Cross-sectional Study

Decreased Regional Grey Matter Volume in Women with Chronic Whiplash-Associated Disorders: Relationships with Cognitive Deficits and Disturbed Pain Processing

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Background: Patients with chronic whiplash-associated disorders (CWAD) are characterized by pain of traumatic origin, cognitive deficits, and central sensitization (CS). Previous neuroimaging studies revealed altered grey matter volume (GMV) in mild traumatic brain injury patients and chronic pain conditions also characterized by CS. It can therefore be hypothesized that GMV alterations also play a role in the persistent complaints of CWAD. However, brain alterations remain poorly investigated in these patients.

Objectives: This study examined regional GMV alterations in patients with CWAD compared to patients with non-traumatic chronic idiopathic neck pain (CINP), who normally do not show CS at a group level, and healthy controls. Additionally, in both patient groups, relationships between regional GMV and measures of cognition as well as pain processing were assessed.

Study Design: A cross-sectional case-control study.

Setting: This study was performed at the Department of Rehabilitation Sciences and Physiotherapy of Ghent University in cooperation with the Ghent Institute for Functional and Metabolic Imaging.

Methods: Ninety-three women (28 healthy controls, 34 CINP patients, and 31 CWAD patients) were enrolled. First, T1-weighted magnetic resonance images (MRIs) were acquired to examine GMV alterations in the brain regions involved in processing cognition and pain. Next, cognitive performance, pain cognitions, and CS symptoms were assessed. Finally, hyperalgesia and conditioned pain modulation efficacy were examined.

Results: Regional GMV of the right lateral orbitofrontal cortex, left supramarginal cortex, and left posterior cingulate cortex was decreased in CWAD patients compared to healthy controls ($P = 0.023$; $P = 0.012$; $P = 0.047$, respectively). Additionally, GMV of the right superior parietal cortex and left posterior cingulate cortex was decreased in CWAD patients compared to CINP patients ($P = 0.008$; $P = 0.035$, respectively). Decreased regional GMV correlated with worse cognitive performance, higher maladapted pain cognitions, CS symptoms, and hyperalgesia in CWAD patients ($r_s = -0.515$ to -0.657; $P < 0.01$). In CINP patients, decreased regional GMV correlated only with worse cognitive performance ($r_s = -0.499$ to -0.619; $P < 0.01$), and no GMV differences compared with the controls could be revealed.

Limitations: No conclusions about the causality of the observed relationships can be drawn.

Conclusions: These results provide the first evidence for reduced GMV in cortical regions involved in processing cognition and pain in patients with CWAD. Accordingly, it is recommended that therapy approaches for CWAD patients should address the brain and take into account neuroplasticity of the central nervous system (CNS).

Key words: Whiplash injuries, neck pain, magnetic resonance imaging, grey matter, cognitive dysfunction, pain catastrophizing, central sensitization

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Chronic neck pain is an enormous healthcare problem and one of the most prevalent musculoskeletal pain conditions worldwide (1,2). Furthermore, this pain condition is associated with unexplained symptoms, reduced quality of life, and poor therapy outcomes, thus representing an important source of disability (3-6). Chronic neck pain can be subdivided, on the basis of its etiology, into 3 categories: specific neck pain, trauma-induced neck pain, and idiopathic (non-traumatic) neck pain. This article focuses on chronic neck pain of a traumatic and an idiopathic non-traumatic nature.

Chronic whiplash-associated disorders (CWAD) are characterized by trauma-induced neck pain lasting more than 3 months resulting from a whiplash injury usually originating from a rear-end motor vehicle crash and caused by acceleration-deceleration forces acting on the neck, head, and torso (7,8). Chronic idiopathic non-traumatic neck pain (CINP) is characterized by neck pain lasting more than 3 months, without the presence of specific pathoanatomical causes.

Based on a paucity of studies comparing patients with CINP and CWAD, indications for different underlying mechanisms can be found (6,9). Cognitive deficits (10), maladapted pain cognitions (11), and central sensitization (CS) (12) have been demonstrated in patients with CWAD. While CS is rare in patients with CINP (13), cognitive deficits and maladapted pain cognitions are present (6,14), however to a significantly lesser extent compared to patients with CWAD (6,13).

Remarkably, although it can be hypothesized that structural brain alterations, including grey matter volume (GMV) alterations, play a role in the persistent and complex complaints of patients with CWAD, studies examining the presence of GM morphological alterations in patients with CWAD compared to patients with CINP are lacking.

Examining the influence of the traumatic acceleration-deceleration injury, the presence of GMV alterations, and exploring the relationships between regional GMV and measures of cognition, pain, and CS is important and could increase our insight into the underlying mechanisms of CINP and CWAD and their possible differences.

During the past decades, a wide range of magnetic resonance imaging (MRI) techniques explored structural brain alterations in vivo in patients with chronic pain (15-17). This neuroimaging research has shown structural neuroplasticity, which refers to the ability of the brain to reorganize itself and thereby adapt or maladapt its morphology (18). Subsequently, the role of maladapted brain alterations, including GMV alterations (16-18), has been gradually elucidated in the persistent pain and associated complaints of various chronic pain conditions (e.g., fibromyalgia (19), chronic low back pain (20), temporomandibular disorders (21), chronic pelvic pain syndrome (22)). Especially, GMV alterations in the regions involved in cognitive processing and sensory-discriminative, as well as affective and cognitive pain processing have been shown in various chronic pain syndromes, such as fibromyalgia and chronic low back pain, sharing the common pathophysiology of CS (19,20). For example, altered GM morphology in the cingulate cortex, insular cortex, orbitofrontal cortex, precuneus, amygdala, and thalamus has been found in these patients. Furthermore, alterations in GM morphology are denoted to be related with persistent pain and cognitive symptoms (19-24), which are commonly reported complaints in these chronic pain conditions (10,25-27). Moreover, these chronic pain patients often show maladapted pain cognitions including pain catastrophizing and hypervigilance (28), which seem to be associated with GM morphology (29).

Research has furthermore demonstrated changes in GMV in patients with mild traumatic brain injury (TBI) (30), where chronic pain is also a common sequel (31,32). In addition, similar to patients with chronic pain, mild TBI patients frequently report persistent cognitive complaints (33) accompanied with reduced cognitive performance (34-36).

Based on the outlined evidence, due to the trauma, cognitive deficits (10), maladapted pain cognitions (11), and CS (12) in CWAD patients, it could be hypothesized that alterations in regional GMV are present in patients with CWAD, but not or to a lesser degree in patients with CINP.

To address the current research gap, the first aim was to examine GMV alterations in the brain regions involved in cognitive processing and the regions implicated in sensory-discriminative, affective, and cognitive pain processing in patients with CINP and CWAD compared to healthy persons. The second aim was to investigate the relationships between regional GMV and cognitive deficits, pain intensity, pain cognitions, local hyperalgesia, and measures of CS in both of the chronic neck pain conditions.

Distinct regional GMV alterations and significant relationships with measures of cognition, pain, and CS were mainly hypothesized in patients with CWAD compared to CINP patients and healthy persons. Ac-

cordingly, important differences between patients with CINP and CWAD were hypothesized with a negative mediating role of the trauma in CWAD patients.

Methods

Study Design and Procedure

This cross-sectional case-control study took place at the Department of Rehabilitation Sciences and Physiotherapy of Ghent University in cooperation with the Ghent Institute for Functional and Metabolic Imaging. The study was performed from February 2014 to September 2015 and was carried out in accordance with the principles of the Declaration of Helsinki. The local Ethics Committee of the Ghent University Hospital (EC/2013/1053) approved the research protocol. All of the patients were thoroughly informed about the study procedures and signed an informed consent statement prior to study enrollment.

First, all of the patients completed a survey to acquire information on demographics and completed a series of questionnaires to obtain information on disability, pain intensity, pain cognitions, and CS symptoms (as described below). Subsequently, assessments to investigate cognitive deficits and pain processing were performed. On a separate test day (10 +/- 7 days apart), high-resolution T1-weighted MRIs and T2*-weighted images of the brain were acquired.

Participants

Ninety-three female patients (34 patients with CINP, 31 patients with CWAD, and 28 healthy, pain-free controls) were enrolled in the present study. In order to exclude the confounding factor of gender, we included only women, as research has demonstrated significant differences between men and women regarding GMV, pain sensitivity, and pain processing in both healthy persons and pain patients (37-41). All of the patients were Dutch native speakers and 18 – 65 years old. The patients were recruited by calls on social media and through advertisements on the Ghent University website, in health magazines, and in an information brochure of an association for patients with whiplash. Furthermore, informative flyers and posters were distributed in different medical institutes and associations in Flanders (various hospitals, physical therapist practices, and medical physician practices).

The inclusion criteria for patients with CINP and CWAD were persistent neck pain lasting more than 3 months (42) with a mean pain intensity of more than 3 of 10 on the numeric rating scale (NRS) during the preceding month. All chronic neck pain patients had to report mild/moderate to severe pain-related disability, established by a score of 10 or more of a maximum of 50 on the Neck Disability Index (43). Additionally, chronic neck pain patients had to report stability of pain medication intake for at least 4 weeks before study participation.

A specific inclusion criterion for patients with CINP was persistent idiopathic (non-traumatic) neck pain. Patients with CINP were excluded if they ever experienced a whiplash trauma or any other specific causes of neck pain, e.g., cervical hernia with clinical symptoms.

Patients with CWAD were included only if they had neck pain resulting from a motor vehicle crash or traumatic event and classifiable as WAD II A, B, or C on the modified (44) Quebec Task Force Scale (45). Patients with CWAD grades I, III (neurological signs), or IV (fracture or dislocation) on the modified Quebec Task Force Scale were excluded. Additionally, CWAD patients who lost consciousness as a result of the motor vehicle crash or traumatic event and patients who had suffered post-traumatic amnesia were excluded (46).

Healthy, pain-free women could participate only if they were pain-free on each test day (NRS score of < 2/10), had no history of neck-shoulder-arm pain for more than 8 consecutive days during the preceding year (with a pain intensity of 2 or more on the NRS), no medical consultation for neck-shoulder-arm pain during the preceding year, and no history of whiplash trauma. Additionally, healthy controls were included only if they had a score of less than 8 of 50 on the Neck Disability Index.

General exclusion criteria for all of the study groups were the presence of major depression, anxiety, psychiatric, neurologic, metabolic, cardiovascular, and inflammatory disorders, fibromyalgia, chronic fatigue syndrome, and a history of neck or shoulder girdle surgery. Furthermore, all patients completed the MRI safety checklist and patients who presented contraindications for MRI were excluded. Finally, brain microhemorrhages related to a traumatic event were excluded based on visual inspection of T2*-weighted brain images. To preclude confounding factors, all of the patients were asked to discontinue intake of non-opioid analgesics 48 hours before study participation. The continuation of intake of narcotic analgesics was allowed and the medication use of each patient was questioned in detail. In addition, the patients were asked to avoid heavy physical activities and to refrain

from consuming alcohol, caffeine, and nicotine on the day of testing.

Self-Reported Pain and Disability Measures

On each test day, the patients scored their current neck pain intensity on an 11-point verbal numeric rating scale (VNRS-11). The scores range from 0 to 10, with 0 reflecting 'no pain at all' and 10 reflecting 'the worst pain imaginable'. In addition, the patients reported the frequency of neck pain complaints in the number of days per week. The Dutch Neck Disability Index was used to investigate self-reported, pain-related disability levels (0 - 50) (43,47). Higher scores on the Neck Disability Index indicate higher levels of pain-related disability. The Dutch language version of the Neck Disability Index has been proven to be reliable and valid to assess self-reported disability in patients with chronic neck pain (48-50).

Cognitive Performance

Subjective Cognitive Performance

The patients completed the Dutch modified Perceived Deficits Questionnaire (mPDQ) to investigate subjective cognitive performance (0 - 72). This questionnaire investigates self-perceived cognitive problems in 4 different cognitive subdomains, i.e., prospective memory, retrospective memory, attention and concentration, and organization and planning, during the preceding 4 weeks. Symptoms are rated on a 5-point Likert scale from never (0) to almost always (4). Higher scores represent more self-perceived cognitive deficits. The validity and reliability of the English mPDQ have been demonstrated in patients with CWAD and healthy persons (51).

