

Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease

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People with Alzheimer's disease are administered fewer analgesics and report less clinical pain than cognitively intact peers with similar painful diseases or injuries, prompting speculation about the likely impact of neurodegeneration on central pain processing. The present study measured pain ratings and functional MRI (fMRI) brain responses following mechanical pressure simulation in 14 patients with Alzheimer's disease and 15 age-matched controls. Contrary to the prevailing hypothesis that this disease is likely to differentially reduce emotional responses to pain, we show that activity in both medial and lateral pain pathways is preserved. Moderate pain was evoked with similar stimuli in both groups, and was associated with a common network of pain-related activity incorporating cingulate, insula and somatosensory cortices. Between-group analyses showed no evidence of diminished pain-related activity in Alzheimer's disease patients compared with controls. In fact, compared with controls, patients showed greater amplitude and duration of pain-related activity in sensory, affective and cognitive processing regions consistent with sustained attention to the noxious stimulus. The results of this study show that pain perception and processing are not diminished in Alzheimer's disease, thereby raising concerns about the current inadequate treatment of pain in this highly dependent and vulnerable patient group.

Keywords: Alzheimer's disease; pain; fMRI; aged

Abbreviations: aMCC = anterior midcingulate cortex; BA = Brodmann area; BOLD = blood oxygen level-dependent; DLPFC = dorsolateral prefrontal cortex; fMRI = functional magnetic resonance imaging; IC = insula cortex; JNP = just noticeable pain; MI = primary motor cortex; MMSE = Mini-Mental State Examination; MP = moderate pain; ROI = region of interest; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; WP = weak pain

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Introduction

Patients with Alzheimer's disease have been shown to receive fewer analgesics and report less clinical pain than cognitively intact peers with similar levels of painful disease or injury (Farrell *et al.*, 1996; Cook *et al.*, 1999; Frampton, 2003). Compared with healthy age-matched controls, patients have also shown higher tolerances to experimental pain (Benedetti *et al.*, 1999). It remains unclear whether the observed difference in pain report and management occurs as a result of impaired communication and memory of pain, and/or whether the perception and experience of pain is altered as a result of the progressive degeneration of cortical and subcortical regions involved in the transmission and processing of nociceptive information (Farrell *et al.*, 1996; Scherder *et al.*, 2003, 2005).

Pain is a complex and subjective perceptual experience, incorporating sensory-discriminative, affective-motivational

and cognitive-evaluative dimensions (Melzack and Casey, 1968). These aspects of the pain experience are subserved by distinct supraspinal pathways. The lateral pain system consists of spinothalamic tract neurons that ascend via the ventro-posterior lateral thalamus onto the primary and secondary somatosensory cortices (S1 and S2) which in turn code the location, intensity, and quality of the sensation. Another major pathway branches at the level of the medulla and ascends via the medial thalamus to hypothalamic nuclei, limbic regions including the cingulate cortex, the insula cortex (IC) and onto prefrontal areas, all of which are known to be involved in the control of emotion, arousal and attention. This medial pain pathway is proposed to mediate the unpleasant, affective dimensions of pain, and the motivation to escape from the noxious event (Treede *et al.*, 1999; Price, 2000).

Converging lines of evidence from brain imaging (Thompson *et al.*, 2003) and patho-histological (Braak and Braak, 1997; Nagy *et al.*, 1997; Rub *et al.*, 2002) research suggest the neurodegenerative changes that occur in Alzheimer's disease selectively target components of the medial pain system, in particular the medial thalamic nuclei, the hypothalamus, cingulate and IC. On the other hand, the cerebral regions comprising the lateral pain pathway are relatively well preserved, suggesting that the disease may compromise the affective-motivational component of pain more so than the sensory-intensity dimension (Scherder and Bouma, 1997; Scherder, 2000). Moreover, a disorder of cognition such as Alzheimer's disease, in which deficits in memory and reasoning are cardinal symptoms, would be expected to have a profound effect on an individual's appraisal of the pain experience and its future implications.

While there is a strong theoretical rationale to expect altered pain transmission and processing in patients with Alzheimer's disease, there has been limited empirical research to address this issue in terms of functional consequences, and studies to date have yielded mixed results with regard to the magnitude and direction of any change in pain perception that occurs in this illness. A dissociation between sensory-discriminative and affective-motivational aspects of pain has been suggested by reports that subjects show comparable thresholds for pain detection, but increased tolerance to strong pain when compared with intact controls (Benedetti *et al.*, 1999), as well as blunted autonomic responses to impending pain (Porter *et al.*, 1996; Rainero *et al.*, 2000; Benedetti *et al.*, 2004). Others have also suggested that the perception of acute pain is preserved, while the experience of chronic pain may be altered (Pickering *et al.*, 2006). In contrast to these reports, Gibson *et al.* (2001) showed that CNS activation, as indexed by the peak amplitude of pain-related event potentials is not diminished in Alzheimer's disease, although a delayed latency to peak response in the patient group suggests the transmission and integration of nociceptive input may be slower in these patients (Gibson *et al.*, 2001). While this study provides some information about the cortical processing of noxious information in Alzheimer's disease, the lack of spatial resolution afforded by EEG measures limits the conclusions that can be drawn regarding the extent to which pain-related CNS processing may be altered by the disease. Finally, a disturbance of the cognitive aspects of the pain experience was recently demonstrated by Benedetti *et al.* (2006), who found that expectation-related pain relief after open analgesic administration was reduced in patients compared with controls.

