Received: 7 March 2023 | Revised: 11 May 2023 | Accepted: 1 June 2023

DOI: 10.1002/ejp.2153

EJP European Journal of Pain

ORIGINAL ARTICLE

Chronic pain is associated with less grey matter volume in the anterior cingulum, anterior and posterior insula and hippocampus across three different chronic pain conditions

Nicola Neumann[1] | **Martin Domin**[1] | **Carsten-Oliver Schmidt**[2] | **Martin Lotze**[1]

[1]Institute of Diagnostic Radiology and Neuroradiology, Functional Imaging Unit, University Medicine Greifswald, Greifswald, Germany

[2]Institute for Community Medicine-Department SHIP/KEF, University Medicine Greifswald, Greifswald, Germany

Correspondence
Martin Lotze, Institute of Diagnostic Radiology and Neuroradiology, Functional Imaging Unit, University Medicine Greifswald, Walther-Rathenau-Str. 46, 17475 Greifswald, Germany.
Email: martin.lotze@uni-greifswald.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: DFG- LO 795/37-1; Federal State of Mecklenburg-West Pomerania

Abstract

Background: Chronic pain of different aetiologies and localization has been associated with less grey matter volume (GMV) in several cortical and subcortical brain areas. Recent meta-analyses reported low reproducibility of GMV alterations between studies and pain syndromes.

Methods: To investigate GMV in common chronic pain conditions defined by body location (chronic back pain, $n = 174$; migraine, $n = 92$; craniomandibular disorder, $n = 39$) compared to controls ($n = 296$), we conducted voxel-based morphometry and determined GMV from high-resolution cranial MRIs obtained in an epidemiologic survey. Mediation analyses were performed between the presence of chronic pain and GMV testing the mediators stress and mild depression. The predictability of chronic pain was investigated with binomial logistic regression.

Results: Whole-brain analyses yielded reduced GMV within the left anterior insula and the anterior cingulate cortex, for a ROI approach additionally the left posterior insula and left hippocampus showing less GMV across all patients with chronic pain. The relationship of pain with GMV in the left hippocampus was mediated by self-reported stressors in the last 12 months. Binomial logistic regression revealed a predictive effect for GMV in the left hippocampus and left anterior insula/temporal pole for the presence of chronic pain.

Conclusions: Chronic pain across three different pain conditions was characterized by less GMV in brain regions consistently described for different chronic pain conditions before. Less GMV in the left hippocampus mediated by experienced stress during the last year might be related to altered pain learning mechanisms in chronic pain patients.

Significance: Grey matter reorganization could serve as a diagnostic biomarker for chronic pain. In a large cohort, we here replicated findings of less grey matter volume across three pain conditions in the left anterior and posterior insula, anterior cingulate and left hippocampus. Less hippocampal grey matter was mediated by experienced stress.

1 | INTRODUCTION

Pain, defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (International Association for the Study of Pain, Raja et al., 2020), involves reorganizational processes in the peripheral and central nervous system (Kuner & Flor, 2017). To take maladaptive plasticity into account, a third mechanistic descriptor in addition to nociceptive and neuropathic pain has been introduced as 'nociplastic pain', which is 'not characterized by obvious activation of nociceptors or neuropathy, but in whom clinical and psychophysical findings suggest altered nociceptive function' (Fitzcharles et al., 2021; Kosek et al., 2016). Depending on the nociceptive input, changes occur at the molecular, synaptic, cellular and network levels along the nociceptive pathways. These may lead to persistent structural changes, which can include an increase or a decrease in the density of synaptic spines, degeneration or regeneration of axons leading to aberrant connectivity, degeneration of neurons and proliferation of astrocytes and microglia (Kuner, 2010). On a macrolevel, grey matter volume changes as well as changes of white matter, cortical thickness and surface have been observed in many studies investigating different chronic pain conditions (for a recent review and ALE-meta-analysis using structural neuroimaging data see Henn et al., 2023). Grey matter reorganization could serve as a diagnostic biomarker for chronic pain, if validated and stable as long as the chronic pain persists and if it differs between chronic pain and other negative mood states (Reckziegel et al., 2019) or psychosocial factors (Cohen & Mao, 2014). However, most studies investigating structural alterations in chronic pain conditions have been done in small groups of subjects, and validation of outcomes is lacking. Henn et al. (Henn et al., 2023) recently calculated a comprehensive ALE meta-analysis including a large sample of experiments that fulfilled certain methodological standards (sufficient sample size, control for multiple comparisons, whole-brain analytical approach) across different pain conditions. There were no significant clusters when correcting for multiple comparisons, but using exploratory threshold-free cluster enhancement analyses, there was less GMV in chronic pain in the amygdala, thalamus, hippocampus, insula, anterior cingulate cortex and inferior frontal gyrus. When subsuming these findings, we are still not certain which chronic pain conditions, and to what extent, share mechanisms with each other (Reckziegel et al., 2019). In addition, some of these brain changes might be elicited and maintained not only by nociception, but also by psychosocial and lifestyle factors or effects of antinociceptive medication (Cohen et al., 2021; Mills et al., 2019). We, therefore, compared grey matter volume (GMV) obtained by voxel-based morphometry (VBM) of high-resolution cranial MRIs of participants from a representative epidemiologic cohort (SHIP Trend 0) who indicated chronic persisting (3–12 months) pain in different regions of the body (lower back pain: $n = 174$, migraine: $n = 92$, craniomandibular pain: $n = 39$) and compared GMV to those of controls ($n = 296$). In the current study, pain was divided by body location, not according to pain mechanism. For example, craniomandibular and back pain could be neuropathic, nociceptive, nociplastic or mixed.

