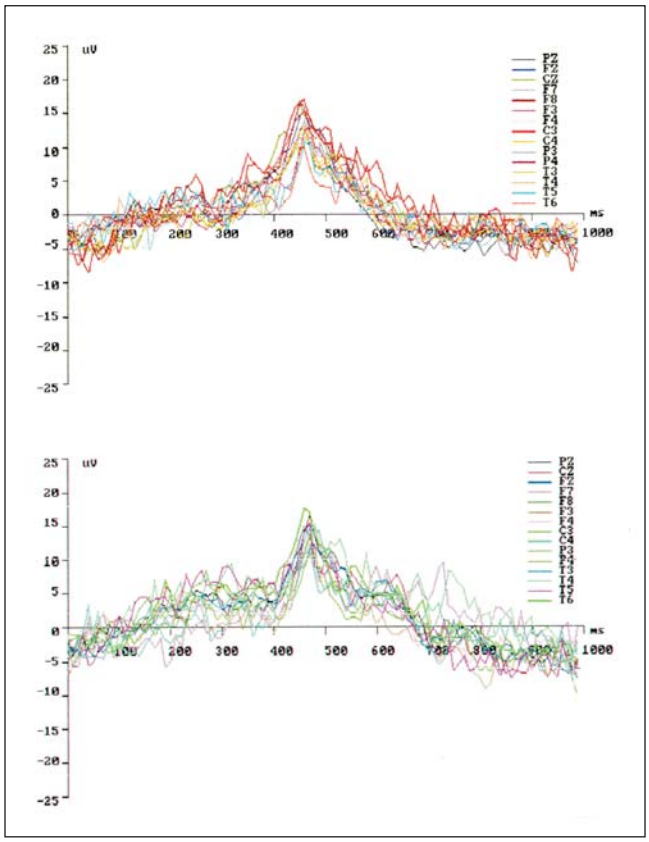

Figure 2) Grand mean cerebral event-related potential response following noxious 25 W laser stimulation in control volunteers (upper panel) and patients with Alzheimer's disease (lower panel)

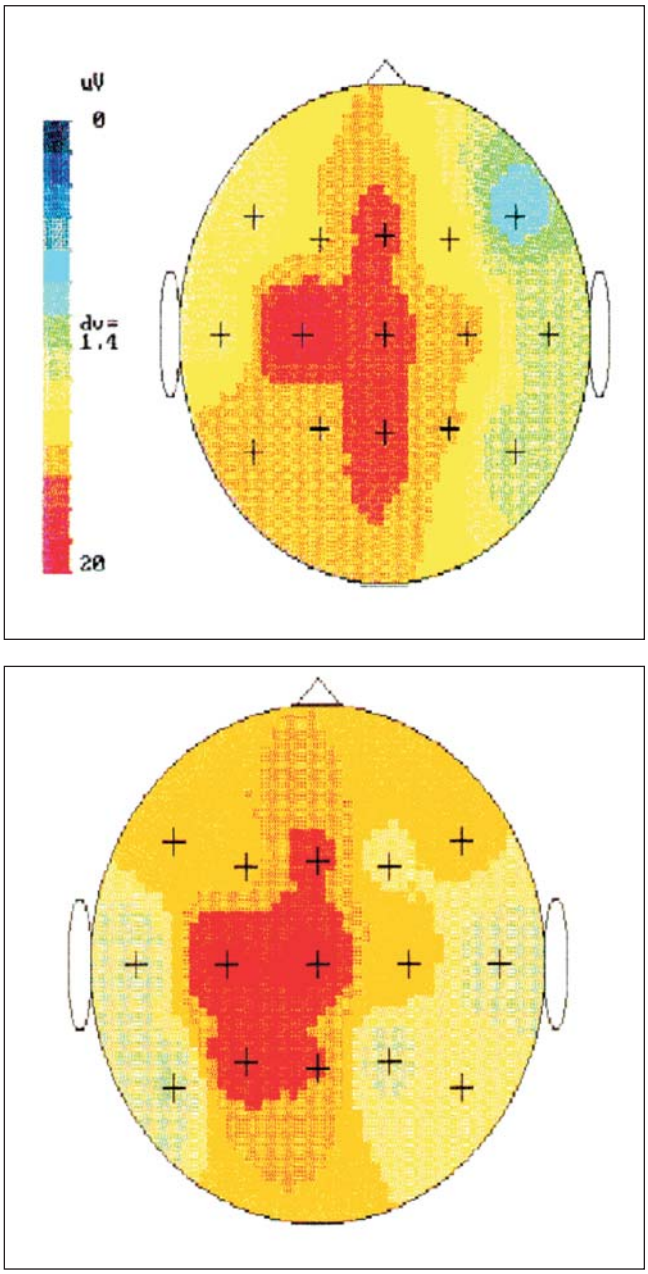

Figure 3) Topographic map of cerebral event-related potential activity at the maximal positive peak in control volunteers (top) and patients with Alzheimer's disease (bottom).