In the present study, we compared pain sensitivity and supraspinal processing of nociceptive input in patients with Alzheimer's disease and cognitively intact controls. Psychophysical measurements were collected to investigate the dissociation between sensory and affective-motivational aspects of pain. A response-dependent method was used to determine the amount of mechanical pressure required to

elicit three levels of sensation: just noticeable pain (JNP), weak pain (WP) and moderate pain (MP). Ratings of unpleasantness in response to stimuli delivered at each of these threshold levels were also collected.

In order to test the assertion that reduced pain report occurs as a result of selective damage to medial thalamic and limbic structures involved in affective-motivational pain processing, functional magnetic resonance imaging (fMRI) measures of CNS pain processing were collected. Research using fMRI has been able to dissociate medial and lateral pain system functioning, thereby demonstrating cerebral activity associated with sensory and emotional pain perception (Ingvar, 1999; Peyron *et al.*, 2000; Bornhovd *et al.*, 2002). To date, no studies have used this method to examine altered CNS pain processing in persons with Alzheimer's disease. Using a group-by-region approach to fMRI data analysis, we aimed to directly compare pain-induced blood oxygenation-level-dependent (BOLD) activity in regions of interest (ROIs) located in medial and lateral pain pathways. We hypothesized that selective impairment of affective-motivational pain processing would be evidenced by significantly less pain-related activity in medial pain-pathway regions in patients compared with controls, coupled with comparable between-group pain-related activity in lateral pain-pathway regions. Given that there have been no previous studies of CNS pain processing on patients with Alzheimer's disease, haemodynamic response properties were also explored in other regions showing between-group differences in pain-related activity.

Material and methods

Participants

Sixteen verbally communicative patients with Alzheimer's disease were recruited from the Melbourne Health Cognitive and Dementia Memory Service in Parkville, Australia. Patients were examined by a trained neurologist, gerontologist and psychogeriatrician, and diagnosed according to the criteria specified by the ICD-10, DSM-IV and NINCDS-ADRDA. Cognitive functioning was further assessed using the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975). A study control group of 16 age- and sex-matched cognitively intact individuals were recruited from a volunteer registry held at the National Aging Research Institute in Parkville, Australia. Two patients who were unable to provide reliable pain ratings, and one control subject whose MRI scan revealed a brainstem lesion were excused from the study. Thus a total of 14 patients (7 males; mean age = 79 ± 5 years; mean MMSE score = 19.4 ± 5.7) and 15 age-matched healthy control volunteers (9 males; mean age = 79 ± 4 years; mean MMSE score = 29.3 ± 0.1) completed the study. All subjects reported no pre-existing pain and were not taking any analgesic medications at the time of testing. Conditions that could potentially alter pain sensitivity, including peripheral neuropathy, diabetes, stroke, hypertension and psychiatric disorders, also served as exclusion criteria. Informed consent was gained from all participants, and in the case of patients, third-party consent was also given by the treating physician and the next of kin. The study protocol was approved by the Human Research Ethics Committees of the Howard Florey

Institute, Melbourne Health, and St Vincent's Hospital as well as the Guardianship Board (VCAT).

Procedures

The study was conducted over two sessions. In an initial psychophysical testing session, mechanical pressure stimuli of 5 s duration were applied to the thumbnail of the right hand in a triple random staircase procedure to determine thresholds for just noticeable pain (JNP), weak pain (WP) and moderate pain (MP). Pressure stimuli were delivered via a 1 cm² circular rubber probe attached to a hydraulically-driven piston which transmits forces generated by calibrated weights in increments of 0.25 kg/cm² (Gracely *et al.*, 2004). Participants rated the intensity of each stimulus trial using a combined numerical and descriptor box scale ranging from 0 to 20 where 0 = no pain sensation, 0.5 = JNP, 5 = WP and 11 = MP (Petzke *et al.*, 2005). Participants were asked to rate the intensity of each stimulus trial immediately after stimulus removal. The subjective rating of pain was used to determine the magnitude of the next stimulus delivered in the respective staircase. To avoid sensitization of the thumbnail, stimuli were delivered at least 20 s apart. In a subsequent session, anatomical and fMRI data were collected on a 1.5 T Siemens Symphony MR scanner located at St Vincent's Hospital, Melbourne, Australia. Anatomical images were acquired in the axial orientation (108 slices, 2 mm slice thickness, 0.94 × 0.94 mm² resolution, TE = 3.08 ms, TR = 1620 ms). Echo planar images were also acquired in the axial plane (36 slices, 4 mm slice thickness, 3.5 × 3.5 mm² resolution, TE = 40 ms; TR = 3000 ms, FA = 90°) as participants were exposed to three levels of pressure stimulation (innocuous pressure, WP, and MP) at the intensity levels determined during the previous psychophysical test session. Pressure stimuli were pseudo-randomly presented in 30 s blocks interspaced with 24 s no-stimulus periods over three functional scans. At the end of each scan participants were asked to rate the pain at its most intense. On the basis of these ratings, the stimulus intensity delivered in subsequent runs was adjusted if necessary.