We controlled for sex, age, income, cigarettes smoked and alcohol consume and mild depression as covariates in our analysis. The impact of stress and mild depression on GMV decrease was investigated in a mediation analysis. It was further investigated if GMV differences between pain and control groups were predictive for the presence of chronic pain.

2 | METHODS

2.1 | Participants

Data used in the current study were obtained from the Study of Health in Pomerania (SHIP), a population-based project consisting of two independent cohorts (SHIP-START and SHIP-Trend) launched to investigate common risk factors, subclinical disorders and manifest diseases in the high-risk population of northeast Germany (Völzke et al., 2011). The study protocol was approved by the Ethics Committee of the University Medicine Greifswald and written informed consent was obtained from each participant (Study of Health in Pomerania, SHIP-Trend Reg.Nr. BB39/08). We here used the baseline examination of the second SHIP cohort (SHIP-TREND-0, $n = 4420$; 2275 women) collected between 2008 and 2012 (Figure 1). Of 4420 participants of SHIP-TREND-0, 2154 took part in an MRI examination. All MRI head scans were visually inspected with regard to image artefacts and clinical abnormalities. Scans with more than slight motion artefacts or intensive magnetic field strength inhomogeneities were excluded ($n = 59$). Participants with a history of stroke, multiple sclerosis, epilepsy, Parkinson's disease, dementia, cerebral tumour, intracranial cyst or hydrocephalus ($n = 139$) or recorded intake of opioids or benzodiazepines ($n = 41$) were excluded. We further excluded participants with a missing value ($n = 62$) or score higher than 14 (moderately and severely depressed) ($n = 31$) on the patient health questionnaire-9 (PHQ-9) for depression (Kroenke et al., 2001). Thus, 1822 data sets were available for the current study.

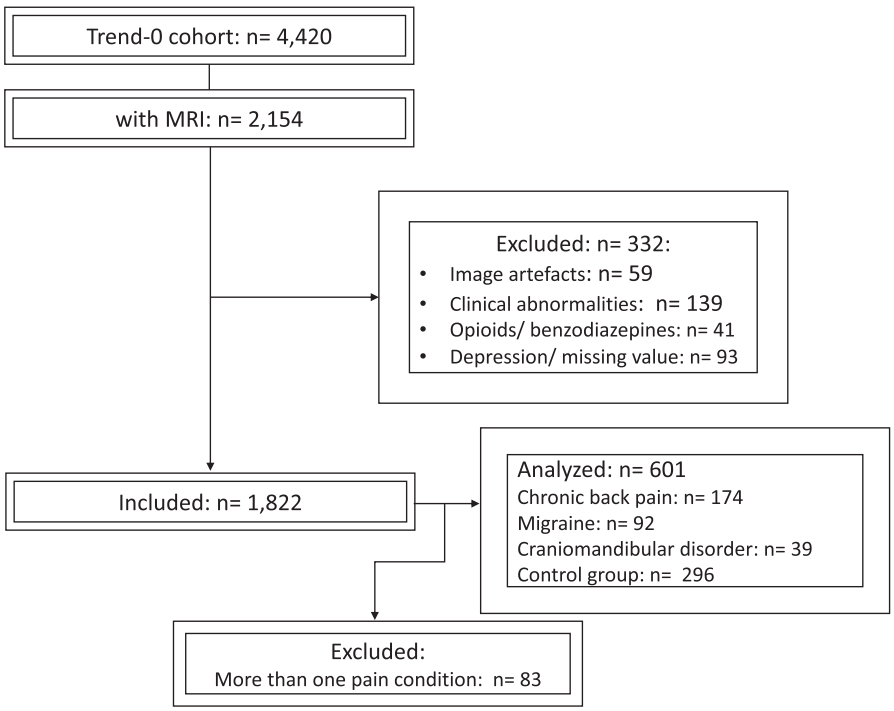

FIGURE 1 Selection of participants within the cohort study.

