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Pain processing in older adults with dementia-related cognitive impairment is associated with frontal neurodegeneration

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ABSTRACT

Experimental pain research has shown that pain processing seems to be heightened in dementia. It is unclear which neuropathological changes underlie these alterations. This study examined whether differences in pressure pain sensitivity and endogenous pain inhibition (conditioned pain modulation (CPM)) between individuals with a dementia-related cognitive impairment (N=23) and healthy controls (N=35) are linked to dementia-related neurodegeneration. Pain was assessed via self-report ratings and by analyzing the facial expression of pain using the Facial Action Coding System. We found that cognitively impaired individuals show decreased CPM inhibition as assessed by facial responses compared to healthy controls, which was mediated by decreased gray matter volume in the medial orbitofrontal and anterior cingulate cortex in the patient group. This study confirms previous findings of intensified pain processing in dementia when pain is assessed using non-verbal responses. Our findings suggest that a loss of pain inhibitory functioning caused by structural changes in prefrontal areas might be one of the underlying mechanisms responsible for amplified pain responses in individuals with a dementia-related cognitive impairment.

1. Introduction

In the last decade, the topic of pain and dementia has attracted considerable attention because of the notion that pain is underdetected and undertreated in dementia (Achterberg et al., 2020; Hadjistavropoulos et al., 2014). Moreover, experimental pain research has shown that pain processing is not diminished but seems to be heightened in dementia. This conclusion is mostly based on studies that focused on non-verbal indicators of pain, given that the loss in verbal communication skills associated with dementia-related cognitive impairment makes the valid assessment of self-report challenging. Among these non-verbal pain indicators, facial responses in people with dementia were repeatedly found to be increased during experimental pain stimulation (Beach et al., 2016; Kunz et al., 2015, 2009, 2007). In line with this, the nociceptive flexion reflex as well as brain activity in response to painful stimulation were also found to be amplified (Cole et al., 2006; Kunz et al., 2009).

It is not yet known which neuropathological changes underlie these alterations in pain processing. Dementia is characterized by a widespread loss of brain tissue, with different subtypes showing different patterns of neurodegeneration (Krueger et al., 2010). It has been hypothesized that neurodegeneration in brain structures involved in descending pain inhibition might contribute to altered pain responses (Kunz et al., 2009). A brain area that plays a key role in descending pain inhibition is the prefrontal cortex (Bingel and Tracey, 2008; Bogdanov et al., 2015). This is one of the brain regions that was found to show altered activity in response to noxious stimulation in Alzheimer patients (Cole et al., 2006). The assumption that dementia-related neurodegeneration in prefrontal areas might affect the processing of pain, especially the descending inhibitory system, is supported by findings of neuropsychological studies. Of all cognitive domains affected by healthy

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aging and dementia-related cognitive impairment, the increase in facial responses and the nociceptive flexion reflex could be best explained by deficits in executive functions (Kunz et al., 2015; Oosterman et al., 2016), which are higher-order cognitive skills that are linked to the function of the frontal cortex (Bunk et al., 2019). Moreover, in healthy older individuals, poorer executive functioning was found to be associated with poorer endogenous pain inhibition as assessed using the conditioned pain modulation (CPM) protocol (Lithfous et al., 2018; Marouf et al., 2014). Thus, there are several indications that a loss in prefrontal functioning might be one mechanism underlying the increased pain responses in dementia-related cognitive impairment, possibly via a loss in endogenous pain inhibition. So far, this has not been tested.

The aim of the present study was to investigate whether increased pain responses in older individuals with dementia-related cognitive impairments can be linked to neurodegeneration especially in prefrontal areas. Given the decline in cognitive and verbal capacities, pain responses were not only based on self-report ratings but also on facial responses. As experimental pain protocols we used phasic pressure pain as well as the CPM protocol to assess pain inhibitory functioning. As for statistical analyses, we used mediation analyses to investigate whether structural brain changes (especially in frontal areas) mediate the relation between cognitive decline and pain responsiveness, including CPM.

2. Methods

2.1. Participants

Individuals with dementia-related cognitive impairment over the age of 60 were recruited at the outpatient memory clinic of the University Medical Center Groningen, through the Dutch online registry Hersenonderzoek.nl that facilitates participant recruitment for neurosciences studies (www.hersenonderzoek.nl), via case managers for community-dwelling people with dementia and through advertisements. Age- and gender-matched controls were recruited among students of the local University of the Third Age and through advertisements.

Sample size calculation (Sample Power 2.0, SPSS Inc., Chicago, IL, USA) was based on previous findings of our group where we investigated pain responses (self-report, facial expression, heart rate) in patients with dementia (mostly Alzheimer disease) (Kunz et al., 2007; Kunz et al., 2009). Given that we were interested in “medium ”to “strong” effects between groups that might be of clinical relevance, sample size calculation was conducted for 80 % power and 0.05 level of significance. Based on these considerations, a sample size of 25 in each group should prove sufficient to reach adequate reliability for between-group comparisons. Previous neuroimaging studies investigating pain in dementia (mostly functional neuroimaging) used similar sample sizes (Beach et al., 2017; Cole et al., 2011, 2006; Fletcher et al., 2015; Monroe et al., 2017). This sample size should also be sufficient for the structural neuroimaging analyses performed in the present study (Scarpazza et al., 2015). Since recruitment of patients with dementia was challenging for this study, we chose a larger sample size for healthy individuals to increase statistical power. In total, 23 cognitively impaired individuals and 35 cognitively healthy older individuals participated in this study.

For the group of cognitively impaired individuals, inclusion criteria were either (1) a diagnosis of one of the most common subtypes of a major neurocognitive disorder according to criteria of the DSM-V (Alzheimer’s disease, vascular dementia or frontotemporal dementia) or (2) a mild neurocognitive disorder (also named mild cognitive impairment) based on subjective memory complaints and impairment in at least one cognitive domain (a score of one standard deviation below the mean score of the control group). Participants were excluded if they had a history of a major neurological or psychological disorder other than dementia or a contraindication to MRI. Participants did not take analgesic medication on the day of testing. Table 1 provides demographic information, the number of participants per dementia subtype and the results of a neuropsychological test battery. One of the tests was the Mini Mental State Examination (MMSE), which was used to assess global cognitive functioning. The MMSE score ranges between 0-30, with a higher score indicating better cognitive performance (Folstein et al., 1975). The patient group scored on average 23.7, suggesting mild dementia-related impairment. Depressive symptoms were assessed using the short form of the Geriatric Depression Scale, which consists of 15 questions, with a higher score indicating more depressive symptoms (Sheikh and Yesavage, 1986). Although there was a significant difference in the number of depressive symptoms, both groups scored below the cut-off (De Craen et al., 2003).

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University Medical Center Groningen. All participants still had legal capacity. After being informed about the study in a way adjusted to the individual intellectual capacities, a written informed consent was obtained from all participants. We monitored the patients continuously for any signs of disproportionate discomfort (verbally or non-verbally), in which case we stopped testing immediately. Participants received a minor monetary compensation for their participation.

2.2. Study procedure

The study consisted of three parts. Part one consisted of an experimental pain protocol of 30 minutes to assess pain responsiveness, part two consisted of a 30 minute neuropsychological examination to evaluate the cognitive status of the participants (MMSE, further neuropsychological tests applied are not part of the present article) and part three consisted of a structural MRI scanning session of 20 minutes. Part one and two were always conducted on the same day and took place in a laboratory room of the department of Elderly Care Medicine of the University Medical Center Groningen. Part three was most often conducted on a separate day, with time intervals between testing days on average being 19 days. The MRI scan was performed at the department of Radiology of the University Medical Center Groningen.

2.3. Experimental pain protocol

2.3.1. Apparatus

Pressure stimuli were applied to the midpoint of the upper border of the trapezius muscle (back shoulder area) using a pressure algometer with a probe area of 1 cm^2 (Algometer type II, Somadic Sales AB, Hörby, Sweden). Heat stimuli were administered to the right inner forearm using a thermal sensory analyzer (Medoc TSA II, Ramat-Yishai, Israel) with a Peltier thermode of 6 cm^2 stimulation surface.