Objective Cognitive Performance

The Trail Making Test (TMT) was administered in order to objectively obtain an instrumented measure of cognitive performance (52). This test consists of 2 parts: trail A and trail B. The TMT part A requires mainly visuoperceptual and processing speed abilities, whereas TMT part B reflects working memory and task-switching ability. In trail A, the patient was instructed to draw lines connecting 25 numbers in ascending order as fast as possible, without lifting the pencil from the page. In trail B, the patient had to draw lines alternating between numbers and letters in ascending order (going from 1 to A, from A to 2, etc.). The goal of the TMT was to finish part A and part B as quickly and as accurate as possible. The researcher explained each part, and the patients completed a practice version containing fewer items. The time taken to complete each part of the test and a switch cost, calculated by subtracting the completion time of part A from part B, were used as outcome measures. The TMT (B-A) difference minimizes visuoperceptual and working memory demands, thus providing an indication of executive function (52). Higher scores on completion time and switching cost denote worse cognitive performance. The TMT has been demonstrated to be valid for assessing cognitive deficits (52).

Self-Reported and Experimental Measures of Pain Processing

Pain Catastrophizing

The Dutch Pain Catastrophizing Scale (PCS) (0 - 52) was used to evaluate 3 components of catastrophizing: rumination, magnification, and helplessness (53). Higher scores represent higher levels of pain catastrophizing. The Dutch PCS has sufficient test-retest reliability (54,55), and the factor structure is confirmed in chronic pain patients and healthy individuals (56).

Pain Hypervigilance

The Dutch Pain Vigilance and Awareness Questionnaire (PVAQ) was administered to assess the level of vigilance towards pain (0 - 80). Higher scores indicate a higher degree of pain vigilance and awareness. The PVAQ has been shown to be valid and reliable to measure pain vigilance in healthy individuals (57) and chronic pain patients (58).

Self-Reported Symptoms of CS

All of the patients completed the Dutch language version of the Central Sensitization Inventory (CSI). The CSI is a self-report screening instrument for the measurement of clinical symptoms of CS (0 - 100) in chronic pain populations (59,60). Higher CSI scores denote a higher degree of CS symptoms. The Dutch CSI has been shown to have good internal consistency, excellent test-retest reliability, and good discriminative power to differentiate between healthy persons and chronic pain patients (59). Neblett et al (61) determined that a CSI score of 40 of 100 best distinguished between a group of CS syndrome patients (CSI scores $\geq$ 40/100) and a group of non-CS syndrome patients (sensitivity = 81%, specificity = 75%).

Local and Distant Hyperalgesia

The pressure pain thresholds (PPTs) were measured unilaterally with a digital pressure algometer with a 1 cm^2 tip (Wagner Instruments, FDX, Greenwich, Connecticut), both at a symptomatic local region (middle trapezius muscle midway between the spinous process of C7 and the lateral border of the acromion) to evaluate local hyperalgesia and at a distant asymptomatic region (quadriceps muscle midway between the anterior superior iliac spine and the basis patellae) to evaluate widespread or distant hyperalgesia (62,63). The PPTs were assessed on the more painful side (64). In healthy women and when patients experienced the same amount of neck pain on both sides, PPTs were tested on the dominant handedness side. The PPTs were assessed in a randomized order (with Research Randomizer, https://randomizer.org). During the test procedure, the patients were seated and pressure was gradually increased at a rate of one kgf/s until the patients reported the first sensation of unpleasantness. The PPT was determined as the mean of 2 consecutive measurements, with 30 seconds in between. Decreased PPTs in the patient groups compared to the healthy controls at the middle trapezius muscle indicate local hyperalgesia, whereas decreased PPTs at the quadriceps muscle indicate distant hyperalgesia. This technique has been found to be reliable (65). In addition, the intratester reliability of PPT measurements has been reported to be satisfactory to good (intraclass correlation coefficient = 0.78 – 0.93) (66).

Efficacy of Conditioned Pain Modulation (CPM)

The presence of dysfunctional endogenous pain inhibition was investigated by evaluating the efficacy of CPM by applying a CPM paradigm. This paradigm relies on the "pain-inhibits-pain" mechanism, in which one noxious stimulus is used as a conditioning stimulus to induce a reduction in the perception of pain from another test stimulus (67). The conditioning stimulus for eliciting CPM was the cold pressor test. The assessment of PPTs was used as the test stimulus. For the conditioning stimulus, the contralateral hand (of the PPT side) (68) was first immersed in water maintained at room temperature (22°C) for one minute to standardize the hand temperature (69) before immersing this hand (up to the wrist) in a refrigerated bath (VersaCool™, Thermo Fisher Scientific, Newington, NH) with circulating cold water maintained at 12 ± 1°C (70). The patients were asked to keep their hand in the water bath for 2 minutes (69). Meanwhile, the PPT was re-evaluated at the quadriceps muscle, 45 seconds after immersing the hand (again twice with an interval of 30 seconds) (71). If the patients removed the hand from the water before the end of the 2 minutes, the measurement was registered as missing. For analysis of CPM efficacy, the mean PPT measured before the cold pressor test was subtracted from the mean PPT measured during the cold pressor test. Hence, a lower CPM value reflected less efficient endogenous pain inhibition. The intrasession and intraclass correlation coefficients for the cold pressor test have been shown to be excellent (0.85) (71).

MRI Data Acquisition

MRIs were acquired on a 3T Siemens Magnetom TrioTim MRI scanner (Siemens, Erlangen, Germany) equipped with a 32-channel matrix head coil, at the Ghent University Hospital. High-resolution T1-weighted images of the brain were acquired using a 3-dimensional magnetization prepared rapid acquisition gradient echo (MP-RAGE) (repetition time [TR] = 2250 ms, echo time [TE] = 4.18 ms, voxel size = 1 x 1 x 1 mm^3, FoV = 256 mm, flip angle = 9°, 176 slices, one mm slice thickness, and acquisition time = 5'14"). All T1-weighted anatomical scans were visually checked for overall quality and motion artifacts.

In addition, axial T2*-weighted brain images were acquired using a T2*-weighted acquisition gradient echo with TR = 839 ms, TE = 18.60 ms, voxel size = 1 x 0.7 x 3 mm^3, FoV = 230 mm, flip angle = 20°, 3 mm slice thickness, and acquisition time of 3'48". All T2*-weighted images were visually inspected by 2 expert neuroradiologists (KD, EG) to evaluate and exclude possible microhemorrhages related to a traumatic event.

MRI Data Processing

The high-resolution T1-weighted anatomical scans were analyzed utilizing the FreeSurfer v5.3.0 software package, which is documented and freely available (http://surfer.nmr.mgh.harvard.edu). The analyses were performed utilizing additional computing resources from the high-performance computing TIER1 cluster at the University of Ghent (www.ugent.be/hpc/). The FreeSurfer analysis suite was used to extract cortical and subcortical GMVs using an automated approach described in detail in prior publications (for an overview see Fischl 2012 (72)). Previous research has shown that this automated procedure yields accurate and reliable results (73). Briefly, image processing included: (1) removal of non-brain tissue using a hybrid watershed/surface deformation procedure (skull stripping) (74), (2)

automated Talairach transformations, (3) segmentation of the subcortical white matter and deep GM volumetric structures (73,75), (4) intensity normalization (76), (5) tessellation of the boundary between GM and white matter, automated topology correction (77,78), and (6) surface deformation along intensity gradients for optimal placement of the borders between GM, white matter, and cerebrospinal fluid (79-81). Automated parcellation of the cerebral cortex into units with respect to gyral and sulcul structures was performed within each hemisphere using the Desikan atlas (82). Furthermore, an automated segmentation (Aseg) of subcortical GM regions within each hemisphere was performed in FreeSurfer (73,75). Also, an estimate of the total intracranial volume was obtained for each patient.

Two independent researchers (IC, RDP) visually checked the data quality of the FreeSurfer processing output including the accuracy of skull stripping, registration, segmentation, and cortical surface reconstruction. Poor data quality, such as inclusion of dura in the pial surface after skull stripping and surface deformations, was revealed in 12 patients (healthy controls = 3, CINP = 3, and CWAD = 6). These datasets were excluded from all further analyses. All other data were of good quality and were used for further analyses.

Regions of Interest

GMV was extracted from regions of interest (ROIs). Cortical and subcortical regions, which have been reported to be involved in processing pain and cognition in previous studies, were selected as ROIs. Furthermore, ROIs were defined based on observations from previous studies in patients with chronic pain regarding GMV alterations (15,19,20,83) and regarding relationships between GMV alterations and measures of cognition and pain (15,84-86). The ROIs constituting pain and cognitive processing regions included 2 subcortical GM structures: amygdala and thalamus (see Fig. 1 for subcortical ROIs) and 12 cortical regions selected from the Desikan atlas (82): caudal anterior cingulate, rostral anterior cingulate, posterior cingulate, rostral middle frontal, medial orbitofrontal, lateral orbitofrontal, superior parietal, insula, postcentral, precuneus, pars orbitalis, and supramarginal cortex (see Fig. 1 for cortical ROIs). For each ROI, GMV was calculated for the right and left hemisphere separately. In addition, the volumes of total subcortical GM and total cortical GM were obtained.

Statistical Analyses

All statistical analyses were performed with SPSS Statistics 22.0 (IBM Corporation, Armonk, NY). First, the normality of variables was checked with the Shapiro-Wilk test and by visual evaluation of quantile-quantile plots and histograms. Additionally, the equality of variance was examined with the Levene's test. Only normally distributed data with an equality of variance were analyzed with parametric tests. Otherwise, non-parametric tests were applied.

The comparability of the study groups for age, cur-

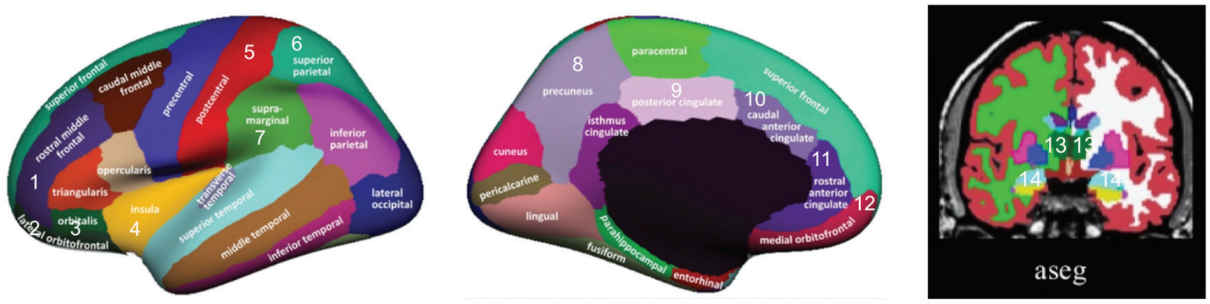

Fig. 1. *Lateral (left fig.) and medial (center fig.) view of the cortical parcellation of the Desikan atlas (82) displayed on an inflated template (https://surfer.nmr.mgh.harvard.edu). Numbered regions indicate the cortical regions of interest: 1) rostral middle frontal, 2) lateral orbitofrontal, 3) pars orbitalis, 4) insula, 5) postcentral, 6) superior parietal, 7) supramarginal, 8) precuneus, 9) posterior cingulate, 10) caudal anterior cingulate, 11) rostral anterior cingulate, and 12) medial orbitofrontal. View (right fig.) of the subcortical parcellation of the Aseg atlas (73) (https://surfer.nmr.mgh.harvard.edu). Numbered regions indicate the subcortical regions of interest: 13) thalamus and 14) amygdala.*

rent neck pain intensity, pain duration, and other demographics was explored with a one-way ANOVA with post-hoc pairwise comparisons using Bonferroni correction (family-wise error rate (FWER) < 0.05) or with the Kruskal-Wallis test with post-hoc pairwise comparisons using the Mann-Whitney U test. Differences measured with the Mann-Whitney U test were assumed to be significant only below the 0.017 (Bonferroni correction: 0.05/3) level. Categorical data were analyzed with the Fisher's exact test.