2.2 | Sample selection

For the selection of groups with chronic pain, the following criteria were applied: The chronic back pain (CBP) group consisted of participants who indicated back pain during 3 months within the last 12 months and were not recovered (pain intensity >0) at the time of examination. The migraine group (MIG) reported migraine that was diagnosed by a physician and lasted at least 12 months. The group with craniomandibular disorder (CMD) indicated pain in the face, masseter, the mandibular joint or in the ear region during the last 6 months with no remission at the time of examination. The control group (CTR) reported no back pain, no headache and no craniomandibular pain and no or little limitation of daily activities at home and at work because of pain during the last 4 weeks (value of 1 or 2 on a scale from 1: not at all to 5: very much). Participants who fulfilled criteria for more than one pain syndrome (CBP & MIG: $n = 29$; CBP & CMD: $n = 27$; MIG & CMD: $n = 27$) were excluded from further analysis. In the end, the CBP group comprised $n = 174$, the MIG group $n = 92$, the group with CMD $n = 39$ and the control group $n = 296$ participants.

2.3 | Assessment of variables

Additionally to pain, the following variables were assessed to compare the different pain and the control group: In a personal interview, net equivalent household income was assessed as income available per month (Euro: 1: <500, 2: 500–900, 3: 900–1300, 4: 1300–1800, 5: 1800–2300, 6: 2300–2800, 7: 2800–3300; 8: 3300–3800, 9: more than 3800) divided by number of persons living in the household. Education was assessed in absolute years. Alcohol intake was measured as the absolute amount of alcohol [g] for each day from data about the last 30 days. Cigarettes were assessed in packyears (1 packyear = 20 cigarettes per day for 1 year). The body mass index (BMI) was measured as body weight by height squared [kg/m^2]. Depression was assessed with the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). Stress was assessed using a subscale of the Questionnaire for the Assessment of Health Behaviour (Dlugosch & Krieger, 1995) comprising eight questions: Were there stressing/burdening events in the following areas of life during the last 12 months: work/school/career; marriage/partnership; family/children; friends; leisure time; financial situation; housing situation; health. Questions were answered on a Likert scale ranging from 1 to 5 (1: no events, 5: very incriminatory events). Because we intended to use this variable in the mediator analysis between the presence of chronic pain and GMV and we assumed a large overlap between the constructs of pain and health stressors, we only averaged questions 1–7 to one parameter, that is, excluded the question related to stress caused by health problems. Stressing/ burdening events were not assessed in all participants, so that there was a reduced number of subjects in each group (CBP: $n = 168$; MIG: $n = 88$; CMD: $n = 38$; CTR: $n = 270$).

2.4 | MRI assessments

Structural MRI images were acquired using a 1.5 T Siemens MRI scanner (Magnetom Verio, Siemens Medical Systems) and a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: 176 slices, matrix 256 × 176 pixels, voxel size = 1.0 mm isotropic, slice thickness = 1.0 mm, repetition time: 1900 ms, echo time = 3.37 ms, flip angle 15°.

2.5 | Data analyses

'T1-weighted images were preprocessed in MATLAB (The MathWorks) using Statistical Parametric Mapping, version 12 (SPM12; Wellcome Department of Cognitive Neurology, University of London) and the Computation Anatomy Toolbox (CAT) for SPM (CAT 12, vs. 12.8.1; http://www.neuro.uni-jena.de/cat/) applying CAT12 default parameters. Images were corrected for magnetic field inhomogenities, spatially normalized using the DARTEL algorithm25, and segmented into GM, white matter (WM) and cerebrospinal fluid (CSF). The segmentation process was further enhanced by accounting for partial volume effects and by using a hidden Markov random field (MRF) model. Finally, the resulting GM segments were smoothed using a Gaussian kernel of 8 mm full-width at half maximum (FWHM). The quality of images was assessed by using the automated image quality rating (IQR) included in the CAT12 toolbox (http://neuro.uni-jena.de/cat). It constitutes a weighted average of the local (noise contrast ratio) and global (inhomogeneity contrast ratio) standard deviations within the optimized white matter segment scaled by the minimum tissue contrast, and the root mean square of the voxel size. The obtained quality ratings range from 0.5 (100 rating points) to 10.5 (0 rating points) with values around 1 and 2 describing (very) good image quality (grad A and B) and values around 5 (grad E) and higher (grad F, <50 rating points) indicating problematic images'. Data analyses have been described before (Lotze et al., 2020, p. 5).