ized by a small negative peak 310 to 380 ms poststimulus, and a high amplitude positive peak at 450 to 480 ms was easily identified in both groups. The topographic distribution of poststimulus electrical activity at the time when the response was maximal (ie, the highest point of the positive peak) is shown in Figure 3 for both groups. There was a concentration of poststimulus electrical activity in the midline centroparietal regions and a progressive decrease in activity at more lateral sites. Analysis of the poststimulus electrical activity using a two-way repeated measures ANOVA (group, site) revealed no significant group difference in the peak to peak amplitude of the waveform ($F_{[1,28]}$=0.02, P=0.898). A significant site main effect ($F_{[14,392]}$=4.4, P=0.001) indicates greater activation over midline central sites (Figure 3), but there was no significant group by site interaction ($F_{[14,392]}$=0.64, P=0.829), suggesting that the topographic spread of the CERP response was similar in patients with Alzheimer's disease and controls. The latency of the major positive peak was found to differ between controls and patients with Alzheimer's disease ($F_{[1,28]}$=8.27, P=0.008) and between electrode sites ($F_{[14,392]}$=10.81, P=0.0001), but there was no site by group interaction effect ($F_{[14,392]}$=0.66, P=0.816). Inspection of Figure 2 reveals a uniform delay of approximately 30 to 40 ms in the latency of the major positive peak in patients with Alzheimer's disease. However, in all participants, the peak response latency occurred earlier at central-midline regions than at more lateral sites.

The subjective appraisal of sensation magnitude and quality in response to the 25 W laser stimulation showed a number of similarities between the study groups. The most commonly used word descriptor was stinging or pricking, both in patients with Alzheimer's disease (selected by 80% of volunteers) and in controls (selected by 87% of volunteers). The remaining participants selected a variety of descriptors, including throbbing, touching and pulsing. The rating of sensation magnitude was also similar in both groups (controls 3.3±1.9, Alzheimer's disease 3.47±2.0),

with the majority of participants selecting weak (43%), mild (20%) or moderate (31%) pain from an eight-item descriptor scale. A nonparametric Mann-Whitney U test revealed no significant difference between groups ($U_{[30]}$=110.0, P=0.916).

DISCUSSION

The present findings indicate that pain sensitivity in response to an acute heat pain stimulus is not diminished in cognitively impaired elderly adults. Patients with Alzheimer's disease may be slightly less reliable in the report of threshold pain sensations, but the subjective rating of laser stimulus intensity and quality as well as the amplitude and topographic spread of poststimulus cortical activation following noxious stimulation were virtually identical to those of healthy control volunteers.

The lack of change in pain threshold between patients with Alzheimer's disease and healthy controls is consistent with a previous report (12), and other evidence showing no difference in the threshold for eliciting a nociceptive flexion withdrawal reflex (13). However, in the present study, a significant increase in laser detection threshold was noted, whereas in the earlier study by Benedetti et al (12), no difference was found in electrical detection thresholds. It is somewhat difficult to reconcile these findings, and further research is needed to resolve this apparent conflict. Nonetheless, it seems likely that the detection of threshold sensory information requires a considerable amount of vigilance and concentration. Given that Alzheimer's disease is known to affect such cognitive abilities (3), the observed increase in detection threshold is perhaps not unexpected. A poorer performance in the reliability of threshold determinations provides further support for the view that concentration and attention are at least partly compromised in patients with Alzheimer's disease. One may question why a deficit in vigilance would not also influence pain threshold values; however, noxious stimuli are compelling by their very nature and demand immediate notice regardless of the preexistent state of attentional focus. In any event, on the basis of the present findings, it is evident that pain sensitivity in response to acute heat pain stimuli is probably not diminished in patients with Alzheimer's disease, although the consistency of pain report may be slightly worse.

The CERP is thought to reflect integrated, secondary cognitive processing of noxious input, including aspects of stimulus recognition, magnitude estimation and stimulus localization (14,18,19,34). The fact that a characteristic CERP could be recorded from adults with Alzheimer's disease is an important finding in itself and suggests that such integrated processing remains intact, even in adults with quite severe cognitive impairment. The peak to peak amplitude and topographic spread of poststimulus electrical activity were almost identical in Alzheimer's disease and healthy controls. This indicates a comparable level of CNS activation in response to noxious laser stimulation and provides further support for the view that pain sensitivity does not diminish in patients with Alzheimer's disease. A significant increase in the latency of the CERP suggests a slower cortical integration of noxious information in individuals with cognitive impairment. The increased latency of CERPs in Alzheimer's disease is consistent with that described in other previous work using somatosensory, auditory and visual stimuli (21,22,24) and highlights the ubiquitous slowing of all CNS sensory processing. However, the magnitude of change is relatively small (approximately 40 ms) and so the clinical implications of this finding remain unclear.

Previous studies have suggested that complaints of pain decrease in frequency with increasing cognitive impairment and that individuals with severe dementia report less intense clinical pain (6-8). While this appears to contrast with the present findings, the retrospective design of the clinical studies, which rely on past recollections of pain, may have contributed to diminished pain report independent of any change in pain sensitivity. Possible differences in the underlying severity of clinical disease states could also account for an altered pain report (34). For instance, the reduced reports of postlumbar puncture headache in patients with dementia may reflect volumetric changes associated with brain atrophy rather than some alteration in pain sensitivity, per se (4). Finally, it should be noted that all potential volunteers with evidence of dysphasia or communication problems that may have interfered with the ability to report pain sensations were excluded from the present experiment, whereas this was not always the case in the studies of clinical pain.

CONCLUSIONS

It is clear that pain sensitivity and perceptual processing of acute noxious information remain largely intact, despite moderate and even severe levels of cognitive impairment. This has important clinical implications because the observed reduction in pain report by older adults with dementia is more likely to reflect problems with memory or communication of pain symptoms rather than some reduction in the actual experience of pain.

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ERRATUM

In the Autumn 2001 issue of *Pain Research & Management*, the qualifications attributed to Dr David Ames, co-author of the article, "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" (pages 126-132), were incorrect. The correct qualifications for Dr David Ames are BA, MD, FRCPsych and FRANCZP.