Subsequently, differences between the study groups regarding cognitive performance and pain processing were explored using one-way ANOVA (post-hoc pairwise comparisons using Bonferroni correction, FWER < 0.05) or the Kruskal-Wallis test (post-hoc pairwise comparisons using the Mann-Whitney U test, $P < 0.017$). An analysis of covariance (ANCOVA) model, controlling for the potentially confounding factor of age, was used to determine significant group differences in GMV of the selected ROIs and total subcortical and cortical GMV (post-hoc pairwise comparisons using Bonferroni correction, FWER < 0.05).

Finally, correlations among measures of cognition and pain on one hand and regional GMV on the other hand in both chronic neck pain conditions were investigated with group-specific Spearman correlation analyses. To correct for multiple comparisons, we deemed only Spearman correlations below the 0.01 level (2-tailed) to be significant. Correlation coefficients were deemed low between 0.30 to 0.50, moderate between 0.50 to 0.70, high between 0.70 to 0.90, and very high between 0.90 to 1.00 (87).

Results

Differences Between Patients with Idiopathic and Traumatic Chronic Neck Pain Compared to Healthy Controls

Demographic Characteristics and Self-Reported Pain and Disability Measures

The results of demographic characteristics and self-reported pain and disability measures of 81 women (25 healthy controls, 31 patients with CINP, and 25 patients with CWAD) are shown in Table 1. All of the study groups were comparable in age, body height, body weight, body mass index, education level, smoking status, menstrual phase, and handedness ($P > 0.05$). Furthermore, both of the groups with chronic neck pain were comparable in medication use, neck pain duration, and frequency of neck pain complaints per week ($P > 0.05$). Patients with CWAD reported significantly higher current neck pain intensity on the clinical and MRI test day and significantly more pain-related disability than patients with CINP ($P < 0.01$).

Ninety-one percent of all patients were right-handed. This is a representative sample regarding handedness because approximately 10 percent of the general population is ambidextrous or left-handed (88). The ANCOVA, with age as the covariate and handedness as the fixed-factor, revealed no significant main effect of handedness on total and regional GMV. Therefore, the GMV results of the left- and right-handed women were analyzed together.

Cognitive Performance

Subjective Cognitive Performance

Compared with the healthy controls, patients with CINP ($P = 0.009$) and patients with CWAD ($P < 0.001$) reported more self-perceived cognitive deficits, as presented in Table 1. Moreover, CWAD patients reported more self-perceived cognitive deficits compared to patients with CINP ($P = 0.001$).

Objective Cognitive Performance

The time needed to perform TMT part A ($P = 0.002$) and TMT part B ($P = 0.004$) was significantly longer in the CWAD group compared to the healthy control group, denoting worse objective cognitive performance in patients with CWAD (Table 1). In addition, the time needed to perform TMT part A ($P = 0.003$) and TMT part B ($P = 0.009$) was significantly longer in CWAD patients compared to CINP patients. Despite the differences in completion time, no significant group differences were revealed for executive control or switching cost (TMT (B-A) difference), (P's > 0.05).

Self-Reported and Experimental Measures of Pain Processing

Pain Catastrophizing and Pain Hypervigilance

As shown in Table 1, maladapted pain cognitions, including pain catastrophizing and hypervigilance, were significantly higher in patients with CWAD compared to healthy women ($P = 0.003$; $P = 0.035$, respectively). No significant differences between CINP patients and healthy controls were found regarding pain catastrophizing and pain hypervigilance ($P > 0.05$).

Table 1. *Demographic characteristics, self-reported pain and disability measures, maladaptive pain cognitions, self-reported symptoms of CS, subjective and objective cognitive performance, local and distant hyperalgesia, and conditioned pain modulation efficacy.*

			Mean	Median	SD	Range (min-max)	IQR	Test Statistic (*P*-Value)	*P*-Value Post-Hoc
Demographic Characteristics	Age (yrs)[a]	**HCON**	30.32	24.00	13.20	18.00 – 62.00	22.50 – 36.50	5.393 (0.067)	N/A
		CINP	34.93	34.00	10.85	18.00 – 54.00	26.00 – 45.00		
		CWAD	35.32	35.00	10.83	21.00 – 58.00	25.00 – 43.50		
	Body Height (cm)[b]	**HCON**	167.16	167.00	6.01	155.00 – 178.00	163.00 – 170.00	0.044 (0.957)	N/A
		CINP	166.76	168.00	5.28	157.00 – 175.00	163.00 – 170.50		
		CWAD	167.12	166.00	5.38	155.00 – 176.00	163.50 – 172.00		
	Body Weight (kg)[a]	**HCON**	60.87	59.00	7.29	51.00 – 81.00	55.35 – 65.00	1.500 (0.472)	N/A
		CINP	63.38	60.50	9.02	50.00 – 86.00	56.75 – 69.25		
		CWAD	62.02	60.00	12.67	48.00 – 95.00	51.00 – 67.50		
	Body Mass Index (kg/m2)[a,†]	**HCON**	21.76	21.80	2.07	18.07 – 26.75	20.45 – 23.06	1.742 (0.418)	N/A
		CINP	22.64	22.74	2.68	18.65 – 29.07	20.31 – 24.45		
		CWAD	22.17	21.14	4.18	16.65 – 32.05	19.14 – 23.59		
			Frequencies						
	Education Level n (%)[c] No degree; lower second.; higher second.; higher edu.	**HCON**	0 (0); 1 (4); 6 (24); 18 (72)					0.782 (0.991)	N/A
		CINP	0 (0); 2 (6.5); 7 (22.6); 20 (64.5)						
		CWAD	0 (0); 1 (4); 5 (20); 19 (76)						
	Smoker n (%)[c] Smoker; former smoker; non-smoker	**HCON**	1 (4); 3 (12); 21 (84)					4.801 (0.299)	N/A
		CINP	1 (3.2); 9 (29); 18 (58.1)						
		CWAD	3 (12); 6 (24); 16 (64)						
	Menstrual Phase Clinical Test Day n (%)[c] Follicular phase (day one to 13); ovulation phase (day 14); luteal phase (day 15 to 28); peri menopause; post-menopause; no menses (intrauterine device, taking pill ceaseless)	**HCON**	14 (56); 2 (8); 4 (16); 1 (4); 2 (8); 1 (4)					10.374 (0.344)	N/A
		CINP	16 (51.6); 1 (3.2); 6 (19.4); 1 (3.2); 4 (12.9); 1 (3.2)						
		CWAD	8 (33.3); 0 (0); 9 (37.5); 0 (0); 3 (12.5); 4 (16.7)						
	Handedness n (%)[c] (LH; RH)	**HCON**	2 (8) ; 23 (92)					0.691 (0.884)	N/A
		CINP	2 (6.5); 29 (93.5)						
		CWAD	3 (12) ; 22 (88)						
Demographic Characteristics: Medication Use	Analgesics - Antipyretics n (%)[c]	**HCON**	0 (0)					2.970 (0.158)	N/A
		CINP	3 (9.7)						
		CWAD	7 (28)						
	Narcotic Analgesics n (%)[c]	**HCON**	0 (0)					1.222 (0.455)	N/A
		CINP	0 (0)						
		CWAD	1 (4)						
	Benzodiazepines n (%)[c]	**HCON**	0 (0)					3.897 (0.082)	N/A
		CINP	1 (3.20)						
		CWAD	5 (20)						
	Antidepressants n (%)[c]	**HCON**	0 (0)					0.849 (1.000)	N/A
		CINP	3 (9.70)						
		CWAD	1 (4)						

Table 1 (cont.). *Demographic characteristics, self-reported pain and disability measures, maladaptive pain cognitions, self-reported symptoms of CS, subjective and objective cognitive performance, local and distant hyperalgesia, and conditioned pain modulation efficacy.*

			Mean	Median	SD	Range (min-max)	IQR	Test Statistic (*P*-Value)	*P*-Value Post-Hoc
Self-Reported Pain Measures	Neck Pain Duration (mos)[a]	**HCON**	N/A	N/A	N/A	N/A	N/A	0.076 (0.783)	N/A
		CINP	92.96	60.00	88.21	4.00 – 30.00	24.00 – 138.00		
		CWAD	86.87	51.50	96.13	6.00 – 44.00	26.25 – 115.00		
	Days/wk Neck Pain[a]	**HCON**	N/A	N/A	N/A	N/A	N/A	3.048 (0.081)	N/A
		CINP	5.14	5.00	1.61	3.00 – 7.00	4.00 – 7.00		
		CWAD	5.95	7.00	1.70	2.00 – 7.00	5.00 – 7.00		
	Current Neck Pain Intensity (VNRS/10)_C[a,†]	**HCON**	0.08	0.08	0.28	0.00 – 1.00	-0.03 – 0.19	44.391 (< 0.001)	< 0.001[d] < 0.001[e] < 0.011[f]
		CINP	3.85	3.85	2.57	0.00 – 8.00	2.91 – 4.80		
		CWAD	5.76	5.76	2.65	0.00 – 10.00	4.67 – 6.85		
	Current Neck Pain Intensity (VNRS/10)_M[a,†]	**HCON**	0.00	0.00	0.00	0.00 – 0.00	0.00 – 0.00	72.467 (< 0.001)	< 0.001[d] < 0.001[e] < 0.001[f]
		CINP	3.43	3.43	1.98	0.00 – 7.00	2.71 – 4.16		
		CWAD	5.98	5.98	2.28	1.00 – 10.00	5.04 – 6.92		
Self-Reported Disability	Neck Disability Index (/50)[a,†]	**HCON**	2.76	2.00	1.61	1.00 – 6.00	1.00 – 4.00	54.439 (< 0.001)	< 0.001[d] < 0.001[e] 0.001[f]
		CINP	16.36	16.00	5.03	10.00 – 27.00	12.00 – 20.50		
		CWAD	23.04	23.00	6.93	10.00 – 37.00	18.00 – 27.50		
Subjective Cognitive Performance	mPDQ Total (/72)[a,†]	**HCON**	11.52	10.00	7.00	1.00 – 25.00	6.00 – 16.00	26.448 (< 0.001)	0.009[d] < 0.001[e] 0.001[f]
		CINP	18.85	14.00	10.34	5.00 – 44.00	11.00 – 22.00		
		CWAD	31.83	28.50	14.61	6.00 – 57.00	19.00 – 46.50		
Objective Cognitive Performance (TMT)	TMT Part A (sec)[a,†]	**HCON**	19.11	18.76	3.83	12.28 – 29.75	16.22 – 21.83	12.757 (0.002)	0.586[d] 0.002[e] 0.003[f]
		CINP	19.80	19.37	4.29	11.56 – 30.13	16.86 – 22.41		
		CWAD	29.00	27.09	14.27	15.06 – 81.00	18.95 – 31.82		
	TMT Part B (sec)[a,†]	**HCON**	41.86	34.37	24.02	21.44 – 128.00	27.86 – 45.89	10.747 (0.005)	0.317[d] 0.004[e] 0.009[f]
		CINP	42.73	37.00	23.38	26.6 – 148.00	31.05 – 44.36		
		CWAD	66.02	44.83	48.62	27.93 – 251.00	37.13 – 79.50		
	TMT (B-A)[a,†]	**HCON**	22.75	16.46	21.60	2.25 – 98.25	11.64 – 24.61	2.333 (0.311)	N/A
		CINP	22.93	17.83	21.09	7.08 – 121.02	13.78 – 24.07		
		CWAD	37.02	20.93	37.83	5.85 – 170.00	13.28 – 57.65		
Maladaptive Pain Cognitions	Pain Catastrophizing (/52)[b]	**HCON**	9.76	10.00	8.61	0.00 – 30.00	1.00 – 18.00	9.740 (0.004)	0.308[d] 0.003[e] 0.166[f]
		CINP	13.65	13.00	7.19	1.00 – 26.00	6.00 – 19.50		
		CWAD	18.24	19.00	10.09	0.00 – 37.00	10.00 – 27.50		
	Pain Hypervigilance (/80)[b]	**HCON**	30.24	32.00	10.88	10.00 – 55.00	20.50 – 39.00	6.560 (0.026)	0.096[d] 0.035[e] 1.000[f]
		CINP	36.97	37.00	12.36	16.00 – 70.00	29.50 – 46.00		
		CWAD	38.48	38.00	10.28	16.00 – 56.00	30.00 – 46.50		
Self-Reported Symptoms of CS	CS Inventory (/100)[a,†]	**HCON**	20.25	20.00	6.42	9.00 – 35.00	16.00 – 23.00	44.731 (< 0.001)	< 0.001[d] < 0.001[e] 0.005[f]
		CINP	40.48	40.00	10.02	22.00 – 68.00	35.00 – 47.50		
		CWAD	49.33	48.50	13.82	13.00 – 67.00	41.00 – 63.25		
Local HA	PPT Trapezius (kgf)[a]	**HCON**	4.42	3.69	1.90	1.86 – 9.81	3.27 – 5.75	12.295 (0.002)	0.009[d] 0.001[e] 0.299[f]
		CINP	3.24	2.76	1.69	1.18 – 7.43	2.01 – 4.04		
		CWAD	2.81	2.46	2.01	0.13 – 9.30	1.68 – 3.41		
Distant HA	PPT Quadriceps (kgf)[b]	**HCON**	4.95	4,38	1.57	2.94 – 8.40	3.71 – 6.16	4.768 (0.011)	0.262[d] 0.008[e] 0.401[f]
		CINP	4.09	3.47	2.03	1.45 – 9.72	2.54 – 5.68		
		CWAD	3.34	3.15	1.87	0.30 – 7.72	1.95 – 4.74		