2.6 | Statistical analyses

A one-way ANOVA with the between-factor group (CBP, MIG, CMD, control) was conducted, using total intracranial volume (TIV) and IQR as nuisance variables to remove the related variance. Further covariates were age and sex. For thresholding, we applied $p < 0.05$ family-wise error (FWE) corrected for multiple comparisons for the whole brain. We additionally applied a region-of-interest (ROI) analysis thresholded with $p \leq 0.05$ FWE-correction for the ROI, using a composite anatomical mask of brain regions showing reduced GMV in patients with chronic pain according to a recent meta-analysis (Henn et al., 2023). The following regions were included using the ROI tool of the Anatomy Toolbox, version 3 (Eickhoff et al., 2005, 2007): bilateral amygdala (Amunts et al., 2005), thalamus (Behrens et al., 2003), hippocampus (Amunts et al., 2005), anterior cingulate cortex (Palomero-Gallagher et al., 2015), frontal pole, area Fp2 (Bludau et al., 2014) and insula (Neuromorphometrics). Because of its relevance for chronic pain (Baliki et al., 2010), additionally a ROI of the ventral striatum (Oxford-GSK-Imanova Structural–anatomical Striatal Atlas, Tziortzi et al., 2011) was added. The following contrasts were calculated: CBP < controls, MIG < controls, CMD < controls, pain groups < controls and the respective reverse contrasts. A linear regression analysis was conducted with pain intensity as independent and GMV as dependent variable.

We performed a mediation analysis (PROCESS macro29 v. 3.5, for SPSS, model 4, 10,000 bootstrap samples) for the association of pain with the correspondent grey-matter clusters (relative amount of GMV averaged over the clusters of significance derived from the whole brain VBM). The mediators were self-reported stressors during the last 12 months (Dlugosch & Krieger, 1995), and mild depression as assessed by the PHQ-9 (Kroenke et al., 2001).

A binomial logistic regression was conducted to determine the effect of GMV clusters (peak voxel) that showed a difference between pain and control groups and predict the likelihood of chronic pain. Linearity was tested assessed using the Box-Tidwell (Box & Tidwell, 1962) procedure. Bonferroni-correction was applied to all terms in the model (Tabachnick & Fidell, 2018).

3 | RESULTS

3.1 | Differences in demographic and clinical scores between pain groups and controls

Groups differed in age (MIG: 47.9 years, CMD: 44.7 years < CBP: 54.1 years, CTR: 55.0 years; $F_{3,597} = 11.7$, $p \leq 0.001$), sex ($Chi^2 = 92.0$, $p \leq 0.001$), ICR ($F_{3,597} = 16.5$, $p < 0.001$), TIV ($F_{3,597} = 11.7$, $p \leq 0.001$), depression score (CTR ≤ pain groups; $F_{3,579} = 36.0$, $p \leq 0.001$), stressors (CTR ≤ pain groups; $F_{3,568} = 21.2$, $p \leq 0.001$), alcohol (MG ≤ CBP, CTR; $F_{3,597} = 8.23$, $p \leq 0.001$); but not in education, income, cigarettes, BMI. CBP patients indicated an average pain intensity (0–10) of 5.23, MIG patients of 3.18 (last 7 days) and CMD of 2.82 with CBP patients having higher pain

intensity ratings than MIG and CMD ($F_{2,257} = 30.1$, $p \leq 0.001$). For the control group without chronic pain, no overall pain intensity data were available; 37 out of 296 participants indicated pain during the last 7 days in different body regions. Limitations of daily activities because of pain were 2.74 for CBP, 2.16 for MIG, 2.13 for CMD and 1.24 for CTR with CBP showing higher limitation ratings than all other groups, and MIG and CMD higher than CTR ($F_{3,597} = 170.2$, $p \leq 0.001$). For further characterization of pain and control groups, please refer to Table 1.