Statistical analysis

fMRI data from individual subjects were pre-processed (realigned to correct for subject movement and scanner drift, normalized to a standard EPI template and smoothed with a 4 mm FWHM Gaussian kernel) and then statistically analysed with FEAT (FMRI Expert Analysis Tool) Version 5.4, in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) (Smith *et al.*, 2004). Higher-level (group) analyses were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). Contrasts were performed to identify regions showing increased activity during moderately painful compared with innocuous pressure stimulation. *Z* (Gaussianized *T/F*) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P < 0.05$. Haemodynamic response properties were also examined using time courses extracted from ROIs in medial and lateral pain pathways. The first medial pathway ROI was located in the anterior midcingulate cortex (aMCC). This region of the cingulate cortex [corresponding with Brodmann area (BA) 24] represents the terminal point of the majority of nociceptive inputs from the medial intralaminar thalamic nuclei (Vogt, 2005), and is consistently activated in studies of functional brain imaging of pain (Farrell *et al.*, 2005; Vogt, 2005). ROIs were also generated for the anterior, mid and posterior subregions of the IC. The lateral pain-pathway ROIs were defined in S1 and S2. We also examined

ROIs from the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) to further investigate our unexpected finding of increased pain-related activity in the patient group. ROI volumes contained all activated voxels situated within the selected region, as defined by the Brodmann map supplied with MRIcro (Rorden and Brett, 2000). A combined group activation map, derived by combining data from all subjects, was used to define ROIs so that data from each subject group contributed equally to region definition (Buckner *et al.*, 2000). ROIs were transformed to each subject's own native space and BOLD signal response time courses extracted for each run in individual subjects. These time courses were then averaged across subjects in each group, and repeated-measures ANOVAs (with Greenhouse–Geisser corrections for non-sphericity) were conducted to examine between-group differences in the temporal characteristics of the haemodynamic response during and after moderately painful stimulation.

Results

Psychophysical results

Pain sensitivity thresholds following mechanical pressure stimulation were determined for the group of patients and the age-matched cognitively intact control group (Fig. 1A). The capacity of subjects to provide consistent ratings of noxious and innocuous stimuli during psychophysical procedures was evaluated by summing the number of stimuli required to resolve each random staircase. Analysis of variance of stimuli number showed no effect for group membership [$F(1,27) = 2.1$, n.s.], a significant effect of threshold level [$F(1,27) = 6.0$, $P < 0.05$], and the absence of any interaction between group and threshold level [$F(1,27) = 1.1$, n.s.]. *Post hoc* testing with paired *t*-tests established that the mean number of stimuli required to

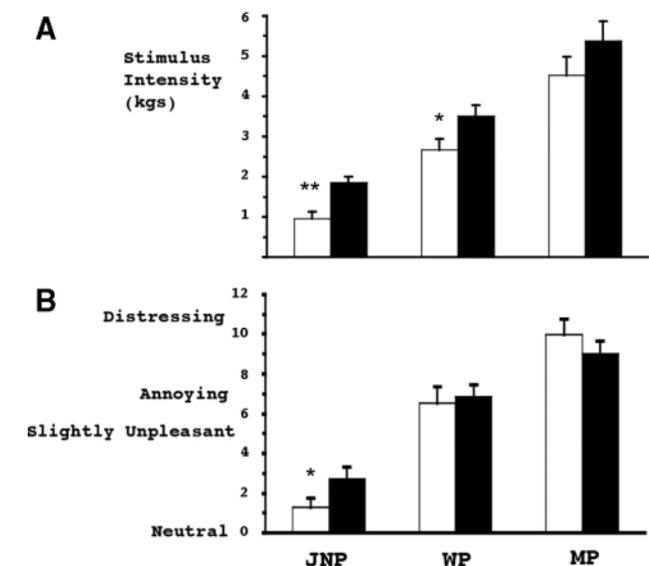


Fig. 1 (A) Mean pain sensitivity thresholds recorded for a group of patients with Alzheimer's disease (solid bars) and an age-matched cognitively intact control group (unfilled bars) following mechanical pressure stimulation. (B) Subjective ratings of the unpleasantness of pressure stimuli delivered at each threshold level. * $P < 0.05$; ** $P < 0.001$. Error bars represent SEM.

resolve thresholds for JNP and WP were greater than the mean number for MP. The mean stimulus intensities required to elicit reports of JNP, WP and MP were higher for the patient group compared with controls [$F(1,27) = 5.79$, $P < 0.05$]. However, contrary to a previous report (Benedetti *et al.*, 1999), the difference was most significant at the level of JNP. Patients did not provide lower ratings for pain unpleasantness as would be predicted by a reduction in medial pain pathway functioning. In fact they gave higher unpleasantness ratings for pain threshold stimuli compared with controls (Fig. 1B).