Table 1 (cont.). *Demographic characteristics, self-reported pain and disability measures, maladaptive pain cognitions, self-reported symptoms of CS, subjective and objective cognitive performance, local and distant hyperalgesia, and conditioned pain modulation efficacy.*

			Mean	Median	SD	Range (min-max)	IQR	Test Statistic (*P*-Value)	*P*-Value Post-Hoc
CPM Efficacy	CPM Quadriceps (PPT quadriceps during CPT minus PPT quadriceps before CPT)[b]	**HCON**	1.19	1.31	0.70	-0.14 – 3.00	0.68 – 1.51	4.978 (0.010)	1.000[d] 0.010[e] 0.054[f]
		CINP	1.04	0.90	1.02	-0.59 – 3.29	0.41 – 1.66		
		CWAD	0.45	0.37	0.68	-0.75 – 1.87	-0.08 – 1.02		

The distribution of the continuous data within each group was assessed by histograms, QQ-plots, and the Shapiro-Wilk test.
[a]Data which were not normally distributed, and subsequently group differences were analyzed using the Kruskal-Wallis test, and for post-hoc pairwise comparisons the Mann-Whitney U test. Shapiro-Wilk test $P < 0.05$ and visual inspection of the QQ-plot and histogram within each group provided information that the data were not normally distributed. To correct for multiple comparisons, differences measured with the Mann-Whitney U test were only deemed significant below the 0.017 level (Bonferonni correction: 0.05/3). [b]Data which were assumed to be normally distributed and variances were equally distributed across groups were analyzed with one-way ANOVA (F-test) and post-hoc pairwise comparisons were applied using Bonferroni correction (**P** < 0.05). [c]Categorical data were analyzed by performing the Fisher's exact test. Significant differences were presented in bold. †Variances were not equally distributed across the groups, Levene's test $P < 0.05$, [d]*P*-value for significant differences between CON-CINP, [e]*P*-value for significant differences between CON-CWAD, [f]*P*-value for significant differences between CINP-CWAD. There were 3 absences (1 HCON, 2 CINP) for the menstrual phase. Abbreviations: CON = healthy, pain-free controls, CWAD = chronic whiplash-associated disorders, CINP = chronic idiopathic neck pain, VNRS = verbal numeric rating scale, SF-36 = Short Form Health Survey, No degr = no degree, Lower second = lower secondary, Higher second = higher secondary, Higher edu = higher education, HA = hyperalgesia, CPM = conditioned pain modulation, CPT = cold pressor test, mPDQ = modified perceived deficits questionnaire, TMT = trail making test, CS = central sensitization, kgf = kilogram force, PPT = pressure pain thresholds, VNRS = verbal numeric rating scale, IQR = interquartile range. Data of 81 patients were analyzed (25 healthy controls, 31 CINP patients, and 25 CWAD patients).

Self-Reported CS Symptoms

Both of the patient groups reported significantly more self-perceived CS symptoms compared to healthy pain-free women ($P < 0.001$) (Table 1). Moreover, patients with CWAD experienced significantly more CS symptoms compared to patients with CINP ($P = 0.005$).

Local and Distant Hyperalgesia

Decreased PPTs were demonstrated at the middle trapezius muscle and quadriceps muscle in patients with CWAD ($P = 0.001$, $P = 0.008$, respectively) but were found only at the middle trapezius muscle in patients with CINP, relative to the results for healthy women ($P = 0.009$) (Table 1).

Efficacy of Conditioned Pain Modulation

The CPM value measured at the quadriceps muscle was significantly lower in patients with CWAD compared to healthy women ($P = 0.010$), as presented in Table 1.

Total Cortical and Subcortical GMV

As shown in supplementary Table A, the ANCOVA with age as the covariate revealed no significant differences between all of the study groups for total intracranial volume ($P = 0.109$), total cortical GMV ($P = 0.198$), and total subcortical GMV ($P = 0.510$). Therefore, we decided not to include these metrics in further analyses.

Regional-Based GMV

The significant results of the ANCOVA with age as the covariate, investigating the differences in GMV of pain and cognitive processing regions between patients with CINP and CWAD and healthy controls, are presented in Fig. 2 and supplementary Table A. The non-significant ANCOVA results for GMV of the ROIs are shown in supplementary Table B.

The ANCOVA revealed decreased GMV in the left posterior cingulate cortex ($P = 0.047$), the right lateral orbitofrontal cortex ($P = 0.023$), and the left supramarginal cortex ($P = 0.012$) in patients with CWAD compared to healthy controls (Bonferroni-adjusted *P*-values). Furthermore, decreased GMV in the left posterior cingulate cortex ($P = 0.035$) and the right superior parietal cortex ($P = 0.008$) in CWAD patients compared to CINP patients was demonstrated with the ANCOVA (Bonferroni-adjusted *P*-values). No significant differences in regional GMV were found between patients with CINP and healthy women (*P*'s > 0.05). In addition, no significant subcortical GMV differences were found in the amygdala and thalamus between all of the study groups ($P > 0.05$).

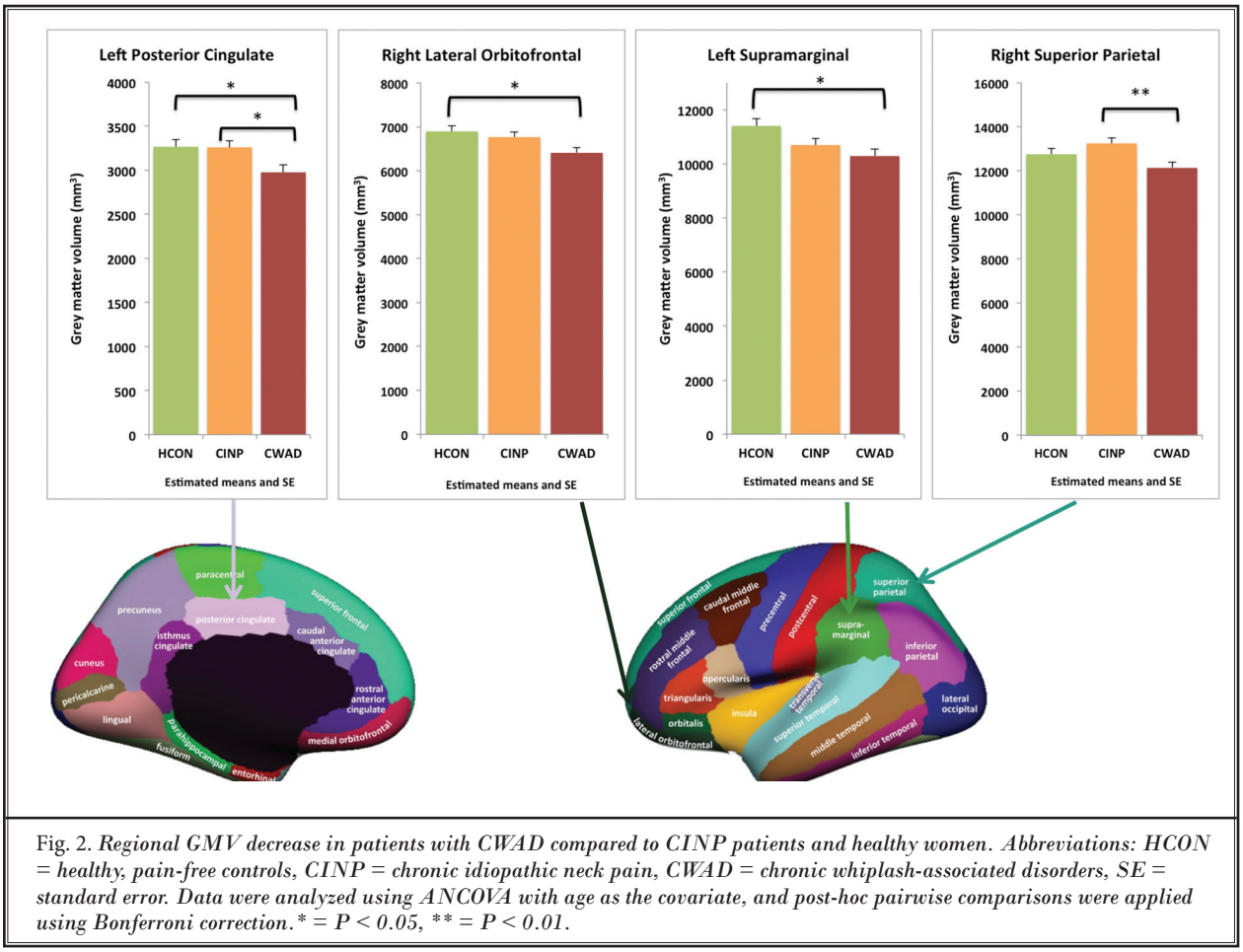

Fig. 2. *Regional GMV decrease in patients with CWAD compared to CINP patients and healthy women. Abbreviations: HCON = healthy, pain-free controls, CINP = chronic idiopathic neck pain, CWAD = chronic whiplash-associated disorders, SE = standard error. Data were analyzed using ANCOVA with age as the covariate, and post-hoc pairwise comparisons were applied using Bonferroni correction.* * = $P < 0.05$, ** = $P < 0.01$.

Relationships Between Regional GMV and Cognitive Deficits, Pain Intensity, and Pain Processing in Patients with Idiopathic and Traumatic Chronic Neck Pain

CINP

The results of the Spearman correlation (r_s) analyses between GMV of regions involved in pain and cognitive processing and cognitive deficits, pain intensity, and pain processing in patients with CINP are shown in Tables 2a and 2b.

In the CINP group, only 4 significant correlations were revealed. A moderate relationship was found between increased severity of self-reported cognitive deficits and decreased GMV of the left rostral anterior cingulate cortex (r_s = -.499; P = 0.008). Furthermore, lower visuoperceptual abilities were moderately correlated with decreased GMV of the right thalamus (r_s = -0.529; P = 0.003). Also, decreased task-switching capacity was moderately correlated with decreased GMV of the left medial orbitofrontal cortex (r_s = -.565; P = 0.001). A moderate relationship was observed between decreased GMV of the left medial orbitofrontal cortex and worse executive control (r_s = -.619; $P < 0.001$).