2.3.2. Pressure pain sensitivity

In order to assess pressure pain sensitivity, four different pressure intensities (50, 200, 400 and 500 kilopascal (kPa)) were applied to the shoulder in an ascending order. An ascending order was chosen to reduce anxiety in participants as well as to be able to stop immediately with the stimulation protocol if a participant found the stimulation too painful. There were two trials, one to the right shoulder and one to the left shoulder, applied in a fixed

Table 1
Demographic and clinical characteristics of cognitively impaired individuals and controls

	Patients (N=23) mean ± SD or N (%)	Controls (N=35) mean ± SD or N (%)	Group difference
Age	72.8 ± 7.6	69.2 ± 6.2	$p = 0.065$
Female	7 (30%)	11 (31%)	$p = 0.936$
Level of education			$p = 0.254$
Primary school	2 (9%)	0 (0%)	
High school	4 (17%)	8 (23%)	
Secondary vocational education	6 (26%)	5 (14%)	
Higher professional education	7 (30%)	14 (40%)	
University education	3 (13%)	8 (23%)	
Dementia subtype	AD=14 (61%) FTD=4 (17%) MCI=4 (17%) VD=1 (4%)	-	
MMSE score	23.7 ± 5.0	28.6 ± 1.4	$p < 0.001$
15 word task immediate recall (number of words)	4.0 ± 2.3	8.2 ± 2.3	$p < 0.001$
15 word task delayed recall (number of words)	1.7 ± 2.0	6.0 ± 2.5	$p < 0.001$
Trail Making Test part A (time in seconds)	72.5 ± 43.6	36.5 ± 12.2	$p < 0.001$
Trail Making Test part B (time in seconds)	169.6 ± 93.6	84.1 ± 41.8	$p < 0.001$
Stroop difference score (number of correct responses)	31.2 ± 11.5	35.0 ± 9.5	$p = 0.174$
Letter Fluency test (number of words)	11.0 ± 6.4	14.8 ± 5.4	$p = 0.018$
Geriatric depression scale	2.6 ± 2.3	1.4 ± 1.7	$p = 0.022$

Statistical significance was determined using independent samples t-tests (age, MMSE and depression) and chi-squared tests for gender and the categorical variable education. The neuropsychological test battery included the Mini-Mental State Examination (MMSE), the 15 word task (a Dutch adaption of the Rey Auditory Verbal Learning Test (Bean, 2011)) to assess episodic memory function (immediate recall after three trials; delayed recall after a distraction period of approximately 20 minutes), the Letter Fluency test to assess updating ability (Bird et al., 2004), the Trail Making Test part A and B to assess processing speed and shifting ability respectively (Bowie and Harvey, 2006) and the Stroop Color and Word to assess inhibition (difference in number of correct responses between the color naming and the color word task) (Golden, 1987).
AD, Alzheimer's disease; FTD, frontotemporal dementia; MCI, mild cognitive impairment; SD, standard deviation; VD, vascular dementia.

order. Pressure was increased steadily for 2 s until the desired intensity was reached and was then kept constant for 5 s.

2.3.3. CPM

Endogenous pain inhibition was assessed using the CPM paradigm, in which a conditioning stimulus and a test stimulus are applied simultaneously to different parts of the body to test the modulating effect of the conditioning stimulus. The test stimuli used in this CPM paradigm were similar to the stimuli used to assess pressure pain sensitivity, namely four pressure intensities of 50, 200, 400 and 500 kPa applied to the right and left shoulder. Tonic heat stimulation served as the conditioning stimulus and consisted of a series of small heat pulses at a frequency of 30 pulses/min with an amplitude of 1.3°C applied on the right inner forearm (Giehl et al., 2014; Kunz et al., 2006; Lautenbacher et al., 1995; Lautenbacher and Rollman, 1997; Teepker et al., 2014). Thus, the test stimuli were presented bilateral and the conditioning stimulus was presented on the right side. We applied a conditioning stimulus twice, once painful and once non-painful. In the first block, the test stimuli (pressure) were applied together with non-painful tonic heat stimulation of 43°C peak temperature (baseline stimulus). In the second block, the test stimuli on the shoulder were applied together with painful tonic heat stimulation of 45°C peak temperature (conditioning stimulus). By using a non-painful and painful conditioning stimulus, we tried to avoid that CPM effects were mere due to distraction of attention by a second stimulus. The blocks lasted for around two minutes. Pain inhibition was indicated by a lower pain response to pressure stimuli paired with painful heat than to pressure stimuli paired with non-painful heat (pressure pain during painful heat – pressure pain during non-painful heat < 0). Pain amplification was indicated by a higher pain response to pressure stimuli paired with painful heat than to pressure stimuli paired with non-painful heat (pressure pain during painful heat – pressure pain during non-painful heat > 0).

2.3.4. Pain responses

Pressure pain sensitivity and CPM were assessed via self-report ratings as well as via facial responses. This resulted in four pain outcomes, namely pressure pain sensitivity measured by rating (Pain-rating), pressure pain sensitivity measured by facial expression (Pain-face), CPM measured by rating (CPM-rating) and CPM measured by facial expression (CPM-face).

2.3.4.1. Ratings. Immediately after each stimulus, participants were asked to rate the pain sensation, evoked by pressure stimulation, using a five-category verbal rating scale (no pain – mild pain – moderate pain – strong pain – very strong pain), which was printed on a large piece of paper and shown to the participant after each stimulus. This type of rating scale was found to be appropriate for older adults with and without mild to moderate cognitive impairment (Lukas et al., 2013; Taylor et al., 2005). For further analyses, the ratings of the pressure stimuli on the right and left shoulder were averaged to obtain one rating per intensity.

2.3.4.2. Facial responses. Facial responses were assessed during each pressure stimulus. A camera was placed approximately 2 m in front of the participants to videotape facial expression. Participants were instructed to look into the camera and were asked not to talk when pain was induced. Facial responses were analyzed using the Facial Action Coding System (FACS) (Ekman and Friesen, 1978). This system describes 44 visually distinguishable action units (AUs). Two FACS coder (qualified by passing the FACS examination) both identified the frequency and intensity of the AUs that occurred during stimulation. One coder was completely blinded, both coders were aware of the study design and objectives. A sub-set of 10% of the video segments was randomly selected across the entire sample and was coded by both coders to calculate inter-rater reliability using the Ekman–Friesen formula (number of AUs agreed upon $\times$ 2 and divided by the overall amount of AUs coded). This inter-rater reliability was found to be 0.80, which compares favorably with other research in the

FACS literature (Karmann et al., 2015; Priebe et al., 2015). The intensity of each AU was scored using a 5-point scale, which was entered into a time-related database from the onset of the stimuli till the end of the stimuli (5 s) using The Observer Video-Pro (Noldus Information Technology, Wageningen, The Netherlands). Some AUs represent facial movements of the same muscle and were therefore combined to reduce the number of variables (AU 1/2, AU 6/7, AU 9/10 and AU 25/26/27). For further analyses, only pain-relevant AUs were included. We based this selection on a recent systematic review that showed that AU 4 (brow lower), AU 6/7 (cheek raise/lid tighten), AU 9/10 (nose wrinkle/upper lip raise) and AU 25/26/27 (mouth opening) are most consistently found to be associated with pain in both cognitively healthy and cognitively impaired individuals (Kunz et al., 2019). To obtain a FACS composite score for each stimulus intensity, the frequency of these AUs was multiplied by the AU intensity scores and then averaged over all four pain-relevant AUs. As for the ratings, the FACS scores of the pressure stimuli on the right and left shoulder were combined to obtain one FACS composite score per intensity. Previous research has demonstrated that facial expressions of pain are sensitive enough to capture CPM effects (Kunz et al., 2021).

2.4. MRI acquisition and preprocessing

MR images of the brain were acquired using a 3T MRI scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). T1-weighted image were acquired using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (176 sagittal slices, repetition time = 2300 ms, echo time = 2.98 ms, inversion time = 900 ms, flip angle = 9°, voxel size = 1 × 1 × 1 mm, field-of-view = 256 mm). Diffusion-weighted images were acquired along 64 directions using a b-value of 1000 s/mm^2 (60 slices, repetition time = 6300 ms, echo time = 66 ms, voxel size is 2.2 × 2.2 × 2.2 mmm, field-of-view = 220 mm). Ten volumes with no diffusion weighting (b-value of 0 s/mm^2) were acquired, one at the beginning and nine at the end of the acquisition.