Functional magnetic resonance imaging results

Analysis of fMRI data revealed a common network of pain-related activity, with both groups showing increased activity in both the medial and lateral pain systems during noxious versus innocuous pressure stimulation (Table 1; Fig. 2). This included increased activity in the aMCC, IC, medial thalamus, S1 and S2. Between-group analyses failed to reveal any evidence of greater pain-related activity in the control group compared with the patient group. However, compared with controls, patients showed significantly greater pain-related activity in several pain-pathway regions, including the aMCC (Talairach co-ordinates: 2, 8, 32) and (0, 10, 46), ventrolateral and dorsomedial thalamus (–10, –10, 12) and (6, –18, 12), S1 (–58, –14, 42), posterior parietal cortex (–4, 12, 68) and frontal regions including the DLPFC (40, 12, 56) and (–22, 36, 46). In addition, several motor pathway regions, including M1 (42, –16, 62) and (–54, –8, 42), supplementary motor area (SMA; –4, 12, 68) and cerebellum (–4, –68, –28) showed greater pain-evoked responses in the Alzheimer's disease group compared with controls (Fig. 3; Supplementary Table 1).

Haemodynamic response properties in selected regions of interest

Haemodynamic response properties were examined in ROIs from the medial pain pathway (aMCC and anterior, mid and posterior subregions of the contralateral IC) and lateral pain pathway (S1 and S2). Time courses of BOLD signal activity from the aMCC and left anterior IC (aIC) reveal between-group similarities in mean percentage signal change amplitude and in the latency to peak response (Fig. 4A and B). However, differences in temporal characteristics of the haemodynamic response can be observed, most notably in the slower return to baseline after moderately painful stimulation in the Alzheimer's disease group. Repeated-measures ANOVAs confirmed significant between-group differences in BOLD signal intensity change over time in the aMCC [$F(5,126) = 3.52$, $P < 0.01$] and aIC [$F(7,180) = 1.80$, $P < 0.05$]. The patient group also showed a perseveration of BOLD signal activity relative to controls in the mid IC [$F(8,215) = 2.08$, $P < 0.05$], which did not differ significantly from the pattern observed in the aIC [$F(8,213) = 1.13$, n.s.]. The temporal profiles of BOLD signal change in the posterior insula did not significantly differ between groups [$F(8,211) = 1.07$, n.s.], with neither group showing sustained activity beyond stimulus removal. Time courses from lateral pain pathway ROIs show that peak response amplitude was greater and had a slower latency in the patient group compared with controls. As seen in medial pathway ROIs, the increase in BOLD signal is also more prolonged for the patient group in S1 [$F(5,143) = 4.36$, $P < 0.005$] and S2 [$F(6,168) = 4.06$, $P < 0.005$] (Fig. 4C and D).

To further explore between-group differences in pain-related activation, BOLD signal time courses were plotted in two prefrontal regions (left and right DLPFC) and two motor regions (left and right M1) (Fig. 5). The patient group

Table 1 Increased activity associated with MP compared with innocuous pressure in selected ROIs from medial and lateral pain pathways

Region	BA	Control group				Z-score	AD patient group				AD group—controls*			
		Peak voxel coordinate			Z-score		Peak voxel coordinate			Z-score	Peak voxel coordinate			Z-score
		x	y	z			x	y	z		x	y	z	
Medial														
aMCC	24	2	26	36	3.31 [†]	0	20	28	3.76	2	18	32	3.26	
	32	–2	36	30	3.01 [†]	0	22	44	3.96	0	10	46	3.67	
a/mIC	13	34	28	0	4.34	38	2	6	5.53					
		–42	–2	10	4.06	–40	2	2	4.41					
Lateral														
S1	1/2/3	58	–22	42	3.64	64	–26	40	3.96					
			–60	–18	48	3.95	–34	–38	58	4.97	–58	–14	42	3.67
S2	40/44	56	12	4	4.24	56	4	6	4.28					
	40	–60	–26	18	3.95	–62	–24	24	4.23					

*No suprathreshold regions identified for the contrast of Control group - AD patient group.

The coordinates of maximally activated voxels are given in MNI space (Evans *et al.*, 1992). All activations identified at cluster-level significance of $P < 0.05$ (corrected), except[†], identified at voxel-level significance threshold of $P < 0.05$ (corrected). a/mIC = anterior/mid insula cortex. A comprehensive list of activated regions is presented in Supplementary Table 1.