No significant correlations among pain intensity, maladapted pain cognitions, CS symptoms, experimental measures of pain processing, and regional GMV were demonstrated ($P > 0.01$).

CWAD

The results of the Spearman correlation (r_s) analyses between GMV of regions involved in pain and cognitive processing and cognitive deficits, pain intensity, and pain processing in patients with CWAD are displayed in Tables 3a and 3b.

In the CWAD group, more robust correlations were found compared to the CINP group. Moderate correlations were revealed between increased severity

Table 2a. *Spearman correlations between regional cortical and subcortical GMV (LH) and self-reported and experimental measures of pain and cognition in patients with CINP.*

	Caudal ACC	Rostral ACC	PCC	Rostral Middle Frontal	Medial OBF	Lateral OBF	Superior Parietal	Insula	Postcentral	Precuneus	Pars Orbitalis	Supra-Marginal	Amygdala	Thalamus
CINP (n = 31)														
Self-Perceived Cognitive Performance (mPDQ)														
Total Score	-0.378	**-0.499**	-0.356	-0.201	-0.084	-0.177	-0.100	-0.335	-0.171	-0.067	-0.066	-0.179	0.006	-0.017
	0.052	*0.008*	*0.068*	*0.315*	*0.678*	*0.377*	*0.619*	*0.088*	*0.394*	*0.739*	*0.745*	*0.372*	*0.978*	*0.932*
Objective Cognitive Performance (TMT)														
Part A	-0.229	-0.208	-0.307	-0.196	-0.293	-0.269	0.030	-0.398	-0.005	0.044	-0.105	-0.337	0.092	-0.120
	0.233	*0.279*	*0.105*	*0.309*	*0.123*	*0.158*	*0.879*	*0.033*	*0.98*	*0.819*	*0.588*	*0.073*	*0.636*	*0.536*
Part B	-0.044	-0.078	-0.334	-0.324	**-0.565**	-0.299	0.158	-0.385	-0.178	0.041	-0.290	-0.38	-0.037	-0.009
	0.821	*0.686*	*0.077*	*0.086*	*0.001*	*0.116*	*0.414*	*0.039*	*0.355*	*0.834*	*0.127*	*0.042*	*0.847*	*0.964*
B – A	-0.041	-0.088	-0.252	-0.369	**-0.619**	-0.250	0.145	-0.366	-0.335	-0.004	-0.308	-0.344	-0.083	-0.010
	0.833	*0.651*	*0.188*	*0.049*	*<0.001*	*0.190*	*0.454*	*0.051*	*0.075*	*0.983*	*0.104*	*0.068*	*0.668*	*0.961*
Self-Reported Pain Measures														
Neck Pain Intensity_M	-0.217	0.120	0.014	0.036	-0.066	0.181	-0.001	0.092	0.227	-0.140	0.108	-0.256	-0.042	0.293
	0.241	*0.520*	*0.939*	*0.847*	*0.723*	*0.329*	*0.994*	*0.623*	*0.219*	*0.453*	*0.564*	*0.164*	*0.823*	*0.109*
Maladaptive Pain Cognitions														
PCS	0.012	-0.001	-0.076	-0.051	-0.343	-0.068	-0.066	-0.122	0.227	0.056	0.039	0.166	0.274	-0.192
	0.95	*0.997*	*0.697*	*0.792*	*0.069*	*0.724*	*0.734*	*0.529*	*0.237*	*0.771*	*0.843*	*0.39*	*0.15*	*0.319*
PVAQ	-0.303	-0.246	-0.294	-0.399	-0.375	-0.227	-0.128	-0.224	-0.134	-0.252	-0.112	-0.084	0.171	-0.124
	0.110	*0.197*	*0.122*	*0.032*	*0.045*	*0.237*	*0.508*	*0.244*	*0.487*	*0.187*	*0.562*	*0.666*	*0.375*	*0.523*
Self-Reported Symptoms of CS														
CSI	0.152	0.145	0.078	0.027	0.045	-0.002	0.044	0.124	0.113	0.104	0.036	0.249	0.001	0.150
	0.432	*0.452*	*0.688*	*0.889*	*0.816*	*0.993*	*0.819*	*0.523*	*0.559*	*0.593*	*0.853*	*0.193*	*0.996*	*0.438*
Local Hyperalgesia														
PPT Trapezius	-0.122	0.106	0.116	0.047	-0.091	-0.040	-0.015	0.009	-0.068	-0.310	-0.130	-0.026	-0.238	-0.127
	0.512	*0.570*	*0.533*	*0.804*	*0.627*	*0.832*	*0.936*	*0.963*	*0.717*	*0.090*	*0.484*	*0.889*	*0.198*	*0.497*
Distant Hyperalgesia														
PPT Quadriceps	0.090	0.225	0.088	0.060	-0.052	-0.084	0.310	0.125	0.140	-0.095	-0.074	0.004	-0.159	-0.230
	0.630	*0.224*	*0.640*	*0.750*	*0.779*	*0.653*	*0.089*	*0.501*	*0.453*	*0.610*	*0.691*	*0.981*	*0.393*	*0.214*
CPM Efficacy														
CPM Quadriceps	-0.057	-0.043	0.089	0.023	-0.038	0.067	-0.165	-0.072	-0.037	-0.017	-0.152	-0.001	-0.236	-0.132
	0.776	*0.832*	*0.661*	*0.911*	*0.849*	*0.738*	*0.411*	*0.721*	*0.854*	*0.934*	*0.450*	*0.998*	*0.235*	*0.512*

Significant correlations are presented in bold. Correlations significant at the 0.05 level (2-tailed) were not deemed significant in order to correct for multiple comparisons. Correlations significant at the 0.01 level (2-tailed) were deemed significant. *P*-values are presented below the correlation coefficient.

Abbreviations: ACC = anterior cingulate cortex, PCC = posterior cingulate cortex, OBF= orbitofrontal, CINP = chronic idiopathic neck pain, mPDQ = modified perceived deficits questionnaire, TMT = trail making test, M= MRI test moment, PCS = pain catastrophizing scale, PVAQ = pain vigilance and awareness questionnaire, CS = central sentization, CSI= central sensitization inventory, PPT = pressure pain thresholds, CPM = conditioned pain modulation, LH = left hemisphere.

Table 2b. *Spearman correlations between regional cortical and subcortical GMV (RH) and self-reported and experimental measures of pain and cognition in patients with CINP.*

	Caudal ACC	Rostral ACC	PCC	Rostral Middle Frontal	Medial OBF	Lateral OBF	Superior Parietal	Insula	Postcentral	Precuneus	Pars Orbitalis	Supra-Marginal	Amygdala	Thalamus
CINP (n = 31)														
Self-Perceived Cognitive Performance (mPDQ)														
Total Score	0.151	0.151	-0.223	-0.135	-0.198	-0.188	-0.219	-0.358	-0.109	-0.218	0.168	-0.331	-0.083	-0.165
	0.453	*0.453*	*0.263*	*0.504*	*0.322*	*0.348*	*0.272*	*0.067*	*0.589*	*0.274*	*0.403*	*0.091*	*0.682*	*0.411*
Objective Cognitive Performance (TMT)														
Part A	0.042	-0.084	0.011	-0.230	-0.218	-0.288	-0.034	-0.285	-0.270	0.05	-0.363	-0.330	0.140	**-0.529**
	0.829	*0.664*	*0.954*	*0.231*	*0.255*	*0.130*	*0.861*	*0.134*	*0.157*	*0.796*	*0.053*	*0.081*	*0.468*	*0.003*
Part B	-0.096	-0.200	-0.061	-0.318	-0.175	-0.268	-0.158	-0.292	-0.377	0.026	0.027	-0.148	0.056	-0.314
	0.622	*0.298*	*0.753*	*0.093*	*0.363*	*0.159*	*0.414*	*0.124*	*0.044*	*0.895*	*0.888*	*0.443*	*0.772*	*0.097*
B – A	-0.088	-0.176	-0.099	-0.288	-0.210	-0.222	-0.238	-0.297	-0.379	-0.065	0.245	-0.100	-0.054	-0.182
	0.649	*0.362*	*0.611*	*0.130*	*0.273*	*0.248*	*0.214*	*0.118*	*0.042*	*0.739*	*0.201*	*0.606*	*0.782*	*0.345*
Self-Reported Pain Measures														
Neck Pain Intensity_M	0.145	-0.163	0.105	-0.190	0.013	0.123	0.170	0.036	0.160	-0.034	-0.075	-0.084	0.133	0.326
	0.437	*0.381*	*0.572*	*0.306*	*0.945*	*0.511*	*0.36*	*0.846*	*0.389*	*0.857*	*0.688*	*0.653*	*0.474*	*0.073*
Maladaptive Pain Cognitions														
PCS	0.174	0.108	0.051	-0.087	-0.156	-0.04	-0.010	-0.158	0.188	0.112	0.288	-0.069	0.109	0.022
	0.365	*0.577*	*0.793*	*0.655*	*0.420*	*0.839*	*0.958*	*0.412*	*0.329*	*0.564*	*0.129*	*0.720*	*0.574*	*0.908*
PVAQ	-0.218	-0.07	-0.138	-0.342	-0.293	-0.157	-0.177	-0.210	-0.085	-0.161	-0.009	0.236	0.022	-0.092
	0.256	*0.718*	*0.475*	*0.070*	*0.123*	*0.416*	*0.359*	*0.273*	*0.662*	*0.404*	*0.964*	*0.218*	*0.910*	*0.635*
Self-Reported Symptoms of CS														
CSI	0.198	0.184	0.142	0.090	-0.051	0.194	-0.025	0.028	0.223	0.183	0.135	-0.031	-0.057	0.222
	0.302	*0.339*	*0.461*	*0.642*	*0.794*	*0.313*	*0.896*	*0.886*	*0.245*	*0.342*	*0.486*	*0.874*	*0.770*	*0.248*
Local Hyperalgesia														
PPT Trapezius	0.001	-0.185	0.255	-0.104	-0.037	0.061	0.283	0.030	-0.111	-0.273	-0.180	-0.207	-0.182	0.132
	0.995	*0.320*	*0.165*	*0.578*	*0.844*	*0.743*	*0.123*	*0.873*	*0.552*	*0.137*	*0.332*	*0.263*	*0.327*	*0.477*
Distant Hyperalgesia														
PPT Quadriceps	0.108	-0.045	0.238	-0.089	0.045	0.022	0.439	0.113	0.027	-0.007	-0.042	-0.052	0.000	-0.032
	0.563	*0.812*	*0.197*	*0.635*	*0.809*	*0.906*	*0.013*	*0.544*	*0.885*	*0.971*	*0.824*	*0.781*	*0.998*	*0.865*
CPM Efficacy														
CPM Quadriceps	-0.053	0.013	0.220	-0.027	-0.007	0.008	0.092	-0.142	-0.292	-0.07	-0.324	-0.229	-0.136	-0.030
	0.795	*0.949*	*0.271*	*0.892*	*0.971*	*0.969*	*0.647*	*0.481*	*0.140*	*0.730*	*0.099*	*0.251*	*0.500*	*0.882*

Significant correlations are presented in bold. Correlations significant at the 0.05 level (2-tailed) were not deemed significant in order to correct for multiple comparisons. Correlations significant at the 0.01 level (2-tailed) were deemed significant. *P*-values are presented below the correlation coefficient.

Abbreviations: ACC = anterior cingulate cortex, PCC = posterior cingulate cortex, OBF = orbitofrontal, CINP = chronic idiopathic neck pain, mPDQ = modified perceived deficits questionnaire, TMT = trail making test, M = MRI test moment, PCS = pain catastrophizing scale, PVAQ = pain vigilance and awareness questionnaire, CS = central sensitization, CSI = central sensitization inventory, PPT = pressure pain thresholds, CPM = conditioned pain modulation, RH = right hemishpere.