2.4.1. Preprocessing of gray matter analyses

Differences in regional gray matter volume between cognitively impaired and cognitively healthy individuals were assessed using voxel-based morphometry (VBM), a voxel-wise statistical analysis (Ashburner and Friston, 2000). Standard VBM was performed using the Computational Anatomy Toolbox (CAT) 12 (Jena University Hospital, Jena, Germany) within Statistical Parametric Mapping (SPM) 12 (Wellcome Department of Cognitive Neurology, London, United Kingdom), implemented in MATLAB 9.8 (MathWorks, Natick, MA, USA). We deliberately decided applying the standard VBM approach instead of the DARTEL VBM method as methodological studies showed either comparable or more restricted (i.e., in the sense of false negative) results with DARTEL based VBM analyses in dementia (Diaz-De-Grenu et al., 2014; Mak et al., 2011). The standard VBM procedure involves segmentation into gray matter images and spatial normalization by registering the images to standard space (to correct for global differences in brain shape). After performing quality control for inter-subject homogeneity and overall image quality as included in the CAT12 toolbox, the gray matter images were smoothed using the default 8 mm full-width at half maximum Gaussian kernel. The smoothed normalized gray matter images of cognitively healthy and cognitively impaired individuals were entered separately in a general linear model together with total intracranial volume as a covariate to correct for differences in brain size. Absolute threshold masking was set at 0.1.

Table 2
Description of regions of interest used for gray matter analyses

Region of interest	MNI coordinate of center of gravity (x, y, z)
Medial orbitofrontal cortex	9, 41, -12 / -9, 41, -12
Lateral orbitofrontal cortex	34, 41, -15 / -34, 41, -15
Anterior cingulate cortex	9, 39, 18 / -9, 39, 18
Rostro-lateral prefrontal cortex	28, 53, 21 / -28, 53, 21
Caudo-lateral prefrontal cortex	44, 30, 27 / -44, 30, 27

Regions based on Bogdanov et al. 2015.
MNI; Montreal Neurological Institute.

2.4.2. Preprocessing of white matter analyses

Differences in white matter structure between the two groups were assessed using tract-based spatial statistics (TBSS), a voxel-wise statistical analysis part of the FMRIB Software Library (FSL version 6.0.0, Oxford, UK) (Smith et al., 2006). Diffusion-weighted MRI allows to measure diffusivity of water molecules within axons (Soares et al., 2013). Given that diffusivity of water is more restricted along an axon than perpendicular to an axon, it is possible to estimate fiber orientations. There exist multiple measures of diffusivity, including axial diffusivity (AD; diffusivity parallel to the fibers), radial diffusivity (RD; average diffusivity of the two directions perpendicular to the fibers), mean diffusivity (MD; average diffusivity of all three directions) and fractional anisotropy (FA; a measure of overall directionality of water diffusion) (Clark et al., 2011; Song et al., 2002). After a visual inspection of the data, FA images were created by fitting a tensor model to the raw diffusion data using the diffusion toolbox and then brain-extracted using the brain extraction tool (Smith, 2002). All subjects' FA data were aligned into standard space using the nonlinear registration tool FNIRT. A mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each subject's aligned FA data was projected onto this skeleton. The nonlinear registration and skeletonization stages were repeated for AD, MD and RD.

2.5. Statistical analyses

2.5.1. Group differences in pain responses

Repeated measures ANOVAs with one between-subject factor (group) and one within-subject factor (pressure intensity) were used to assess whether facial and subjective responses increased across the four pressure intensities, whether this increase differed depending on the cognitive status and whether there was an interaction effect between group and pressure intensity. Moreover, independent-samples t-tests were used to compare facial and subjective pain responses (pressure pain sensitivity and CPM) to painful stimuli between cognitively impaired and cognitively healthy individuals.

2.5.2. Group differences in gray and white matter

To assess group differences in gray matter volume, first, whole brain VBM analyses were performed. Second, VBM analyses were restricted to areas associated with descending pain modulation, given our hypothesis that endogenous pain inhibition might be affected in dementia. Based on previous MRI studies, Bogdanov et al. (2015) defined five descending pain modulation clusters, listed in Table 2. We used these clusters for region-of-interest analyses using the small volume correction function implemented in SPM. The threshold for significance was set at $p < 0.05$ family-wise error (FWE) corrected at cluster level for both whole brain analyses as well as region of interest analyses.

Group differences in white matter structure were assessed by investigating differences in diffusivity (FA, AD, RD, MD) within the

white matter skeleton. Voxel-wise statistical analyses were performed using FSL randomize with 5000 permutations. The threshold for significance was set at $p < 0.05$ corrected using threshold-free cluster enhancement (TFCE).

Brain areas that showed significant differences between the two groups were used for further analysis (see 2.6.3). Gray matter volume was extracted from significant gray matter clusters using a 6 mm sphere centered on the peak coordinate. Average values of the diffusivity measures were extracted from significant white matter clusters.

2.5.3. Mediation analyses: Is the effect of cognitive impairment on pain responses mediated by loss in gray and white matter?

Mediation analyses were performed to test whether observed differences in pain responses between the two groups can be explained by differences in brain structure. A mediation analysis consists of four steps: (1) confirm a significant relation between the potential mediators (extracted gray matter volume and white matter structure) and cognitive decline (MMSE score), (2) confirm a significant relation between the potential mediators and pain responses when controlling for cognitive decline, (3) assess the strength of the relation between cognitive decline and pain responses and (4) confirm that the effect of step 3 reduces when controlling for the potential mediator. Step 1 is described under 2.6.2 and step 3 is described under 2.6.1. However, since a continuous variable was needed for the mediation analyses, these analyses were repeated using MMSE score as a continuous measure for cognitive decline instead of using "group" as a dichotomous factor. All four steps of the mediation analyses were performed using PROCESS 3.4 implemented in SPSS 26 (Hayes, 2013). PROCESS performs regression analyses for step 1-4. The mediation (or indirect) effect is equal to the product of the regression coefficients of step 1 and 2. PROCESS uses a non-parametric bootstrap approach (5000 samples), resulting in a 95% confidence interval used to assess the significance of the mediation effect. This method is suitable for small sample sizes (Creedon and Hayes, 2015).

3. Results

3.1. Influence of cognitive decline on pain responsiveness

The majority of participants was able to provide a self-report rating for each pressure stimulus. Only three individuals with cognitive impairments (13% of that group) were not able to provide a rating for every stimulus (this means no pain rating was given after being asked to rate the stimulus on the category scale). Fig. 1A shows that pain ratings increased across the four pressure intensities (main effect of intensity: $F(3, 162)=222.1$, $p < 0.001$). There was no significant effect of group on pain ratings ($F(1, 54)=2.2$; $p = 0.140$) and no significant interaction effect between group and intensity ($F(3,162)=0.7$, $p = 0.584$), indicating that the pressure stimuli were rated similarly by cognitively impaired individuals and cognitively healthy individuals. As can be seen in Fig. 1A, only the pressure intensities of 400 and 500 kPa were on average rated as being painful. Fig. 1B shows the average pain-indicative FACS composite score for each pressure intensity. There was a significant main effect of intensity ($F(3, 168)=19.4$, $p < 0.001$) as well as a significant effect of group ($F(1, 56)=9.0$, $p = 0.004$) and a significant interaction effect between group and intensity ($F(3, 168)=6.5$, $p < 0.001$). This indicates that cognitively impaired individuals showed more pain-indicative facial responses, which was most pronounced for higher pressure intensities.

Given our interest in pain responses, we decided to average subjective as well as facial responses to 400 and 500 kPa in order to gain responses that lie certainly in the painful range. The averaged pain responses ("subjective pain responses" and "facial pain responses") were used for all further analyses.

3.1.1. Subjective pain responses

Pain-rating: As can be seen in Table 3, individuals with cognitive impairment did not rate the painful stimuli as more or less painful compared to healthy older individuals.