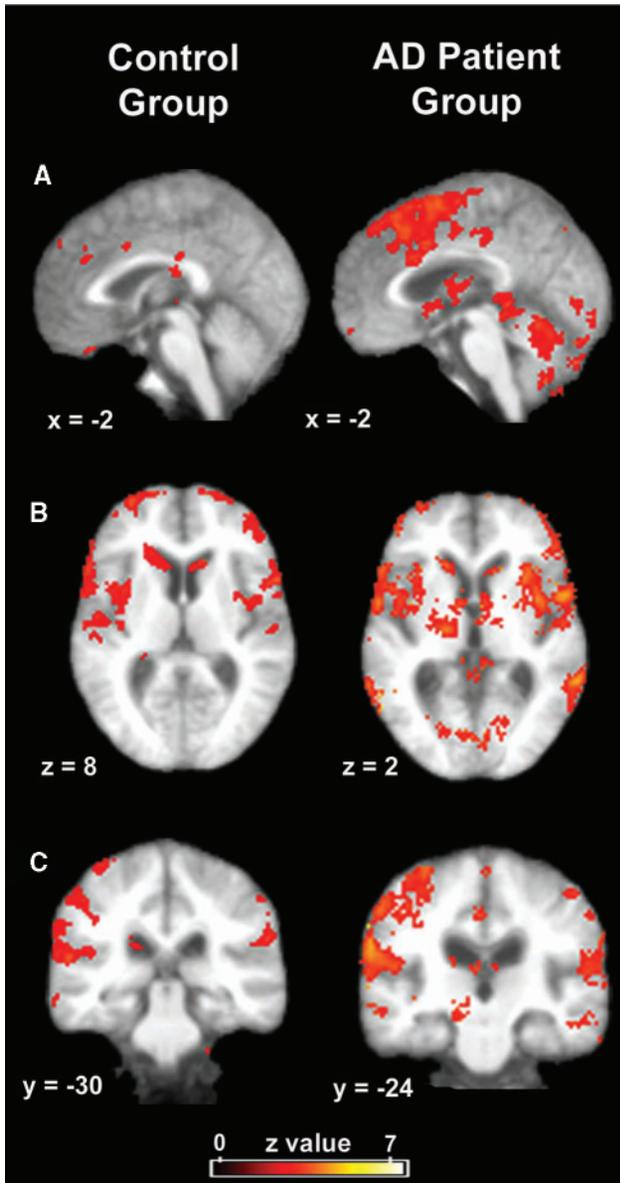


Fig. 2 Regional increases in BOLD signal activity during the experience of MP compared with innocuous pressure stimulation. (A) Mid-sagittal slices showing discrete regions of aMCC, (BA24 and BA32) activity in the control group, and aMCC activity spreading to SMA and medial frontal cortex in the Alzheimer's disease group. Patients also show increases in the medial thalamus, hypothalamus and cerebellum. (B) Axial slices showing bilateral insula and S2 activity in both groups. (C) Coronal sections showing increased bilateral activity in S1 and S2 in both groups, as well as increased primary motor cortex activity (on the contralateral side to the stimulus in the control group, and bilaterally in the patient group). Images are shown in neurological convention, with the left hemisphere on the left side of the image. Statistical maps are displayed on the respective group's average T_1 -weighted anatomical image, normalized into standard space.

showed greater peak response amplitude compared to controls in both left and right DLPFC (Fig. 5A and B). There was also significant perseveration of response in the patient group in left DLPFC [$F(6,148) = 2.54, P < 0.05$].

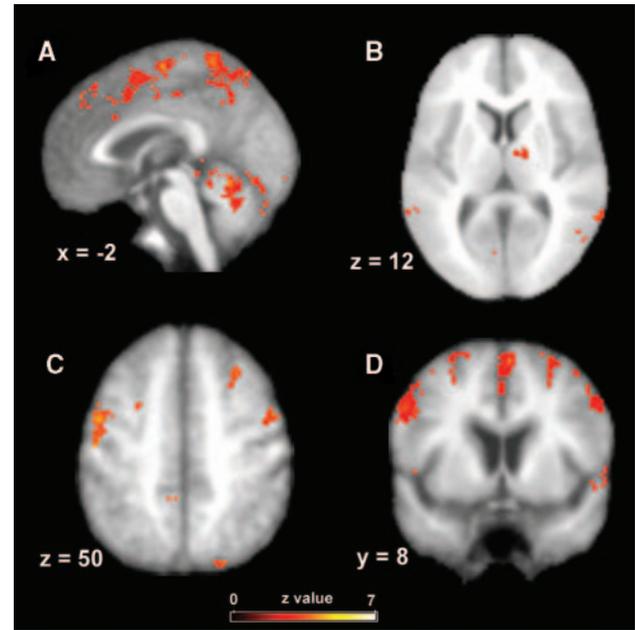


Fig. 3 Regions showing significantly greater pain-related activity in the Alzheimer's disease patient group compared with controls for the contrast between MP and innocuous pressure. (A) Mid anterior cingulate cortex (BA24 and BA32), supplementary motor area, superior parietal lobule (BA40) and cerebellum. (B) Medial thalamus. (C) Bilateral M1 and ipsilateral dorsolateral prefrontal cortex. (D) Mid anterior cingulate cortex (BA32), SMA (BA6) and premotor cortex (BA8). The images are shown in neurological convention with the left hemisphere on the left side of the image. Statistical maps are displayed on the average of all subjects' T_1 -weighted anatomical image, normalized into standard space.