3.2 | Grey matter volume across chronic pain conditions

The whole-brain ANOVA with the between-factor 'group' showed a significant effect for the contrast 'pain' (all pain groups) < controls on GMV in the left anterior insula/temporal pole (Montreal Neurologic Institute (MNI) coordinates: −46, 14, −10; $k = 3362$ voxels, $t = 4.87$, $p = 0.014$; FWE-corrected for whole brain) and bilateral paracingulate/ anterior cingulate cortex (MNI: 2, 44, −6; $k = 2951$ voxels, $t = 4.86$, $p = 0.014$; FWE-corrected for whole brain). Using the regions of interest approach composite mask described above, there were additional effects for the left inferior posterior insula/planum polare (MNI: −42, −3, −12, $k = 266$ voxels, $t = 4.14$, $p = 0.035$, FWE-corrected for ROI) and left hippocampus/ posterior cingulate gyrus (MNI: −15, −45, 2, $k = 219$ voxels, $t = 4.12$, $p = 0.036$ FWE-corrected for ROI). The reverse contrast (pain > controls) did not yield any significant voxel, not even with a more liberal threshold of $p < 0.001$ (uncorrected). No other contrast showed a significant effect, when FWE correction was applied to the whole brain or ROI. Table 2 and Figure 2 provide an overview on the ROI-based GMV analysis.

3.3 | Grey matter volume for each pain condition

Using our composite anatomical mask including brain regions relevant for chronic pain (see above), there were uncorrected results ($p < 0.001$) for CBP < controls in the left anterior insula (MNI: −39, 16, −2, $t = 3.54$, $p = 0.001$), and superior frontal gyrus medial segment (MNI: 3, 46, −3, $t = 3.11$, $p = 0.01$), for migraine < controls, in the right anterior cingulate gyrus (MNI: 3, 32, −9, $t = 3.95$, $p = 0.001$), left planum polare (MNI: −45, −6, −14, $t = 3.83$, $p = 0.001$), left superior frontal gyrus medial segment (MNI: −12, 51, −2, $t = 3.49$, $p = 0.001$) and left hippocampus (MNI: −15, −45, 2, $t = 3.27$, $p = 0.001$), and for CMD < controls, in the right superior frontal gyrus medial segment (MNI: 10, 46, 16, $t = 3.33$, $p = 0.001$). We found no significant differences in GMV between groups with different pain syndromes. In addition, the linear regression between pain intensity and GMV yielded no significant result.

TABLE 1 Description of pain and control groups (mean [standard deviation]).

Group	Chronic back pain (CBP)	Migraine (MIG)	Cranio-mandibular pain (CMD)	Controls (CTR)	$F_{3,597}$ value/ significance	Group differences (Tukey-HSD $p < 0.05$)
Age	54.06 (12.7)	47.89 (12.1)	44.74 (14.9)	54.95 (14.2)	11.7/$p < 0.001$	MIG, CMD < CBP, CTR
Sex [m/f]	73/101	15/77	8/31	197/99	92.0/$p < 0.001$	CBP ≠ MIG, CMD ≠ CTR
TIV	1532 (149)	1503 (128)	1489 (154)	1550 (150)	11.7/$p < 0.001$	CBP, MIG, CMD < CTR
IQR	2.77 (0.32)	2.64 (0.23)	2.56 (0.17)	2.84 (0.35)	16.5/$p < 0.001$	MIG, CMD < CBP, CTR
Education	12.67 (2.3)	12.47 (2.1)	13.00 (2.4)	13.1 (2.6)	1.82/$p = 0.14$	
Income	1264 (608)	1407 (672)	1322 (600)	1491 (731)	0.08/$p = 0.97$	
Alcohol (g/day)	7.75 (11.6)	3.66 (6.94)	8.33 (13.3)	10.3 (12.1)	8.23/$p = 0.001$	MIG < CBP, CTR
Cigarettes (packyears)	7.47 (13.9)	3.98 (8.72)	6.17 (13.3)	7.40 (12.3)	2.03/$p = 0.11$	
BMI	28.3 (4.6)	27.1 (4.9)	27.2 (4.4)	27.9 (4.2)	1.74/$p = 0.16$	
PHQ9	4.43 (3.0)	4.35 (3.4)	5.92 (3.5)	2.24 (2.5)	36.0/$p < 0.001$	CTR < CBP, MIG < CMD
Stressors	1.98 (0.84)	2.05 (0.81)	2.08 (0.64)	1.64 (0.69)	21.2/$p < 0.001$	CTR < CBP, MIG, CMD
Pain intensity[a]	5.23 (2.00)	3.18 (3.12)	2.82 (1.45)		30.06/$p < 0.001$	MIG, CMD < CBP
Pain limitation degree[b]	2.74 (0.96)	2.16 (0.83)	2.13 (0.80)	1.24 (0.43)	170.2/$p < 0.001$	CTR < MIG, CMD < CBP

Abbreviations: BMI, body mass index; IQR, image quality rating; PHQ9, patient health questionnaire for depression; TIV, total intracranial volume.