CPM-rating: Similarly, CPM measured by rating also did not differ significantly between the groups. As shown in Table 3, the average CPM effect for both groups was around zero, indicating no pain modulation due to the application of a noxious conditioning stimulus. This was confirmed by paired sample t-tests, which showed that there were no significant differences in pain rating between pressure stimuli paired with painful heat and pressure stimuli paired with non-painful heat for both cognitively healthy older individuals ($t(34)=1.1$, $p = 0.246$) and individuals with a dementia-related cognitive impairment ($t(21)=-0.1$, $p = 0.920$).

3.1.2. Facial pain responses

Table 4 presents the frequency of occurrence of the facial AUs used to compute the FACS composite score. It shows that all selected AUs are significantly more frequent during painful pressure stimulation than during non-painful pressure stimulation. Cognitively healthy individuals and cognitively impaired individuals showed the same AUs during painful pressure stimulation, corroborating earlier findings that the type of facial responses being displayed during pain is not affected by cognitive decline (Kunz et al., 2019).

Pain-face: When considering the frequency as well as the intensity of the selected AUs, the average facial response to 400 and 500 kPa was significantly higher in cognitively impaired individuals compared to cognitively healthy individuals, as can be seen in Table 3.

CPM-face: The average CPM effect measured by facial expression for 400 and 500 kPa stimuli also differed significantly between the groups. As shown in Table 3, individuals with cognitive impairment showed pain amplification.

3.1.3. Summary

Together, these results show that the influence of cognitive decline on pain responsiveness in our sample is restricted to facial responses, with cognitively impaired individuals demonstrating increased facial responses to pressure stimuli and decreased pain inhibition when the CPM effect is assessed using facial expression.

3.2. Influence of cognitive decline on gray matter volume

Fig. 2 and Table 5 show the results of the VBM analysis comparing gray matter volume between the groups. At the whole brain level, cognitively impaired individuals showed significantly less gray matter volume in a large area of the temporal lobe and three smaller areas in the frontal cortex and the parietal cortex, specifically in the rostral prefrontal cortex, posterior cingulate cortex and supramarginal gyrus. Regions of interest analyses revealed additional significant clusters of reduced gray matter volume within the medial orbitofrontal cortex, lateral orbitofrontal cortex and anterior cingulate cortex. No areas showed increased gray matter volume in patients relative to controls.

3.2.1. Mediation analyses: Are gray matter changes mediating the association between dementia-related cognitive decline and pain responsiveness?

Mediation analyses were conducted to examine whether the observed changes in pain responses associated with cognitive de-

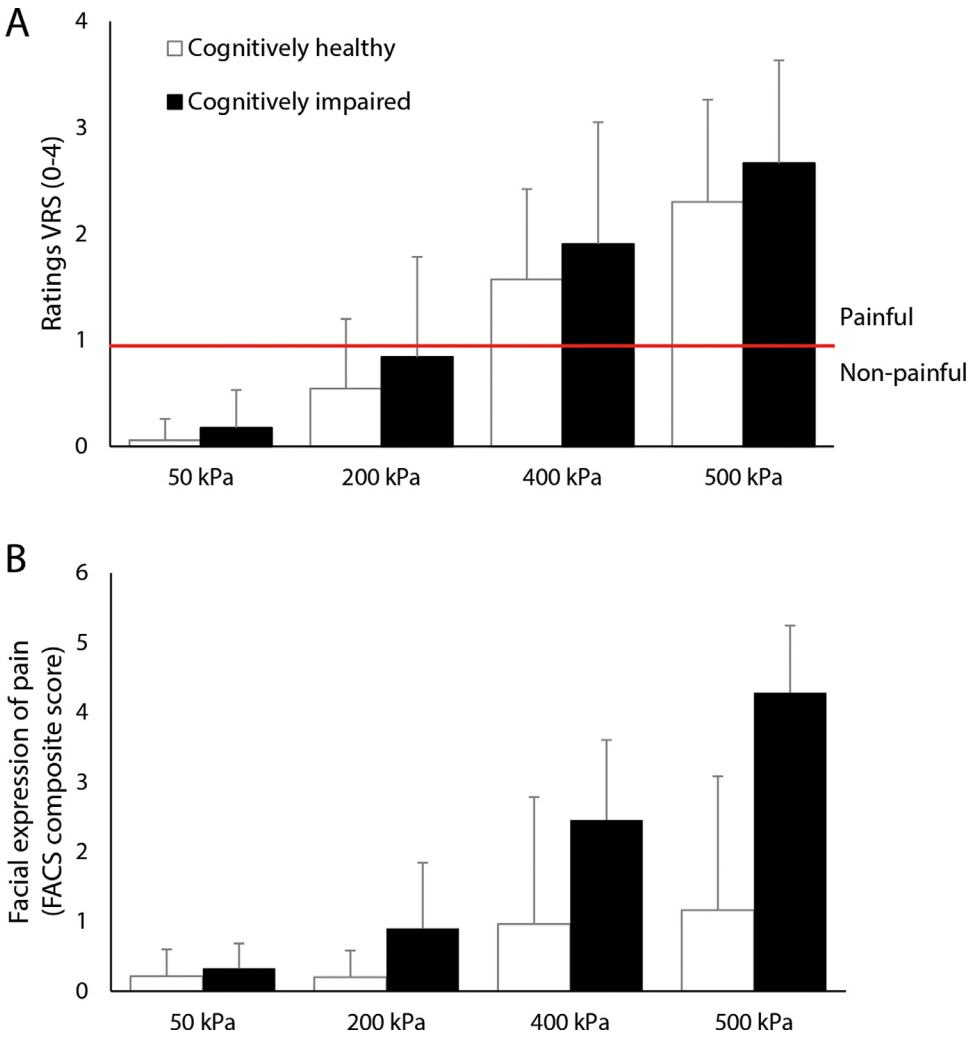

Fig. 1. Mean and standard deviation of pain ratings (A) and facial responses (B) to the four pressure intensities. KPa, kilopascal; FACS, facial action coding system; VRS, verbal rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = strong pain, and 4 = very strong pain).

Table 3
Group difference in the pain responses: pressure pain sensitivity and conditioned pain modulation (CPM) measured by ratings and facial responses

	Patients (Mean ± SD)	Controls (Mean ± SD)	Significance
Pain-rating	2.3 ± 1.0	1.9 ± 0.9	t(54)=-1.4, $p = 0.176$
CPM-rating	-0.1 ± 0.5	0.06 ± 0.3	t(55)=0.6, $p = 0.532$
Pain-face	3.4 ± 4.5	1.1 ± 1.8	t(56)=-2.7, $p = 0.008$
CPM-face	0.9 ± 2.0	-0.3 ± 1.4	t(55)=-2.7, $p = 0.008$

A CPM effect higher than zero indicates pain amplification, while a CPM effect lower than zero indicates pain inhibition. Facial response is a composite score of the frequency and intensity of selected facial action units as defined by the Facial Action Coding System.
SD, standard deviation.

Table 4
Pain-relevant facial action units (AUs) used to compute the FACS composite score

		Patients		Controls	
Action unit	Description	Occurrence[a]	Signficance[b]	Occurrence	Signficance
AU 4	Brow lower	31.3%	t(21)=3.8, $p = 0.001$	11.0%	t(34)=3.2, $p = 0.003$
AU 6/7	Cheek raise/lid tighten	67.2%	t(21)=4.9, $p < 0.001$	28.1%	t(34)=3.8, $p = 0.001$
AU 9/10	Nose wrinkle/upper lip raise	47.0%	t(21)=3.7, $p = 0.001$	13.8%	t(34)=3.5, $p = 0.001$
AU 25/26/27	Mouth opening	49.3%	t(21)=2.9, $p = 0.008$	28.6%	t(34)=2.6, $p = 0.015$

FACS, facial action coding system.
[a] Cumulative percentage of occurrence during all 400 and 500 kPa pressure stimuli.
[b] Paired-samples t-test between frequency of occurrence during all 50 kPa stimuli and during all 400 and 500 kPa stimuli (frequency of occurrence of 50 kPa was multiplied by two in order to calculate this).