However, in the right DLPFC, the temporal characteristics of the haemodynamic response did not differ significantly between groups [$F(4,106) = 2.29, n.s.$]. Response amplitudes did not differ between groups in the left M1; however, the activation was more prolonged in the patient group compared with controls [$F(6,154) = 2.28, P < 0.05$] (Fig. 5C). Finally, BOLD signal time courses from the right M1 show significantly increased BOLD signal in the patient group during moderately painful stimulation, with an absence of response from controls (Fig. 5D).

In order to check whether the between-group differences in BOLD signal change observed with noxious stimulation reflect differences in central pain processing, and not simply an overall slowing of the haemodynamic response, the temporal characteristics of BOLD responses during innocuous pressure were also analysed. The perseveration of BOLD signal activity in patients relative to controls observed with MP stimulation was not in evidence during innocuous pressure stimulation. Repeated-measures analysis of variance revealed no significant between-group difference in the BOLD signal response following innocuous pressure stimulation [$F(1,26) = 0.406, n.s.$], and there were no significant interactions between group \times time [$F(7,172) = .57, n.s.$] nor group \times time \times region [$F(14,364) = 0.94, n.s.$].

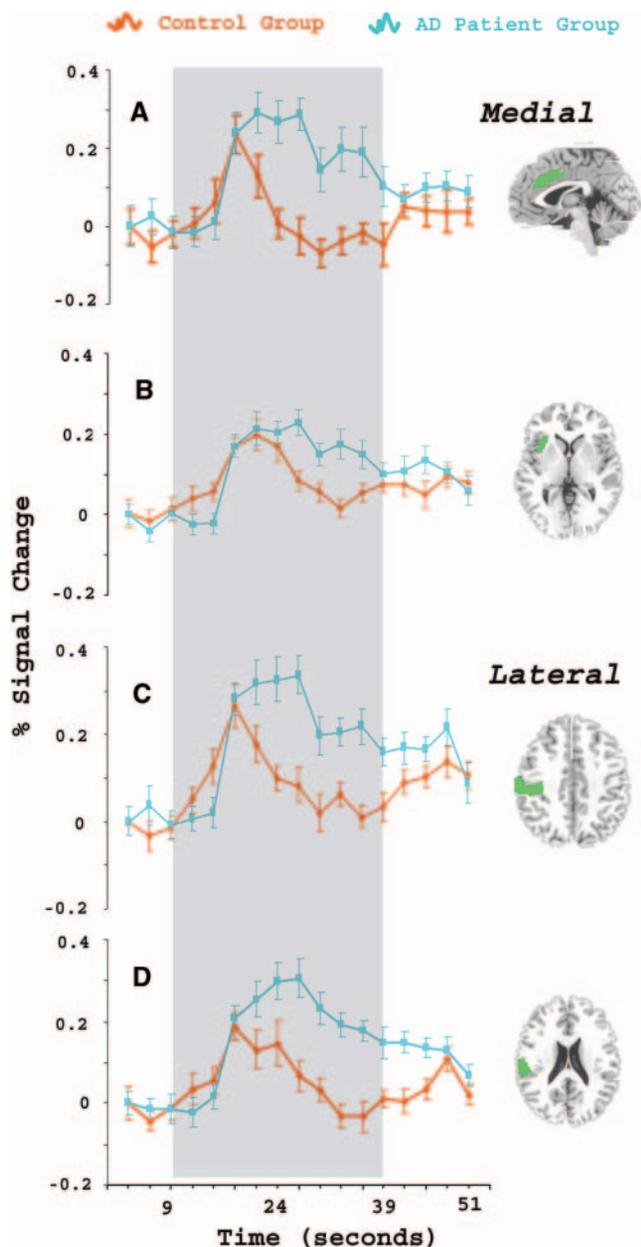


Fig. 4 Mean BOLD signal time courses from selected medial and lateral pain-pathway ROIs during moderately painful stimulation. (A) Mid anterior cingulate cortex (BA24), (B) contralateral anterior insula, (C) contralateral S1, and (D) contralateral secondary somatosensory cortex. ROI volumes were delineated by all activated voxels situated within a selected region defined by a standard-space Brodmann map supplied with MRICro [<http://www.mricro.com> (Rorden and Brett, 2000)]. Shaded area represents stimulus delivery period (averaged 7×30 s blocks). ROI volumes are displayed in neurological convention, with the left hemisphere on the left side of image.