Table 3a. *Spearman correlations between regional cortical and subcortical GMV (LH) and self-reported and experimental measures of pain and cognition in patients with CWAD.*

	Caudal ACC	Rostral ACC	PCC	Rostral Middle Frontal	Medial OBF	Lateral OBF	Superior Parietal	Insula	Postcentral	Precuneus	Pars Orbitalis	Supra-Marginal	Amygdala	Thalamus
CWAD (n = 25)														
Self-Perceived Cognitive Performance (mPDQ)														
Total Score	-0.154	-0.158	-0.389	-0.394	-0.170	-0.324	-0.375	-0.235	-0.427	-0.462	**-0.543**	0.078	**-0.598**	-0.355
	0.474	*0.460*	*0.060*	*0.057*	*0.428*	*0.123*	*0.071*	*0.268*	*0.037*	*0.023*	*0.006*	*0.718*	*0.002*	*0.089*
Objective Cognitive Performance (TMT)														
Part A	-0.122	-0.214	-0.326	-0.243	-0.016	-0.016	0.014	-0.151	-0.333	-0.129	-0.218	0.350	-0.445	0.065
	0.569	*0.314*	*0.120*	*0.252*	*0.942*	*0.941*	*0.947*	*0.482*	*0.112*	*0.549*	*0.305*	*0.094*	*0.029*	*0.764*
Part B	-0.145	-0.326	-0.505	**-0.604**	-0.314	-0.446	-0.365	**-0.539**	-0.155	-0.354	-0.498	-0.197	-0.513	-0.358
	0.498	*0.120*	*0.012*	*0.002*	*0.135*	*0.029*	*0.080*	*0.007*	*0.470*	*0.089*	*0.013*	*0.355*	*0.010*	*0.086*
B – A	-0.063	-0.158	-0.398	**-0.617**	-0.374	**-0.539**	-0.349	**-0.634**	0.041	-0.341	-0.451	-0.343	-0.417	-0.457
	0.771	*0.460*	*0.054*	*0.001*	*0.072*	*0.007*	*0.095*	*0.001*	*0.850*	*0.103*	*0.027*	*0.100*	*0.043*	*0.025*
Self-Reported Pain Measures														
Neck Pain Intensity_M	-0.410	-0.214	-0.193	-0.263	0.024	-0.426	-0.216	-0.179	-0.057	-0.484	-0.387	-0.086	-0.335	-0.360
	0.042	*0.305*	*0.356*	*0.204*	*0.908*	*0.034*	*0.301*	*0.393*	*0.786*	*0.014*	*0.056*	*0.683*	*0.101*	*0.078*
Maladaptive Pain Cognitions														
PCS	0.150	0.021	-0.016	-0.389	-0.228	-0.450	-0.207	-0.373	-0.291	**-0.522**	**-0.56**	-0.010	-0.252	-0.361
	0.474	*0.92*	*0.939*	*0.054*	*0.274*	*0.024*	*0.320*	*0.066*	*0.158*	*0.007*	*0.004*	*0.961*	*0.224*	*0.076*
PVAQ	-0.169	-0.336	-0.458	**-0.576**	-0.23	-0.365	-0.167	-0.358	-0.204	-0.293	-0.457	-0.254	-0.303	**-0.572**
	0.419	*0.100*	*0.021*	*0.003*	*0.268*	*0.073*	*0.426*	*0.079*	*0.327*	*0.155*	*0.022*	*0.221*	*0.141*	*0.003*
Self-Reported Symptoms of CS														
CSI	0.054	-0.135	-0.389	-0.455	-0.143	-0.284	-0.261	-0.081	-0.351	-0.324	-0.491	0.16	**-0.636**	-0.333
	0.802	*0.529*	*0.06*	*0.026*	*0.506*	*0.179*	*0.218*	*0.708*	*0.093*	*0.123*	*0.015*	*0.455*	*0.001*	*0.112*
Local Hyperalgesia														
PPT Trapezius	0.165	0.222	0.317	0.304	0.015	0.209	0.257	0.115	**0.551**	0.354	0.482	-0.079	0.302	0.402
	0.429	*0.287*	*0.123*	*0.14*	*0.942*	*0.317*	*0.215*	*0.583*	*0.004*	*0.083*	*0.015*	*0.707*	*0.143*	*0.047*
Distant Hyperalgesia														
PPT Quadriceps	0.208	0.234	0.318	0.162	0.002	0.095	0.125	-0.043	0.200	0.156	0.240	-0.074	0.370	0.306
	0.317	*0.261*	*0.121*	*0.440*	*0.994*	*0.65*	*0.553*	*0.838*	*0.338*	*0.456*	*0.248*	*0.726*	*0.069*	*0.137*
CPM Efficacy														
CPM Quadriceps	0.064	-0.099	0.029	0.278	-0.157	-0.077	0.195	-0.186	0.468	0.372	0.024	-0.079	0.311	0.264
	0.782	*0.668*	*0.902*	*0.222*	*0.498*	*0.741*	*0.397*	*0.420*	*0.033*	*0.097*	*0.918*	*0.733*	*0.170*	*0.248*

Significant correlations are presented in bold. Correlations significant at the 0.05 level (2-tailed) were not deemed significant in order to correct for multiple comparisons. Correlations significant at the 0.01 level (2-tailed) were deemed significant. *P*-values are presented below the correlation coefficient.

Abbreviations: ACC = anterior cingulate cortex, PCC = posterior cingulate cortex, OBF = orbitofrontal, CWAD = chronic whiplash associated disorders, mPDQ = modified perceived deficits questionnaire, TMT = trail making test, M = MRI test moment, PCS = pain catastrophizing scale, PVAQ = pain vigilance and awareness questionnaire, CS = central sensitization, CSI = central sensitization inventory, PPT = pressure pain thresholds, CPM = conditioned pain modulation, LH = left hemisphere.

Table 3b. *Spearman correlations between regional cortical and subcortical GMV (RH) and self-reported and experimental measures of pain and cognition in patients with CWAD.*

	Caudal ACC	Rostral ACC	PCC	Rostral Middle Frontal	Medial OBF	Lateral OBF	Superior Parietal	Insula	Postcentral	Precuneus	Pars Orbitalis	Supra-Marginal	Amygdala	Thalamus
CWAD (n = 25)														
Self-Perceived Cognitive Performance (mPDQ)														
Total Score	-0.186	-0.329	-0.277	-0.171	**-0.548**	-0.091	-0.271	-0.401	-0.402	-0.452	-0.272	-0.303	-0.351	-0.072
	0.384	*0.117*	*0.191*	*0.426*	*0.006*	*0.673*	*0.201*	*0.052*	*0.051*	*0.026*	*0.198*	*0.150*	*0.093*	*0.737*
Objective Cognitive Performance (TMT)														
Part A	-0.190	-0.354	-0.115	-0.014	-0.242	0.063	-0.038	-0.144	-0.069	-0.160	-0.272	0.092	-0.216	0.275
	0.375	*0.090*	*0.592*	*0.949*	*0.255*	*0.770*	*0.861*	*0.502*	*0.748*	*0.455*	*0.198*	*0.668*	*0.311*	*0.193*
Part B	-0.262	**-0.588**	**-0.538**	-0.319	-0.485	-0.421	-0.364	-0.284	-0.299	-0.477	-0.419	-0.174	-0.356	-0.168
	0.216	*0.002*	*0.007*	*0.128*	*0.016*	*0.041*	*0.08*	*0.179*	*0.156*	*0.018*	*0.042*	*0.415*	*0.088*	*0.433*
B – A	-0.227	-0.495	**-0.594**	-0.342	-0.489	**-0.569**	-0.241	-0.312	-0.194	-0.45	-0.432	-0.213	-0.373	-0.302
	0.286	*0.014*	*0.002*	*0.102*	*0.015*	*0.004*	*0.257*	*0.138*	*0.364*	*0.028*	*0.035*	*0.318*	*0.073*	*0.152*
Self-Reported Pain Measures														
Neck Pain Intensity_M	0.112	-0.109	-0.081	-0.186	-0.392	-0.397	-0.104	-0.249	-0.125	-0.285	-0.384	-0.317	-0.222	-0.102
	0.593	*0.605*	*0.701*	*0.374*	*0.053*	*0.049*	*0.619*	*0.230*	*0.550*	*0.168*	*0.058*	*0.122*	*0.285*	*0.628*
Maladaptive Pain Cognitions														
PCS	-0.024	-0.400	-0.397	-0.232	**-0.535**	-0.355	-0.215	**-0.515**	-0.153	-0.412	-0.482	-0.322	-0.221	-0.210
	0.91	*0.047*	*0.049*	*0.265*	*0.006*	*0.082*	*0.303*	*0.008*	*0.466*	*0.041*	*0.015*	*0.116*	*0.287*	*0.313*
PVAQ	-0.277	-0.501	**-0.657**	-0.243	-0.441	-0.249	-0.088	-0.420	-0.152	-0.384	-0.325	-0.265	0.101	-0.199
	0.18	*0.011*	*<0.001*	*0.241*	*0.027*	*0.230*	*0.676*	*0.037*	*0.468*	*0.058*	*0.113*	*0.200*	*0.631*	*0.340*
Self-Reported Symptoms of CS														
CSI	-0.246	-0.436	-0.317	-0.283	-0.406	-0.137	-0.154	-0.212	-0.365	-0.440	-0.421	-0.123	-0.444	-0.105
	0.247	*0.033*	*0.131*	*0.181*	*0.049*	*0.524*	*0.471*	*0.320*	*0.080*	*0.031*	*0.040*	*0.568*	*0.030*	*0.625*
Local Hyperalgesia														
PPT Trapezius	0.232	0.271	0.202	-0.012	0.437	-0.066	0.002	0.345	0.409	0.336	0.107	0.361	0.035	0.091
	0.265	*0.190*	*0.334*	*0.953*	*0.029*	*0.753*	*0.994*	*0.091*	*0.042*	*0.100*	*0.610*	*0.076*	*0.870*	*0.666*
Distant Hyperalgesia														
PPT Quadriceps	0.063	0.022	0.187	0.098	0.427	-0.053	-0.114	0.004	0.252	0.139	0.113	0.154	0.168	0.094
	0.763	*0.919*	*0.371*	*0.642*	*0.033*	*0.801*	*0.588*	*0.985*	*0.225*	*0.507*	*0.592*	*0.463*	*0.421*	*0.655*
CPM Efficacy														
CPM Quadriceps	-0.093	0.086	-0.041	-0.003	-0.026	-0.205	-0.063	0.232	0.409	0.349	0.084	0.253	-0.097	0.177
	0.689	*0.712*	*0.86*	*0.989*	*0.910*	*0.372*	*0.786*	*0.312*	*0.066*	*0.120*	*0.717*	*0.268*	*0.676*	*0.442*

Significant correlations are presented in bold. Correlations significant at the 0.05 level (2-tailed) were not deemed significant in order to correct for multiple comparisons. Correlations significant at the 0.01 level (2-tailed) were deemed significant. *P*-values are presented below the correlation coefficient.

Abbreviations: ACC = anterior cingulate cortex, PCC = posterior cingulate cortex, OBF = orbitofrontal, CWAD = chronic whiplash associated disorders, mPDQ = modified perceived deficits questionnaire, TMT = trail making test, M = MRI test moment, PCS = pain catastrophizing scale, PVAQ = pain vigilance and awareness questionnaire, CS = central sensitization, CSI = central sensitization inventory, PPT = pressure pain thresholds, CPM = conditioned pain modulation, RH = right hemisphere.

of self-reported cognitive deficits and decreased GMV of the left pars orbitalis (r_s = -.543; *P* = 0.006), the left amygdala (r_s = -0.598; *P* = 0.002), and the right medial orbitofrontal cortex (r_s = -0.548; *P* = 0.006). Furthermore, decreased task-switching capacity was moderately correlated with decreased GMV of the right rostral anterior cingulate cortex (r_s = -.588; *P* = 0.002), the right posterior cingulate cortex (r_s = -0.538; *P* = 0.007), the left rostral middle frontal cortex (r_s = -0.604; *P* = 0.002), and the left insula (r_s = -0.539; *P* = 0.007). In addition, worse executive control was moderately correlated with decreased GMV of the left rostral middle frontal cortex (r_s= -0.617, *P* = 0.001), the left lateral orbitofrontal cortex (r_s = -0.539, *P* = 0.007), the left insula (r_s = -0.634, *P* = 0.001), the right posterior cingulate cortex (r_s = -0.594, *P* = 0.002), and the right lateral orbitofrontal cortex (r_s = -0.569, *P* = 0.004).