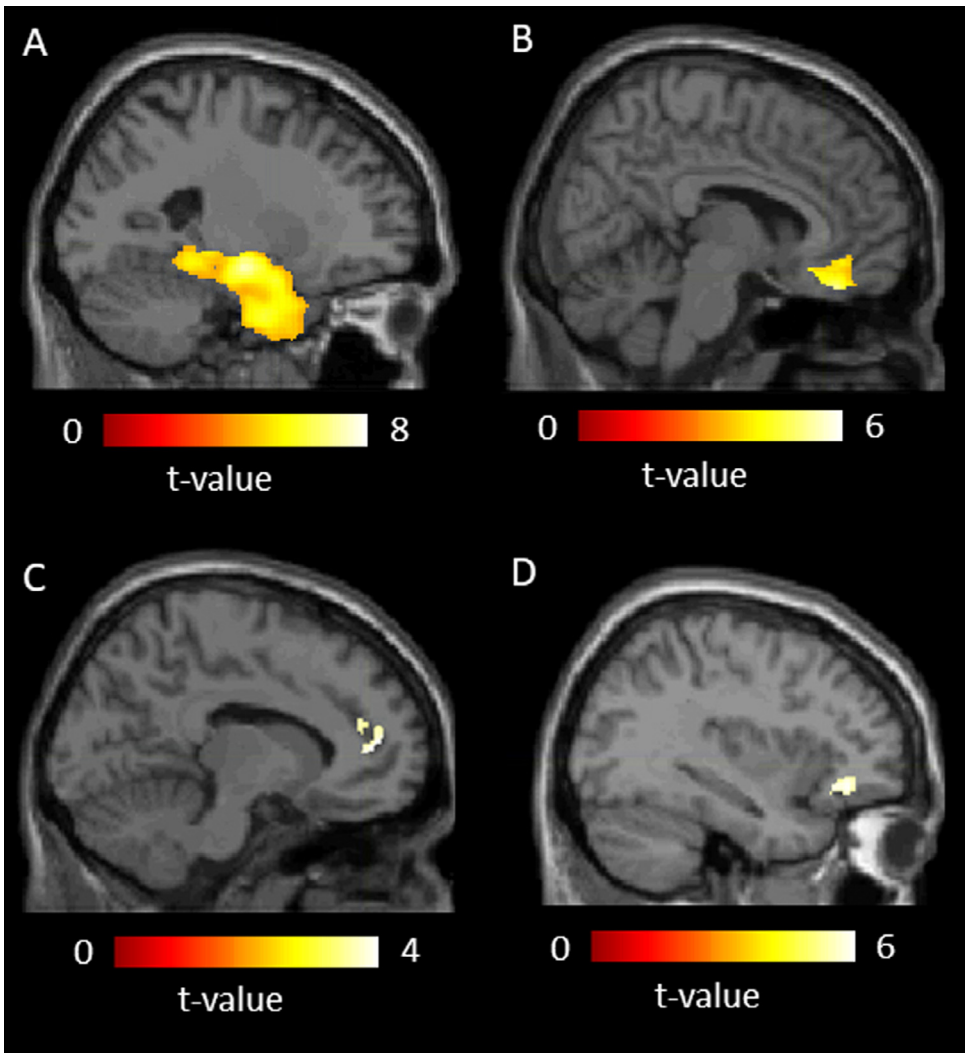

Fig. 2. Results of the voxel-based morphometry (VBM) analyses showing regions with gray matter volume loss in patients relative to controls. Results are presented at $p < 0.05$ FWE corrected including t-value maps. (A) Displays the results of the whole brain analysis, which shows a large significant area in the temporal lobe (sagittal view, x=-24). (B-D) Displays the results of the region-of-interest analyses, which shows the medial orbitofrontal cortex (x=8), anterior cingulate cortex (x=-11) and the lateral orbitofrontal cortex (x=-34). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

Table 5
Clusters of voxels that showed significantly less gray matter volume in patients compared to controls in a VBM analysis (FWE-corrected, $p < 0.05$)

Anatomical Region	MNI Peak Coordinate (x, y, z)	Peak *T* Value	Cluster Size (Number of Voxels)
Whole brain analysis			
Temporal lobe	-30, -12, -14	9.85	78501
Rostral prefrontal cortex	18, 65, 2	4.99	944
Posterior cingulate cortex	-2, -56, 29	4.64	3921
Supramarginal gyrus	-44, -47, 44	4.45	1060
Region-of-interest analysis			
Medial orbitofrontal cortex	-11, 35, 21	5.95	1150
Lateral orbitofrontal cortex	-32, 33, -9	3.72	256
Anterior cingulate cortex	-11, 50, 11	3.81	115
	12, 47, 8	3.55	35

FWE, family-wise error; MNI, Montreal Neurological Institute; VBM, voxel-based morphometry.

cline could be explained by the decrease in gray matter volume. Gray matter volume values were therefore extracted from the significant clusters resulting from the VBM analyses. The results of the mediation analyses are shown in Fig. 3.

Cognitive decline, measured by MMSE score, could significantly predict CPM-face (Fig. 3B-C, path c), which is in accordance with the results of the independent-samples t-test comparing CPM between the groups. This total effect was attenuated when controlling for gray matter volume specifically in the anterior cingulate cortex (ACC) and the medial orbitofrontal cortex (mOFC) (Fig. 3B-C, path c'). Gray matter volume in these areas could also significantly predict CPM-face when controlling for MMSE (Fig. 3B-C, path b).