Discussion

There has been much speculation concerning the nature of pain perception in Alzheimer's disease, and the potential disease-related changes to the CNS transmission and processing of nociceptive information that may occur (Scherder *et al.*, 2005). This study is the first to directly

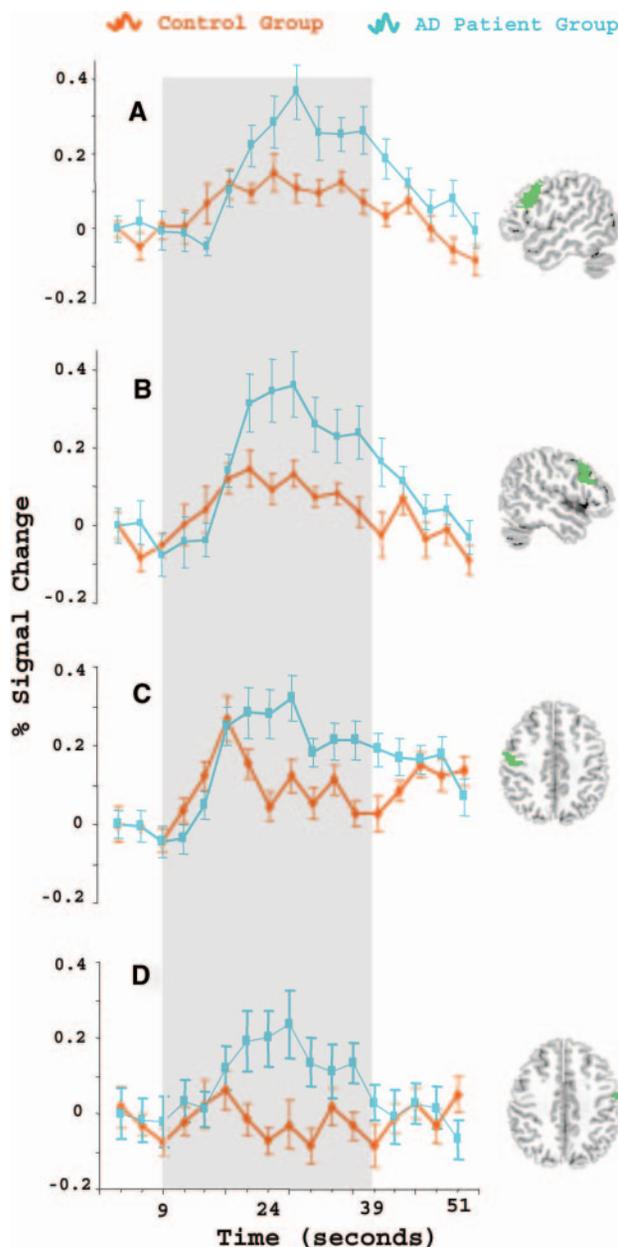


Fig. 5 Mean BOLD signal time courses from selected prefrontal and motor cortex ROIs during moderately painful stimulation. (A) Left dorsolateral prefrontal cortex, (B) right dorsolateral prefrontal cortex, (C) left M1, and (D) right M1. ROI are displayed in neurological convention and were defined as described in Fig. 4.

investigate these issues using both psychophysical and fMRI measures of responses to pain.

Our finding of higher thresholds for pain sensitivity in Alzheimer's disease patients compared with control subjects is in partial agreement with previous reports (Benedetti *et al.*, 1999; Rainero *et al.*, 2000). However, ratings given for the unpleasantness of painful stimuli delivered at comparable perceptual intensities were not significantly lower in patients compared with controls. The elevated JNP threshold in the patient group was accompanied by elevated

unpleasant ratings compared with the healthy controls. The most parsimonious explanation for this outcome is that the patients adopted a more stringent internal benchmark for what constituted JNP. Preliminary instructions to subjects emphasized the need to draw a distinction between the experience of innocuous pressure, and just detectable degrees of pain. Memory impairment could diminish the efficacy of preliminary instructions in the patient group, possibly resulting in a tendency to dismiss very low levels of pain as inconsequential. Unpleasantness ratings of frankly painful levels of stimulus in the patient group would consequently exceed the rating of near-threshold levels of pain in the control group.

Functional brain imaging data produced no evidence of reduced pain-related activity in medial pain regions in patients compared with healthy controls, indicating that the affective/emotional aspects of the pain experience are not selectively diminished in these patients, in contrast to the previously hypothesized view (Scherder and Bouma, 1997; Scherder *et al.*, 2003, 2005). In fact, compared with controls, the Alzheimer's disease group showed perseveration of pain-related activity across all components of the pain network, including the aMCC and a/mIC.

While our data provide no evidence for diminished emotional responsiveness to moderately painful stimulation in patients, prolonged activation in the pain pathway along with increased activity in cognitive processing regions such as the DLPFC indicate that the cognitive integration of the painful experience may be altered. Attenuation of BOLD signal responses, with signal decay occurring prior to the removal of a noxious stimulus, has previously been reported in studies of the temporal dynamics of the pain-evoked brain activation (Kurata *et al.*, 2002; Ibinson *et al.*, 2004). This observed decay in BOLD signal following noxious input can be explained in terms of diminished attention to a painful stimulus (Peyron *et al.*, 1999; Brooks *et al.*, 2002). Engagement in attention-demanding cognitive tasks has also been shown to decrease pain-related activity in several components of the pain network, including S1, S2 and IC (Seminowicz *et al.*, 2004). Alternatively, it may be argued that the decay in haemodynamic response with pain observed in the control subjects may reflect habituation to the stimulus. However, previous psychophysical evaluations of responses elicited by the same stimulus modality have reported no evidence of habituation. The stimulus has been shown to produce replicable sensations (Gracely *et al.*, 2002, 2004), and serial pain intensity ratings have been previously found to slightly increase over 30 s stimulus trials, suggesting that subjects are more likely to sensitize than habituate to the stimulus (unpublished observations). Moreover, it is unlikely that patients and controls differentially habituated to the stimulus, given that the number of stimulus trials required to determine pain thresholds did not significantly differ between groups. Thus, the perseveration of pain-related brain activity observed in patients compared with controls more likely reflects sustained attention to the stimulus, rather than impaired habituation.