Moderate correlations were demonstrated between higher levels of pain catastrophizing and decreased GMV of the left precuneus (r_s = -0.522; *P* = 0.007), the left pars orbitalis (r_s = -0.560; *P* = 0.004), the right medial orbitofrontal cortex (r_s = -0.535; *P* = 0.006), and the right insula (r_s = -0.515; *P* = 0.008). Furthermore, moderate correlations were found between higher levels of pain hypervigilance and decreased GMV of the left rostral middle frontal cortex (r_s = -0.576; *P* = 0.003), the left thalamus (r_s = -0.572; *P* = 0.003), and the right posterior cingulate cortex (r_s = -0.657; *P* < 0.001). A moderate relationship was observed between more self-perceived CS symptoms and decreased GMV of the left amygdala (r_s = -0.636; *P* = 0.001).

Moreover, a moderate relationship was found between lower PPTs at the trapezius muscle and decreased GMV of the left postcentral cortex (r_s = 0.551; *P* = 0.004). Finally, no significant correlations were detected between regional GMV and the efficacy of CPM (*P* > 0.01).

Discussion

The results of the present innovative study provided evidence for decreased GMV in cortical regions known to be associated with processing cognition and pain in patients with CWAD compared to CINP patients and healthy persons. In contrast, regional GMV alterations were not observed in CINP patients compared to healthy persons. Furthermore, this study revealed for the first time that increased cognitive deficits, maladapted pain cognitions, CS symptoms, and local hyperalgesia were moderately correlated with decreased regional GMV in CWAD patients. In CINP patients, regional GMV was only correlated with cognitive deficits.

Group Differences in Regional GMV

The observed cortical GMV decrease in patients with CWAD compared to CINP patients and healthy controls was in line with our hypothesis and could be explained because CWAD patients have a traumatic origin of neck pain and are characterized by CS in contrast to CINP patients, who have a non-traumatic origin of neck pain and do not show CS at a group level. In the present study, decreased GMV was demonstrated in the left posterior cingulate cortex and the right superior parietal cortex in patients with CWAD compared to CINP. This is the first study investigating and revealing these regional GMV differences between women with CINP and CWAD. Compared to healthy women, decreased GMV could also be revealed in the left posterior cingulate cortex, right lateral orbitofrontal cortex, and left supramarginal cortex in women with CWAD. These findings are in line with accumulating evidence of decreased regional GMV in other chronic pain populations characterized by CS, such as fibromyalgia and chronic low back pain (19-21,89,90). In particular, decreased GMV has previously been observed in the posterior cingulate cortex, lateral orbitofrontal cortex, and supramarginal cortex in the latter chronic pain populations compared to healthy persons (19,20,83,91-94).

One previous study of patients who developed chronic headache after a whiplash injury also observed regional GMV decrease, however in the anterior cingulate cortex and the dorsolateral prefrontal cortex in the patient group compared to healthy controls (95). To our knowledge, only one previous study has examined GMV alterations in patients with non-traumatic chronic neck pain, more specifically in patients with chronic myofascial pain resulting from active trigger points in the trapezius muscle. The authors found decreased GMV in the left parahippocampal cortex, and the right fusiform cortex in the patient group compared to healthy persons (96). Despite these promising results, the authors did not correct for multiple comparisons.

Nevertheless, contrary to previous evidence regarding GMV alterations in regions such as the insula, anterior cingulate cortex, and amygdala in other chronic pain patients, we could not find GMV alterations in all other ROIs. Although, this can be due to methodological factors (e.g., MRI acquisition parameters, MRI processing, poor control in previous studies for age, pain duration, and comorbidities (97)); unique pathology-specific GM morphology alterations in different chronic pain types (85,91) may also account for these differences.

On the basis of the results of a quantitative meta-

analysis investigating GMV alterations in patients with chronic pain, the observed estimated mean differences in regional GMV (mm^3) of the present study in patients with CWAD compared to healthy controls are rather comparable with the results of GMV changes in other chronic pain patients (83). However, caution is warranted when comparing the results of studies that applied different MRI acquisition, analyzing, and processing techniques (e.g., FreeSurfer versus voxel-based morphometry).

Group Differences in Measures of Cognition, Pain, and CS

Furthermore, patients with CWAD displayed higher neck pain intensity, more severe pain-related disability, more pronounced cognitive deficits, and more signs of CS compared to patients with non-traumatic CINP. One previous study comparing CINP and CWAD patients also observed significant features of CS in CWAD patients and not in patients with CINP (98). Moreover, higher levels of pain catastrophizing and hypervigilance were only present in the CWAD group compared to healthy persons. Accordingly, based on the present study results, it is plausible that more severe cognitive deficits and disturbed pain processing in CWAD patients are associated with a larger extent of maladapted GM morphology reorganization compared to patients with CINP.

Relationships Between Regional GMV and Measures of Cognition, Pain, and CS

The results of our correlation analyses have demonstrated relationships between decreased regional GMV and debilitating symptoms in CWAD patients. In particular, we revealed that decreased GMV in cognitive and pain processing regions (left pars orbitalis, left amygdala, left rostral middle frontal cortex, lateral orbitofrontal cortex bilateral, insula bilateral, left precuneus, left thalamus, left postcentral cortex, right medial orbitofrontal cortex, right rostral anterior cingulate cortex, and right posterior cingulate cortex) coincided with increased cognitive deficits, maladapted pain cognitions, CS symptoms, and local hyperalgesia in CWAD. Noteworthy, in CINP patients, decreased GMV (left rostral anterior cingulate cortex, left medial orbitofrontal cortex, and right thalamus) was only associated with increased cognitive deficits but not with pain cognitions, CS symptoms, and local hyperalgesia. The present study could not detect relationships between CPM efficacy and regional GMV in both chronic neck pain groups in contrast to a previous morphological MRI study in patients with irritable bowel syndrome (99). This study revealed a relationship between endogenous pain inhibition and cortical thickness in the lateral orbitofrontal cortex. This inconsistent result could be, however, explained by a different CPM paradigm and a different macrostructural metric (cortical thickness versus GMV) (99).

Remarkably, only GMV of the right lateral orbitofrontal cortex was sensitive in detecting significant group differences and was also correlated with measures of cognition and pain. Specifically, decreased GMV in the right lateral orbitofrontal cortex in CWAD patients correlated with worse executive control. Functional neuroimaging combined with neuropsychological data have provided evidence which indicates an important role of the orbitofrontal cortex in decision-making (100) and executive control of information processing by inhibiting neural activity associated with painful sensations (101).

Furthermore, the present study showed associations between increased self-reported cognitive deficits and worse objective cognitive performance (working memory capacity, task-switching capacity, and executive control) and decreased regional GMV in CINP and CWAD patients. Similarly, Luerding et al (24) demonstrated associations between reduced working memory performance and decreased GMV in the left dorsolateral prefrontal cortex in fibromyalgia patients.

Higher levels of pain catastrophizing and pain hypervigilance were correlated with decreased GMV in the precuneus, inferior frontal gyrus (pars orbitalis), medial orbitofrontal cortex, insula, thalamus, posterior cingulate cortex, and rostral middle frontal cortex in patients with CWAD. Our results are consistent with previous studies exploring associations between pain catastrophizing and GM morphology. For example, Hubbard et al (102) observed associations between higher pain catastrophizing and lower GMV in pain processing regions in migraine patients.

Furthermore, increased local hyperalgesia, as revealed by lower PPTs at the trapezius muscle in CWAD patients, was correlated with decreased GMV in the left postcentral cortex, which is a region involved in pain perception and processing nociceptive stimuli (103). Recently, Niddam et al (96) demonstrated an association between decreased PPTs at the trapezius muscle (local hyperalgesia) and decreased GMV in the right middle frontal cortex in patients with chronic myofacial pain.

Lastly, our study found that increased self-reported symptoms of CS were correlated with decreased GMV in

the left amygdala in CWAD. Interestingly, the amygdala is a key region involved in pain processing and cognitive factors of pain anticipation (104) and has a crucial role in negative emotions and pain-related memories (105).

Limitations and Strengths

With regard to interpretation of the present study results, the following limitations must be taken into account. First, the cross-sectional nature of this study implies that no conclusions about the causality of the observed relationships can be drawn. Second, the generalizability of the study results might be reduced because only women were included and only CWAD patients classified as WAD II A, B, or C were included; however, this results in less heterogeneity in the included study sample, which is also a strength.

Nonetheless, the present study also had several strengths. First, this study is the first to address the relationships between GMV alterations on one hand and self-reported and experimental features of cognition, pain, and CS on the other hand in CINP and CWAD patients. Second, all of the groups were comparable in age, body mass index, education level, smoking status, menstrual phase, medication use, neck pain duration, and frequency of neck pain (for the patient groups). In addition, the researchers anticipated sources of bias such as use of medications, caffeine, alcohol, and nicotine on the assessment days. A final strength is the use of FreeSurfer, which has some advantages over voxel-based morphometry.

Clinical Message

Our results indicate that chronic pain in CWAD patients should be interpreted, at least in part, as a result of neural reorganization of the central nervous system (CNS), associated with alterations in GMV of regions involved in various aspects of pain and cognitive processing.

Importantly, increased cognitive deficits, maladapted pain cognitions, and CS symptoms were found to be associated with decreased GMV in regions implicated in processing cognition and pain in CWAD patients. Therefore, it can be recommended that therapy approaches for CWAD should address the brain and take into account neuroplasticity of the CNS. Cognitive behavioral therapy can be advocated and has been demonstrated to reverse regional GMV decreases associated with reduced pain catastrophizing and decreased cognitive deficits in other chronic pain patients characterized by CS (106,107).

In CINP patients, only cognitive deficits were related to decreased regional GMV, and no GMV alterations or CS could be revealed. Accordingly, fewer indications are currently available for a role of brain alterations and CNS reorganization in the pathophysiology of CINP at a group level. Nevertheless, at the individual patient level, it is still possible that CNS mechanisms play a role, and subsequently, the therapeutic approach should be personalized for each specific patient regardless of diagnosis.

Encouragingly, multiple studies have shown in other chronic pain conditions that decrease in GM morphology, including GMV, is at least partially reversible when underlying pain is adequately treated (96,108,109). These studies are clinically relevant as they suggest that at least some of the morphological GM changes must be a direct consequence of the presence of pain and related sequel and possibly the underlying mechanism is based on synaptic plasticity (92).

To summarize, the current study results pave the way for the development of novel and more effective treatment approaches for patients with chronic neck pain.

Recommendations for Further Research

The exact underlying mechanisms responsible for decreased regional GMV in CWAD patients remain unclear. The potential underlying mechanisms for GMV changes include changes in synaptic density and dendritic spine structure, among others (110). It is possible that the observed GMV decrease reflects tissue shrinkage, which can be caused by affected neural tissue or extracellular and microvascular volume without substantially impacting neuronal properties (111). Further research should investigate the underlying neurobiological mechanisms of the observed GMV alterations. In addition, future research should investigate possible alterations in white matter microstructure in patients with CWAD compared to CINP.

The regional GMV decrease can also be interpreted in the light of maladapted neuroplasticity (97). This is relevant when considering the dynamic features of GMV alterations associated with persistent pain. Neural reorganization can range from synaptic plasticity to changes in neural circuitry (e.g., long-term potentiation, synaptic sprouting, neurogenesis (112), and glial reorganization).

Whether these GMV changes are the consequence of pain or whether pre-existent alterations of these regions make patients more susceptible to the develop-

ment of CWAD remains to be elucidated. Longitudinal research is warranted and research should unravel if therapy can re-shape the brain and diminish the associated burden in CWAD patients. Noteworthy, the current study has investigated only one piece of the puzzle regarding possible brain alterations in patients with CINP and CWAD. Accordingly, future brain imaging research has to further disentangle possible structural and functional brain changes in patients with chronic neck pain.