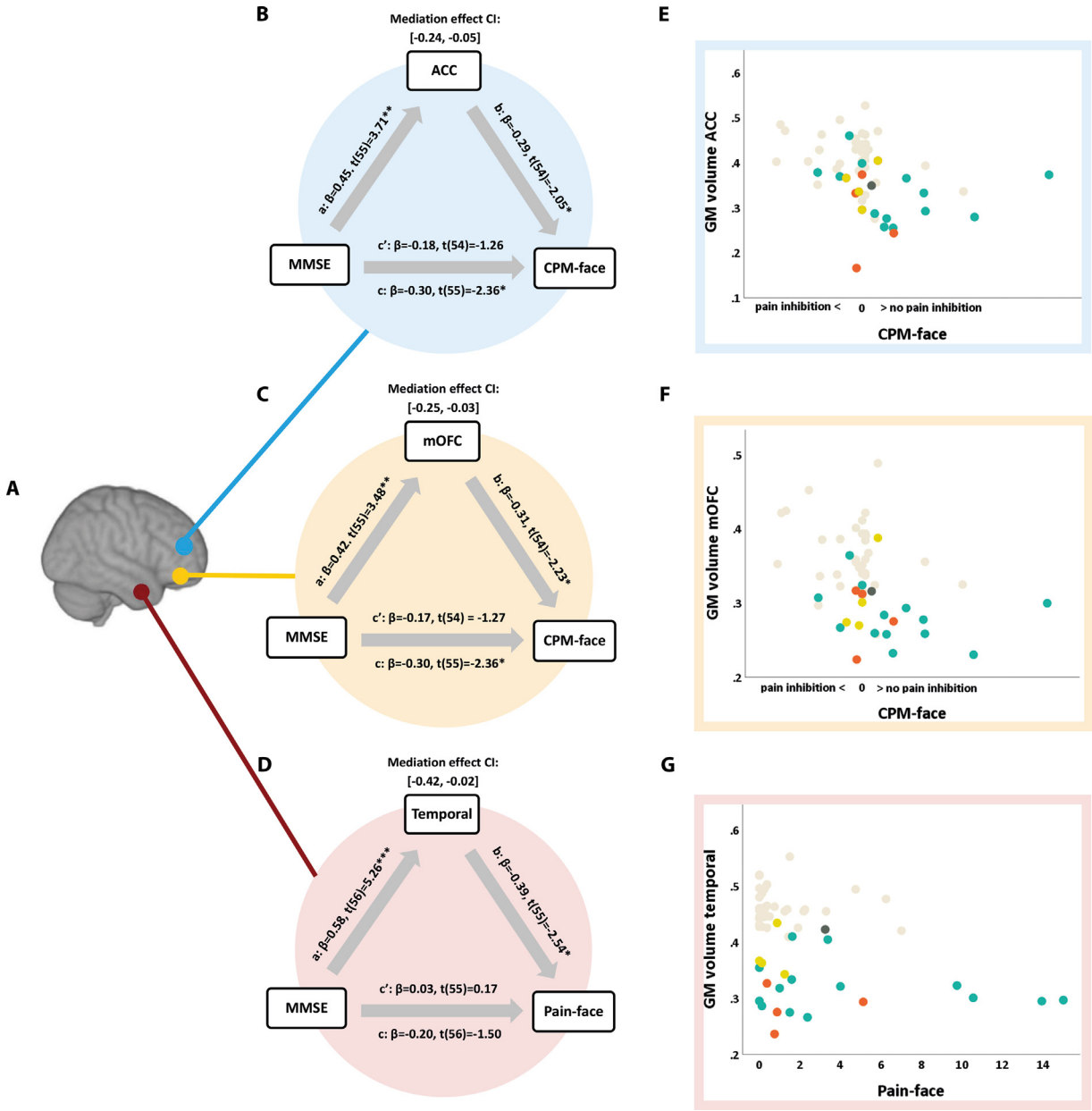

Fig. 3. Results of mediation analyses showing the mediating effect of gray matter volume on the relation between cognitive decline and pain responses measured by facial expression. (A) Schematic overview of the locations of the significant gray matter mediators. (B-D) Mediation diagrams showing the total effect of MMSE on pain (c), the direct effect of MMSE on pain when controlling for gray matter volume (c'), the effect of MMSE on gray matter volume (a) and the effect of gray matter volume on pain when controlling for MMSE (b). The significance of the mediation effect (path a*b) is shown using a 95% confidence interval. (E-G) Scatterplots of the relation between gray matter volume and pain coded by dementia subtype. ACC, anterior cingulate cortex; AD, Alzheimer's disease; CI, confidence interval; CPM, conditioned pain modulation; FTD, frontotemporal dementia; GM, gray matter; MCI, mild cognitive impairment; MMSE, mini-mental state examination; mOFC, medial orbitofrontal cortex; VD, vascular dementia. β; standardized regression coefficient, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Together, this indicates that the observed decrease in CPM-face associated with cognitive decline was indeed mediated by reduced gray matter volume in the ACC and mOFC. This mediation effect was significant for both areas based on the confidence intervals. Other significant gray matter clusters resulting from the VBM analyses did not show a mediation effect for CPM-face.

In contrast to CPM-face, pain-face could not significantly be predicted by MMSE (Fig. 3D, path c). However, because the independent-samples t-test did show a significant difference in pain-face between the groups, we still performed mediation analyses for this type of pain response. These analyses revealed that the (non-significant) effect of MMSE on pain-face was attenuated when controlling for gray matter volume specifically in the temporal cluster (Fig. 3D, path c'). Gray matter volume extracted from the temporal cluster could also significantly predict pain-face when controlling for MMSE (Fig. 3D, path b). This indicates that the increase in facial responses to pressure pain in cognitively impaired individuals was mediated by reduced gray matter volume in the temporal area. This mediation effect was significant based on the confidence interval. Other significant gray matter clusters resulting from the VBM analyses did not show a mediation effect for pain-face.

In Fig. 3E-G, the relation between gray matter volume and pain are shown in scatterplots coded by subtype.

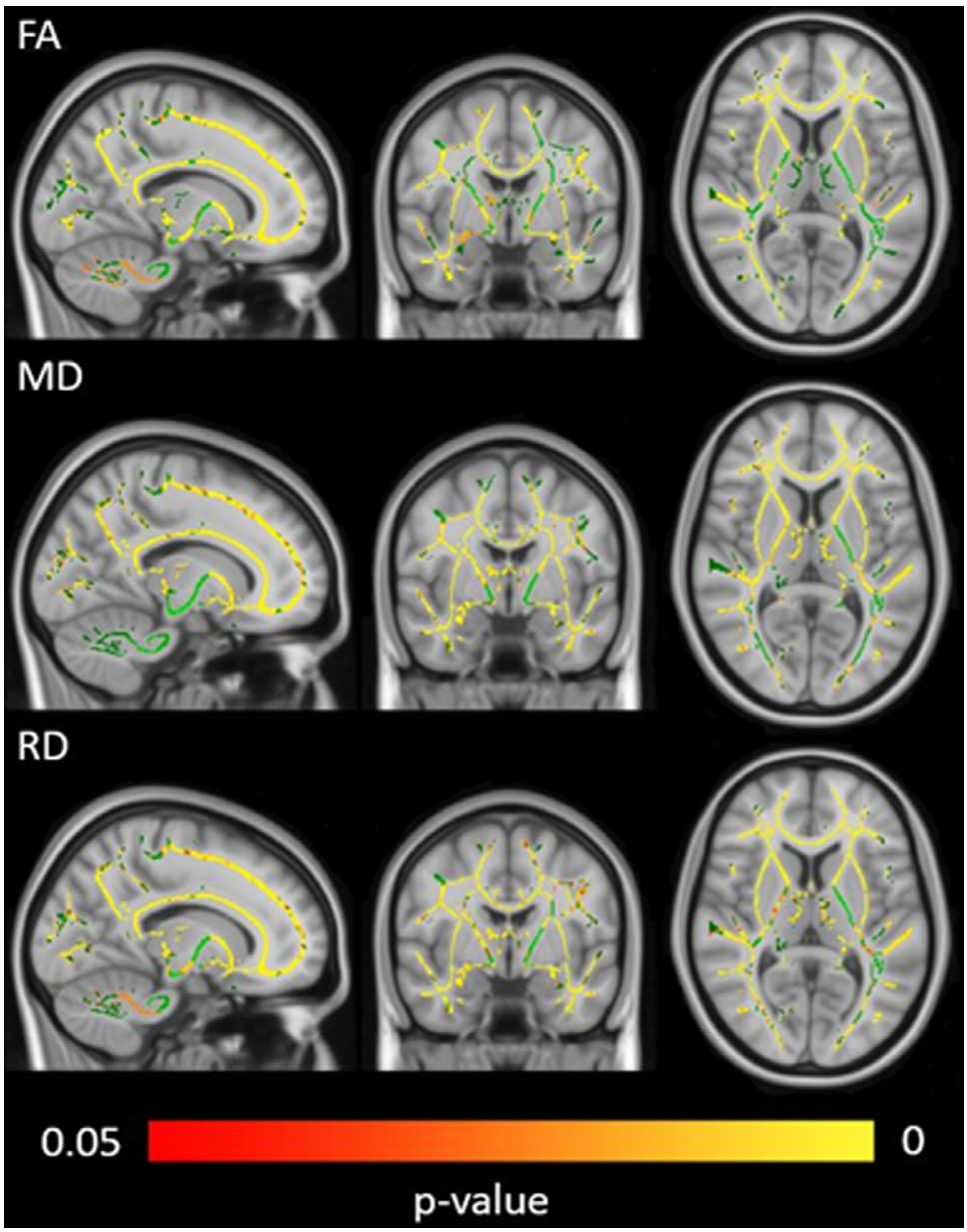

Fig. 4. Results of the white matter analysis showing widespread differences in FA, MD and RD between cognitively impaired individuals patients and controls. The significant results (yellow) are overlaid on top of the mean skeleton (green), obtained using the TBSS analysis. Reduced FA in patients relative to controls was observed in one large cluster of 75355 voxels covering almost the entire brain and one smaller cluster of 66 voxels in the cingulum. An increase in MD and RD in patients was observed in two large clusters of 80728 and 89654 voxels respectively. Results are TFCE corrected at a threshold of $p < 0.05$. Sagittal view (x=-14), coronal view (y=-4), axial view (z=7). FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; FWE, family-wise error; TBSS, tract-based spatial statistics; TFCE, threshold-free cluster enhancement. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

3.3. Influence of cognitive decline on white matter structure

The voxel-wise TBSS analysis revealed widespread differences in white matter structure between the groups. The group of cognitively impaired individuals showed a decrease in FA and an increase in MD and RD in white matter tracts throughout the entire brain, while no significant differences for AD were found. As can be seen in Fig. 4, the most widespread differences between the groups were found for RD. No white matter tracts showed an increase in FA or a decrease in MD, RD or AD in cognitively impaired individuals relative to cognitively healthy individuals.