Pain demands attention by its very nature. However, in situations where the threat of tissue damage is low, such as the experimental pain environment, the propensity to escape from the stimulus is necessarily suppressed. Under such circumstances, it is more adaptive to disengage attention from the experience of pain. In the present study, the attenuation in pain-evoked activity in the older control group of subjects can be interpreted as an accurate appraisal of pain in an experimental setting, and consequent disengagement of attention from the sensation. On the other hand, the perseveration of the initial pain response seen in the Alzheimer's disease group may be modulated by ongoing attention to the stimulus, due to an impaired capacity to integrate novel and recent somatosensory experiences with contextual information. Compared with controls, the patient group also had greater pain-related activity across the motor network, including M1, premotor cortex, SMA and cerebellum. This increase in motor activity suggests inadequate inhibition of withdrawal responses, and provides further evidence of impaired cognitive integration of the pain experience.

Further evidence of an altered cognitive response to pain is provided by the increased DLPFC activity in this group of patients. The DLPFC is known to be involved in working memory processing and attention (Barch *et al.*, 1997; Mesulam, 1998; Smith and Jonides, 1999; MacDonald *et al.*, 2000). Previous research has shown increased prefrontal activity in Alzheimer's disease patients compared with controls during the performance of cognitive tasks (Grady *et al.*, 2003; Pariente *et al.*, 2005a; Starr *et al.*, 2005). The increase in prefrontal activity has been found to correlate with improved memory performance (Remy *et al.*, 2005) and may reflect heightened attentional engagement in difficult tasks (Pariente *et al.*, 2005a). Recent evidence from pain imaging research suggests that the DLPFC may also play a role in the cognitive modulation of pain (Bornhord *et al.*, 2002; Lorenz *et al.*, 2002, 2003; Brighina *et al.*, 2004; Gracely *et al.*, 2004; Graff-Guerrero *et al.*, 2005; Pariente *et al.*, 2005b; Zubieta *et al.*, 2005). For instance, Lorenz *et al.* (2002) found increased DLPFC activity during the stimulation of chemically-sensitized skin with a normally innocuous thermal stimulus (heat allodynia) compared with stimulation of non-sensitized skin with a noxious thermal stimulus (heat pain), even though the perceived intensity of the stimuli was the same for both conditions. The authors note that increased activity in the DLPFC is usually seen in pain studies involving real or perceived tissue pathology, such as allodynia, abdominal pain or neuropathic pain. Given that the future implications of pathological pain states differ to those of normal experimental pain conditions, increased DLPFC activity may reflect altered emotional and cognitive responses to potentially harmful noxious stimulation. Following this line of reasoning, the increased DLPFC activity in Alzheimer's disease group compared with cognitively intact controls in the present study may indicate an increased threat value of the pain for the patients,

on account of their impaired ability to appropriately appraise the likely consequences of the experimental pain stimulus. This is consistent with a recent report of altered expectations of pain-relief in patients (Benedetti *et al.*, 2006). First and foremost, Alzheimer's disease is a disorder of cognition, and consequently it is not surprising that the disease is likely to impact on the cognitive domain of the pain experience.

It is important to note that while our cohort of patients all had a clinical diagnosis of Alzheimer's disease, they were still in the early stages of disease progression, with the group mean MMSE score (19.4 ± 5.7) indicating a mild-to-moderate degree of cognitive impairment. It is possible that the nature of pain perception may differ between cases with mild Alzheimer's disease and those with more advanced stages. Thus, the difference between our psychophysical results and those previously reported may be related to differences in the level of cognitive impairment of the respective samples. However, given that the disease follows a predicted course, with medial thalamic nuclei and medial temporal structures such as the cingulate cortex among the first regions to become degraded (Rub *et al.*, 2002; Thompson *et al.*, 2003), any reduction in the cognitive-emotional aspects of the pain experience would be expected to manifest in the early stages of the disease.

Overall, the pattern of pain-related brain activity observed with fMRI suggests that the central processing of nociceptive information is not diminished in Alzheimer's disease patients. In fact, the experience of pain may be more distressing for these patients on account of their impaired ability to accurately appraise the unpleasant sensation and its future implications. The results of the present study therefore have significant clinical implications, and raise important concerns about the current inadequate treatment of pain in this highly dependent and vulnerable group.

Supplementary material

Supplementary data are available at *Brain* Online.

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