[a]0–10.

[b]1–5.

TABLE 2 Results of the region of interest (ROI) analysis with a composite mask comprising the bilateral amygdala, thalamus, hippocampus, insula, anterior cingulate cortex, ventral striatum and frontal pole, area Fp2.

Region	Hemisphere	*T* value	*p* value, (FWE-corrected for ROI)	Cluster size	MNI coordinates		
					x	y	z
Paracingulate gyrus, anterior cingulate, area s32	R	4.79	0.003	2208	3	42	−8
Insular cortex, area ld6 (dorsal anterior)	L	4.17	0.027	655	−40	16	−3
Insular cortex, area ld3 (inferior posterior), planum polare	L	4.14	0.035	266	−42	−3	−12
Hippocampus, subiculum, CA1; posterior cingulate gyrus	L	4.12	0.036	219	−15	−45	2

Note: *p*-values are family wise error-corrected ($p < 0.05$) for the ROI.

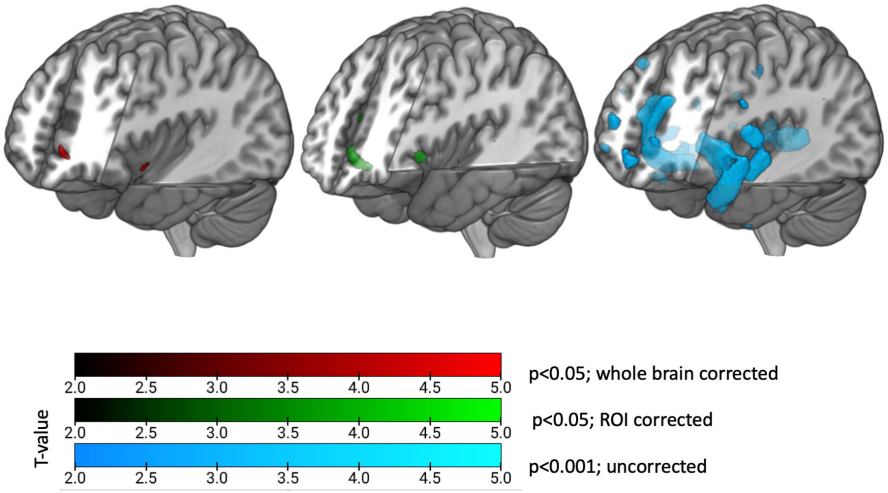

FIGURE 2 Overlay of the three statistical maps of the contrast pain < controls for three thresholds: For the FWE-corrected for the whole brain correction, there was less GMV in the ACC and anterior left insula (red). For the FWE correction within the ROI, left posterior insula and left hippocampus were additionally significant (green). For the uncorrected comparison ($p < 0.001$), bilateral trends for less GMV were evident (blue).

3.4 | Mediators of chronic pain

The relationship of pain (pain groups vs. controls) with GMV in the left hippocampus was mediated by self-reported stressors (burdening life events) in the last 12 months (direct effect x on y = 0.0229, $t = 4.45$, $p = 0.00001$; indirect effect x on y = −0.00282, 95% CI −0.00614273 to 0.00001919) (Figure 3). There was no mediating effect of mild depression.

3.5 | Prediction of chronic pain by grey matter volume

All variables were found to follow a linear relationship. Correlations between predictor variables were low ($r < 0.46$), indicating that multicollinearity was not a confounding factor in the analysis. Goodness-of-fit was assessed using the Hosmer–Lemeshow test, indicating a good model fit, $\chi^2(8) = 4.71$, $p > 0.05$. The binomial logistic regression model was statistically significant, $\chi^2(4) = 22.7$, $p < 0.001$, resulting in a small amount of explained variance, as shown by Nagelkerke's $R^2 = 0.049$. The overall percentage of accuracy in classification was 58.4%, with a sensitivity of 64.4% and a specificity of 52.2%. Of the four GMV clusters entered into the regression model, the left hippocampus ($p = 0.011$) and left anterior insula/temporal pole ($p = 0.043$) contributed significantly in predicting chronic pain, and the paracingulate/anterior cingulate cortex ($p = 0.069$) showed a trend, but not the left inferior posterior insula/planum polare.