3.3.1. Mediation analyses: Are white matter changes mediating the association between dementia-related cognitive decline and pain responsiveness?

Our original aim was to extract diffusivity measures from the white matter tracts that differed significantly between patients and controls and investigate whether these could mediate the relation between MMSE and pain responses (similar as we have done for gray matter). However, since dementia did not affect specific white matter tracts but rather the whole brain, we decided to focus on the white matter tracts close to the gray matter areas that showed a significant mediation effect (see 3.2.1).

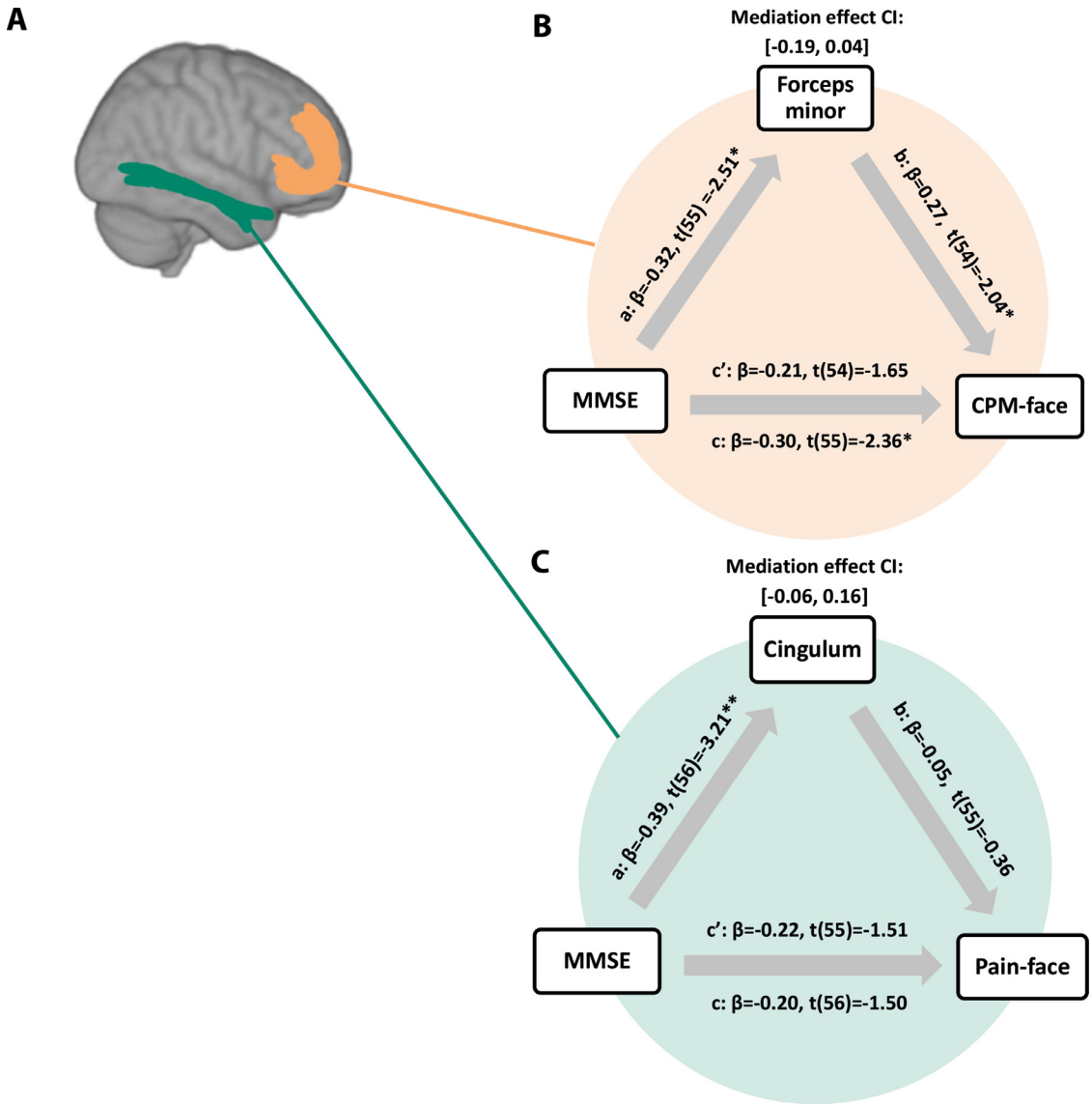

Fig. 5. Results of mediation analyses showing the mediating effect of white matter structure (radial diffusivity) on the relation between cognitive decline and pain responses measured by facial expression. (A) Schematic overview of the locations of the white matter tracts. (B-C) Depict the mediation diagrams showing the total effect of MMSE on pain (c), the direct effect of MMSE on pain when controlling for white matter structure (c'), the effect of MMSE on white matter structure (a) and the effect of white matter structure on pain when controlling for MMSE (b). The significance of the mediation effect (path a*b) is shown using a 95% confidence interval. CI, confidence interval; CPM, conditioned pain modulation; MMSE, mini-mental state examination. β; standardized regression coefficient, $^{*}p < 0.05$, $^{**}p < 0.01$.

With regard to CPM-face, we focused on the forceps minor, a tract close to the mOFC and ACC. Given that RD showed the most widespread differences, we extracted average RD from this tract using the John Hopkins University (JHU) white matter tractography atlas implemented in FSL. The total effect of MMSE on CPM-face was attenuated when controlling for RD (Fig. 5B, path c vs c'). RD of the forceps minor could also significantly predict CPM-face when controlling for MMSE (Fig. 5B, path b). This suggests that the observed decrease in CPM-face in cognitively impaired individuals might be mediated by white matter structure of the forceps minor. However, this mediation effect was not significant based on the confidence intervals.

With regard to pain-face, we extracted mean RD of the cingulum of the hippocampal part using the JHU white matter tractography atlas. This white matter tract runs through the temporal gray matter cluster (see 3.2.1). However, RD of this tract could not significantly predict pain-face when controlling for MMSE (Fig. 5C, path b). Thus, RD of the hippocampal part of the cingulum did not mediate the increased facial response to pressure pain in cognitively impaired individuals.

4. Discussion

4.1. Association of cognitive decline and pain responsiveness

In line with previous studies investigating subjective responses to experimental pain in individuals with dementia (Cole et al., 2006; Jensen-Dahm et al., 2014; Kunz et al., 2009), we could not demonstrate differences in subjective responses to pressure pain between cognitively healthy and cognitively impaired participants, despite using a cognitively less challenging rating scale. Similarly, we also could not demonstrate a significant group difference in CPM when pain responses were measured by self-report.

In contrast, facial responses to pain revealed significant group differences. Cognitively impaired individuals showed significantly increased pain-related facial responses to pressure pain stimuli compared to cognitively healthy individuals, which supports previous experimental studies investigating the facial expression of pain in dementia (Beach et al., 2016; Kunz et al., 2009, 2007; Lints-Martindale et al., 2007). Cognitively impaired individuals displayed the same types of facial movements during painful pressure stimuli as cognitively healthy individuals (Table 4) but the frequency and intensity of these facial movements were increased. This is in accordance with previous research that found that cognitive decline does not affect the type of facial response elicited during pain (Kunz et al., 2019).

The use of facial responses as a measure of pain also revealed significant group differences in CPM in our study. Cognitively impaired individuals showed decreased endogenous pain inhibition compared to cognitively healthy individuals. Facial responses in cognitively impaired individuals were even increased due to the application of a noxious conditioning stimulus. Previous studies repeatedly found reduced endogenous pain inhibition in healthy older individuals compared with healthy young individuals (Lautenbacher, 2012). The present study shows that endogenous pain inhibition measured via facial responses is even more reduced in older individuals with dementia-related cognitive impairments.