Conclusion

The present innovative study provided evidence for decreased GMV in cortical regions associated with pain and cognitive processing in women with CWAD compared to women with CINP and healthy women. Additionally, in women with CWAD, decreased GMV in cognitive and pain processing regions was associated with increased cognitive deficits, maladapted pain cognitions, self-perceived CS symptoms, and local hyperalgesia. In women with CINP, decreased GMV was only associated with increased cognitive deficits, but compared with healthy controls no GMV alterations could be revealed. These findings indicate a possible negative mediating role of the trauma in patients with CWAD. The underlying neurobiological mechanisms of these GMV alterations remain to be elucidated and no conclusions about the causality of the observed relationships can be drawn. Accordingly, longitudinal research is warranted to unravel whether these GMV alterations occur as a result of chronic pain or vice versa. Based on the present study results, it can be recommended that therapy approaches for CWAD should take into account the role of CNS neuroplasticity.

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Supplementary Table A. *Differences in grey matter volume of ROIs involved in processing of cognition and pain in CWAD patients, CINP patients and healthy women.*

Estimated means					**Tests of between-Subjects Effects**							
	Mean*	Std. Error	95% Confidence Interval		F-value	P-value	Pairwise comparisons Adjustment for multiple comparisons: Bonferroni.					
			Lower Bound	Upper Bound				Estimated Mean Difference	Std. Error	P-value	95% Confidence Interval for Difference	
											Lower Bound	Upper Bound
Posterior cingulate cortex volume (left hemisphere) (mm^3)												
HCON	3267.763	82.534	3103.418	3432.108	4.213	0.018	HCON-CINP	6.072	111.036	1.000	-265.678	277.823
CINP	3261.691	73.356	3115.621	3407.760			HCON-CWAD	289.223	116.929	0.047	3.051	575.394
CWAD	2978.540	81.757	2815.742	3141.339			CINP-CWAD	283.150	109.525	0.035	15.099	551.202
Lateral orbitofrontal cortex volume (right hemisphere) (mm^3)												
HCON	6895.475	125.968	6644.641	7146.310	4.103	0.020	HCON-CINP	129.357	169.471	1.000	-285.407	544.121
CINP	6766.118	111.960	6543.177	6989.060			HCON-CWAD	488.418	178.464	0.023	51.643	925.192
CWAD	6407.058	124.783	6158.583	6655.532			CINP-CWAD	359.061	167.164	0.105	-50.057	768.179
Supramarginal cortex volume (left hemisphere) (mm^3)												
HCON	11399.953	264.636	10872.995	11926.911	4.504	0.014	HCON-CINP	705.567	356.027	0.153	-165.776	1576.910
CINP	10694.386	235.208	10226.027	11162.745			HCON-CWAD	1112.305	374.921	0.012	194.722	2029.888
CWAD	10287.648	262.146	9765.649	10809.648			CINP-CWAD	406.738	351.181	0.751	-452.744	1266.220
Superior parietal cortex volume (right hemisphere) (mm^3)												
HCON	12753.563	269.306	12217.305	13289.820	4.839	0.010	HCON-CINP	-492.403	362.31	0.534	-1379.124	394.317
CINP	13245.966	239.359	12769.342	13722.590			HCON-CWAD	619.364	381.537	0.326	-314.413	1553.140
CWAD	12134.199	266.772	11602.988	12665.411			CINP-CWAD	1111.767	357.379	0.008	237.117	1986.417
Total Intracranial volume (mm^3)												
HCON	1455072.696	35504.319	1384374.565	1525770.826	2.284	0.109	HCON-CINP	NA				
CINP	1369525.631	31556.148	1306689.312	1432361.949			HCON-CWAD					
CWAD	1357070.762	35170.249	1287037.849	1427103.675			CINP-CWAD					
Total grey matter volume (mm^3)												
HCON	626666.100	8789.236	609164.496	644167.704	1.655	0.198	HCON-CINP	NA				
CINP	620007.734	7811.850	604452.353	635563.115			HCON-CWAD					
CWAD	604746.527	8706.535	587409.601	622083.454			CINP-CWAD					
Subcortical volume (mm^3)												
HCON	56059.367	670.566	54724.098	57394.635	0.680	0.510	HCON-CINP	NA				
CINP	56311.981	595.998	55125.198	57498.764			HCON-CWAD					
CWAD	55297.537	664.257	53974.832	56620.241			CINP-CWAD					

*Covariates appearing in the model are evaluated at the following values: age = 33.630

HCON n = 25; CINP n = 31; CWAD n =25

Abbreviations: HCON = healthy controls, CINP = chronic idiopathic neck pain, CWAD = chronic whiplash associated disorders, ROIs = regions of interest, NA = not applicable

Supplementary Table B. *Non-significant differences in grey matter volume of ROIs involved in processing of cognition and pain in CWAD patients, CINP patients and healthy women.*

Estimated means					**Tests of between-Subjects Effects**
	Mean*	Std. Error	95% Confidence Interval		F-value (*P*-value)
			Lower Bound	Upper Bound	
Caudal anterior cingulate volume (left hemisphere) (mm^3)					
HCON	2022.697	84.968	1853.504	2191.890	1.146 (0.323)
CINP	1849.925	75.519	1699.546	2000.303	
CWAD	1933.957	84.169	1766.356	2101.558	
Caudal anterior cingulate volume (right hemisphere) (mm^3)					
HCON	2238.221	88.037	2062.916	2413.526	0.662 (0.519)
CINP	2103.819	78.247	1948.008	2259.629	
CWAD	2182.124	87.209	2008.469	2355.779	
Rostral anterior cingulate volume (left hemisphere) (mm^3)					
HCON	2815.528	95.081	2626.197	3004.859	1.857 (0.163)
CINP	2595.038	84.508	2426.761	2763.314	
CWAD	2592.465	94.187	2404.916	2780.015	
Rostral anterior cingulate volume (right hemisphere) (mm^3)					
HCON	2223.509	78.969	2066.262	2380.756	1.058 (0.352)
CINP	2148.890	70.187	2009.129	2288.650	
CWAD	2061.148	78.226	1905.381	2216.915	
Posterior cingulate volume (right hemisphere) (mm^3)					
HCON	3239.293	87.813	3064.435	3414.151	1.755 (0.180)
CINP	3080.014	78.048	2924.600	3235.427	
CWAD	3012.570	86.987	2839.357	3185.782	
Rostral middle frontal volume (left hemisphere) (mm^3)					
HCON	15797.621	340.979	15118.645	16476.597	1.027 (0.363)
CINP	15447.520	303.061	14844.048	16050.992	
CWAD	15105.454	337.771	14432.867	15778.042	
Rostral middle frontal volume (right hemisphere) (mm^3)					
HCON	15021.037	343.129	14337.780	15704.294	0.347 (0.708)
CINP	14776.898	304.972	14169.621	15384.174	
CWAD	14618.770	339.900	13941.942	15295.598	
Medial orbitofrontal volume (left hemispere) (mm^3)					
HCON	4624.112	108.906	4407.251	4840.973	2.305 (0.107)
CINP	4540.005	96.796	4347.260	4732.750	
CWAD	4307.561	107.882	4092.741	4522.381	
Medial orbitofrontal volume (right hemispere) (mm^3)					
HCON	4786.377	97.557	4592.116	4980.637	1.228 (0.298)
CINP	4583.517	86.708	4410.859	4756.175	
CWAD	4701.462	96.639	4509.030	4893.895	
Lateral orbitofrontal volume (left hemisphere) (mm^3)					
HCON	7556.569	150.887	7256.115	7857.023	1.161 (0.319)
CINP	7396.945	134.108	7129.902	7663.988	
CWAD	7230.979	149.467	6933.351	7528.606	

Estimated means					Tests of between-Subjects Effects
	Mean*	Std. Error	95% Confidence Interval		F-value (*P*-value)
			Lower Bound	Upper Bound	
Insula volume (left hemisphere) (mm^3)					
HCON	6650.029	135.783	6379.651	6920.407	1.807 (0.171)
CINP	6619.807	120.683	6379.495	6860.118	
CWAD	6326.050	134.505	6058.216	6593.884	
Insula volume (right hemisphere) (mm^3)					
HCON	6759.804	131.606	6497.743	7021.865	1.419 (0.248)
CINP	6677.191	116.971	6444.272	6910.110	
CWAD	6458.759	130.368	6199.164	6718.355	
Postcentral volume (left hemisphere) (mm^3)					
HCON	9350.764	227.937	8896.884	9804.645	0.590 (0.557)
CINP	9683.044	202.590	9279.637	10086.452	
CWAD	9517.861	225.792	9068.251	9967.471	
Postcentral volume (right hemisphere) (mm^3)					
HCON	9045.141	267.322	8512.835	9577.447	0.028 (0.973)
CINP	8984.258	237.595	8511.146	9457.370	
CWAD	8958.659	264.807	8431.362	9485.957	
Precuneus volume (left hemisphere) (mm^3)					
HCON	9579.739	220.170	9141.325	10018.153	1.011 (0.369)
CINP	9593.422	195.686	9203.761	9983.083	
CWAD	9214.218	218.098	8779.929	9648.506	
Precuneus volume (right hemisphere) (mm^3)					
HCON	992.580	200.089	9530.152	10327.008	2.240 (0.113)
CINP	10015.495	177.838	9661.373	10369.617	
CWAD	9478.566	198.206	9083.887	9873.245	
Pars Orbitalis volume (left hemisphere) (mm^3)					
HCON	2201.797	56.529	2089.233	2314.361	1.609 (0.207)
CINP	2218.293	50.243	2118.247	2318.340	
CWAD	2091.079	55.997	1979.574	2202.584	
Pars Orbitalis volume (right hemisphere) (mm^3)					
HCON	2649.025	71.052	2507.542	2790.509	1.406 (0.251)
CINP	2580.656	63.151	2454.906	2706.406	
CWAD	2481.601	70.384	2341.449	2621.753	
Supramarginal cortex volume (right hemisphere) (mm^3)					
HCON	10579.946	287.451	10007.558	11152.334	1.700 (0.190)
CINP	10192.171	255.486	9683.434	10700.908	
CWAD	9829.081	284.746	9262.079	10396.084	
Superior parietal volume (left hemisphere) (mm^3)					
HCON	13092.699	301.360	12492.614	13692.784	1.212 (0.303)
CINP	13000.016	267.848	12466.663	13533.370	
CWAD	12486.401	298.525	11891.962	13080.839	

Estimated means					Tests of between-Subjects Effects
	Mean*	Std. Error	95% Confidence Interval		F-value (*P*-value)
			Lower Bound	Upper Bound	
Amygdala volume (left hemisphere) (mm^3)					
HCON	1502.540	33.352	1436.128	1568.952	2.428 (0.095)
CINP	1601.342	29.643	1542.315	1660.369	
CWAD	1555.476	33.038	1489.689	1621.263	
Amygdala volume (right hemisphere) (mm^3)					
HCON	1464.975	29.053	1407.123	1522.827	1.652 (0.198)
CINP	1535.188	25.822	1483.769	1586.607	
CWAD	1514.461	28.780	1457.153	1571.768	
Thalamus volume (left hemisphere) (mm^3)					
HCON	7818.711	170.216	7479.768	8157.655	1.043 (0.357)
CINP	7792.152	151.288	7490.900	8093.404	
CWAD	7511.332	168.615	7175.578	7847.087	
Thalamus volume (right hemisphere) (mm^3)					
HCON	7046.965	117.792	6812.411	7281.518	1.947 (0.150)
CINP	6999.345	104.693	6790.875	7207.816	
CWAD	6745.843	116.683	6513.497	6978.189	

*Covariates appearing in the model are evaluated at the following values: age = 33.630. HCON n = 25; CINP n = 31; CWAD n =25
Abbreviations: HCON = healthy controls, CINP = chronic idiopathic neck pain, CWAD = chronic whiplash associated disorders, ROIs = regions of interest

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