4 | DISCUSSION

The current study set out to investigate the association of different chronic pain syndromes (chronic back pain, migraine, craniomandibular disorder) and the brain's grey-matter volume in a population-based cohort under consideration of confounding variables and mediators as well as the potential predictive value of altered grey matter for chronic pain. Significantly less GMV was found in clusters of the left dorsal anterior insula/temporal pole,

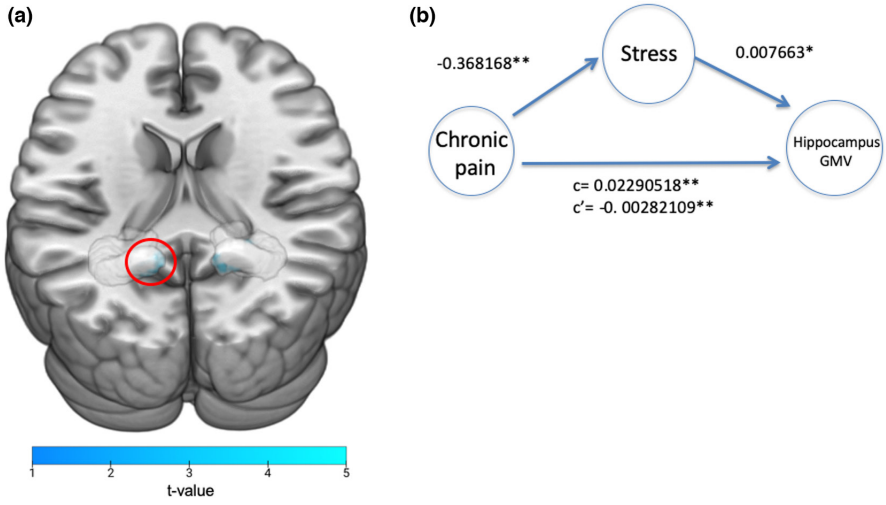

FIGURE 3 Stressors of the last 12 months as mediator of the association between chronic pain (X) with grey matter volume in the left hippocampus (Y). All regression coefficients were significant as indicated with *p*-values ($p < 0.05$*; $p < 0.01$**). (a) Less hippocampal GMV (coded in blue—see colour coding for T-values below; hippocampus ROI visualized) showed to be rather symmetric but was significant only for the left hemisphere after correction for multiple comparisons within all ROIs predefined. (b) Mediation analysis demonstrated significant mediation of chronic pain intensity by experienced stress on GMV of the left hippocampus GMV (effect for the highest significant voxel: $t = 4.12$; MNI-coordinates: −15, −45, 2).

bilateral paracingulate/anterior cingulate cortex, left posterior insula and the left hippocampal/posterior cingulate region when contrasting all three pain syndromes together with controls; no region showed larger GMV. Single pain conditions did not show altered GMV in comparison to controls when correcting for multiple comparisons. One reason for this may be the still too low number of included participants because effect sizes of comparisons between GMV in individuals with chronic pain and controls are generally very small (Tagliaferri et al., 2022). Second, the diagnosis of chronic pain in population-based cohort studies is based on self-reported questionnaire data, what may reduce their validity. Third, in the current study, groups were comparable with regard to psychosocial variables, so that GMV differences between groups were not confounded and may be smaller than in other studies.

Overall, our analysis suggests a common mechanism for the reduction of grey matter volume across the three different pain syndromes investigated here. With respect to the localization, less GMV in the left anterior and posterior insula and bilateral cingulate cortex has been often replicated across different types of chronic pain (Baliki et al., 2011; Cauda et al., 2014; Henn et al., 2023; Mayr et al., 2022) with these structures constituting major hubs for pain processing (Bliss et al., 2016; Kohoutová et al., 2022; Kuner & Flor, 2017; Kurth et al., 2010). The posterior insula has been framed as an interoceptive system receiving information about pain as well as temperature, itch, sensual touch, muscular and visceral sensations, vasomotor activity, hunger and thirst, whereas the anterior insula forms a meta-representation of interoceptive and exteroceptive information providing the basis for subjective awareness (Craig, 2003). The ACC, on the other hand, has a role in behavioural drive and volition (Craig, 2003). Both are part of a salience network integrating information about the significance of a stimulation into decision-making in the context of pain (Seeley et al., 2007; Wiech et al., 2010). Chronic pain goes along with long-term changes in synaptic transmission in the anterior cingulate and insula (Bliss et al., 2016; Zhuo, 2020). Neuropathic pain, using nerve compression models in rodents, revealed a loss of GMV after surgery in the primary somatosensory cortex, anterior cingulate and insula (Seminowicz et al., 2009), which has also been observed in human patients (Rodriguez-Raecke et al., 2009).