There might be several reasons why dementia-related cognitive impairment differentially affects subjective and facial responses to pain. Facial responses capture more autonomic behavior that is less subject to voluntary control (Hadjistavropoulos and Craig, 2002) and it might therefore be a more valid response than self-report because it does not depend on cognitive resources. Moreover, facial responses to pain have been shown to be governed by a prefrontal network (especially the medial PFC) that regulates the intensity of facial expression of pain and thus, functions as an inhibitory gate for facial expression (Karmann et al., 2016; Kunz et al., 2020, 2011). Due to the neural loss in prefrontal structures in cognitive impaired individuals, the function of this inhibitory gate might be reduced, rendering individuals with a dementia-related cognitive impairment more facially responsive to pain.

4.2. Association of cognitive decline and brain structure

Whole brain group comparisons of brain structure revealed a large area in the temporal lobe and smaller clusters in the frontal and parietal lobe that showed reduced gray matter volume in cognitively impaired individuals. This is a typical finding for dementia, especially for Alzheimer's disease (Burton et al., 2009; Karas et al., 2004). Given our hypothesis that endogenous pain inhibition might be affected in cognitively impaired individuals, additional region-of-interest analyses were performed within regions known to be involved in descending pain modulation (Bogdanov et al., 2015). These analyses revealed that cognitively impaired individuals also show reduced gray matter volume within several of these areas, namely the mOFC, lOFC and ACC. With regard to white matter, widespread differences throughout the brain were found between cognitively impaired individuals and cognitively healthy individuals, which corroborates earlier findings (Li et al., 2018; Palesi et al., 2018).

4.3. Mediating effect of structural brain changes on the relation between pain responses and cognitive decline

Increased facial responses to pressure pain: Although the independent-samples t-test revealed a significant increase in pain-related facial responses to pressure pain stimuli in cognitively impaired compared to cognitively healthy individuals, this increase does not seem to be gradually linked to the magnitude of cognitive decline in our sample, given that we found no significant correlation with the MMSE score. Given the lack of significant correlation, results of the mediation analyses for facial responses to pressure pain (pain-face) must be interpreted with caution. With regard to gray volume, there was a significant mediation effect for the temporal lobe, indicating that the increase in facial responses to pressure pain in cognitively impaired individuals was mediated by reduced gray matter volume in the temporal area. Again, these results should be interpreted with caution although the role of temporal lobe in pain processing has been demonstrated before. A recent meta-analysis found that a specific area of the temporal lobe, the medial temporal lobe, shows altered brain activity during pain, with increased activity during experimental pain stimulation and decreased activity in chronic pain patients compared to healthy individuals (Ayoub et al., 2019). The most reported subregion that showed abnormal activity was the hippocampus, which is known as a critical brain structure not only for memory formation (Bartsch and Wulff, 2015) but also for emotion regulation together with the amygdala, another medial temporal structure (Phelps, 2004; Simons et al., 2014). Although the temporal cluster of the present study covered more than only the medial temporal lobe, our observation may support the hypothesis that gray matter atrophy in the temporal lobe including the hippocampus might play some role in the elevated facial responses to pain in cognitively impaired individuals; possibly due to a lack of regulating the affective dimension of pain and its facial output.

Amplification of facial responses during the CPM paradigm: The observed decrease in CPM measured by facial expression in cognitively impaired individuals was found to be mediated by the reduction in gray matter volume in the frontal cortex, specifically in the mOFC and ACC. This was based on the findings that gray matter volume of these areas could significantly predict CPM measured by facial expression when controlling for MMSE and that the association between MMSE and CPM measured by facial expression was reduced when controlling for gray matter volume of these areas. This was not found for the other gray matter clusters. Continuing on this finding, we studied the mediating effect of white matter structure of the forceps minor, a tract close to the mOFC and ACC. Even though this mediation effect missed the set level of significance, the relation between MMSE and CPM measured by facial expression was reduced when controlling for the white matter structure of this tract, thus, pointing to a mediation effect and therefore corroborating the gray matter findings.

The mOFC and ACC clusters result from the VBM region-of-interest analyses based on areas known to be involved in descending pain modulation (Bogdanov et al., 2015). Thus, our finding that these structures indeed mediate the link between cognitive impairment and loss in endogenous pain inhibition (CPM facial expression) clearly suggests that a loss in frontal control seems to result in a loss in pain inhibitory functioning in cognitively impaired older individuals. Previous functional imaging studies repeatedly found that the ACC and mOFC are involved in pain modulation in cognitively healthy individuals. Changes in brain activity in these areas were observed during CPM (Bogdanov et al., 2015; Moont et al., 2011; Piche et al., 2009; Sprenger et al., 2011), but also during placebo analgesia (Petrovic and Ingvar, 2002; Wager et al., 2004) and cognitive-emotional pain modulation by distraction (Bantick et al., 2002; Petrovic et al., 2000; Rainville et al., 1999) and reward (Becker et al., 2017). Studies investigating the relation between brain structure and descending pain modulation are more scarce. One study found that a decrease in CPM was associated with a thicker cortex in the lateral orbitofrontal cortex in both healthy individuals as well as chronic

pain patients, but no such association was reported for the mOFC (Piché et al., 2013). Another study found that placebo analgesic responses in healthy individuals are associated with white matter structure of the ACC and the tracts connecting the ACC with the periaqueductal gray (Stein et al., 2012).

The findings of the present study indicate that a loss of gray matter in the mOFC and ACC as well as structural changes in the white matter tracts connecting these prefrontal areas are associated with deficits in endogenous pain inhibitory functioning in cognitively impaired individuals. This supports our hypothesis that neurodegeneration in brain structures involved in descending pain inhibition might contribute to altered pain responses in dementia-related cognitive impairments.

4.4. Limitations

The small sample size did not allow to investigate differences between dementia subtypes. The scatterplots coded by subtype in Fig. 3 give a first indication of the variance between different dementia subtypes. However, larger sample sizes, especially for patients with vascular dementia and frontotemporal dementia, are needed to really explore differences between dementia subtypes. Moreover, we only investigated individuals with mild cognitive impairment and mild forms of dementia, and thus, we cannot draw conclusions about more advanced forms of dementia. With regard to the facial expression of pain, an important question is whether this is a pain specific increase or just an unspecific increase in emotional arousal. Previous studies have shown that dementia patients mainly show an increase in pain-indicative facial responses in response to noxious stimuli and not an overall unspecific increase in pain-irrelevant facial responses, which suggest that indeed the pain experience is encoded in the elevated facial responses to noxious stimuli (Beach et al., 2016; Kunz et al., 2007). Another limitation refers to the fact, that patients and controls were not rigorously matched for education. Although education did not differ significantly between groups, there were more highly educated individuals in the control group, which might have slightly influenced the outcomes. Finally, a disadvantage of using VBM to assess gray matter volume in dementia is that local neurodegeneration can impact the accuracy of registration. While smoothing may help to account for this, it may have an impact on the results.

5. Conclusions

This study confirms previous findings of intensified pain processing in dementia-related cognitive impairment when pain is assessed using non-verbal responses; especially facial responses. These increased pain responses were mediated by dementia-related neurodegeneration, with different brain areas mediating different aspects of pain responsiveness. The observed increase in pain-related facial responses to pressure pain was mediated by reduced gray matter volume within the temporal lobe, while the observed decrease in endogenous pain inhibition assessed by facial responses was mediated by reduced gray matter volume within the mOFC and ACC. This latter finding suggests that a loss of pain inhibitory functioning caused by structural changes in prefrontal areas might be one of the underlying mechanisms responsible for amplified pain responses in individuals with a dementia-related cognitive impairment.

Disclosure statement

The authors report no conflicts of interest.

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Verification

We verify that the data contained in the manuscript being submitted have not been previously published, is not under publication elsewhere and will not be published elsewhere while under consideration at Neurobiology of Aging. We verify that the manuscript is approved by all authors.

CRediT authorship contribution statement

Steffie Bunk: Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. **Sytse Zuidema:** Resources, Writing – review & editing, Supervision. **Kathrin Koch:** Formal analysis, Writing – review & editing. **Stefan Lautenbacher:** Writing – review & editing. **Peter P. De Deyn:** Resources, Writing – review & editing. **Miriam Kunz:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization, Supervision, Funding acquisition.

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