Hippocampal grey matter reduction recently moved into focus and may be a 'key player for the development of chronic pain in the first place' (Barroso et al., 2021). Hippocampal abnormalities have been demonstrated in animals and human patients with persistent pain (e.g., Mutso et al., 2012), especially in women (Reckziegel et al., 2021). It is well known that stress and pain cause dendritic shrinkage and loss of spine in the hippocampus by elevated levels of glucocorticoids along with excitatory amino acid neurotransmitters (McEwen, 2006; McEwen et al., 2015). In a mouse model of neuropathic pain, lower hippocampal connectivity was accompanied by enhanced glutamate concentrations in the hippocampus contributing to pain chronification (Bilbao et al., 2018). Hippocampal dysfunction may be also responsible for maladaptive emotional learning and motivation in chronic pain (Barroso et al., 2021;

Nees et al., 2020). Local morphological alterations of the brain going along with chronic pain were found to be partly reversible when pain ceased to exist after surgery (Rodriguez-Raecke et al., 2009). On the other hand, the smaller hippocampal volume also constitutes a predisposition to develop a maladaptive stress response and persistent pain (Vachon-Presseau et al., 2013). This may be in line with the relationship of pain with left hippocampal GMV being mediated by self-reported stressors in the last 12 months in the current study. Mild depression was not a mediator in this study, what may be due to the fact that participants with moderate and high depression scores were excluded from it.

Left hippocampal and anterior insula GMV was able to predict the presence or absence of chronic pain in a model that had a classification accuracy of 58.4%, even if the explained variance was minimal. A previous study forming subgroups of patients with chronic back pain on the basis of psychosocial and brain structural and connectivity variables using machine learning demonstrated that classification accuracy dropped considerably, when a control group was added to the model derived (Tagliaferri et al., 2022). This reflects the fact that neither psychosocial nor brain-derived measures are specific for pain, but may occur in other conditions and functional networks (attention, emotion, memory, interoception, reward; Cauda et al., 2012). Brain structural measures did not contribute to classification in the above-mentioned study (Tagliaferri et al., 2022). Using variables reflecting pain modulation in individuals rather than those which differ between pain and control groups may be a promising way to obtain clinically useful predictors on pain at the individual level (Mouraux & Iannetti, 2018; see also Mayr et al., 2022). Rather than being specific for the sensation of pain per se, these predictors only need to vary systematically with pain intensity in order to effectuate mechanism-based stratification of pain conditions, prognosticate response to medication and provide personalized treatment (Mouraux & Iannetti, 2018). To this end, brain structural measures as well as physical and psychosocial variables (see also Mills et al., 2019) may contribute to composite biomarkers.

We, therefore, corroborated the results of previous studies showing less GMV in well-known regions activated via ascending nociceptive pathways (anterior and posterior insula, anterior and posterior cingulate cortex (Kuner & Flor, 2017)), and the left hippocampus.

4.1 | Limitations

The current study analysed data from community-dwelling adults gathered in a population-based survey (Völzke et al., 2011) not specifically aimed to investigate pain, so that the different pain conditions were not equally characterized and the collected variables were based on self-report. The outcome of comparisons between pain groups and the control group is naturally determined by the composition of the control group. While in the current study, the control group was comparable to the pain groups with regard to many possible confounders, they differed in other variables, what may have had an impact on the results. However, we reduced the influence of these variables by including them as covariates in our VBM analyses (sex, age, TIV, IQR) or investigating them as possible mediators (stress, depression). Additionally, it cannot be ruled out that some control participants had chronic pain apart from the three pain conditions investigated here that had no or little significant impact on daily activities, what may limit comparisons.

Participants with pain that may have different underlying mechanisms were evaluated: Low back pain and craniofacial pain, in most cases, may have a nociplastic component as the major mechanism, but neuropathic, nociceptive origin or even mixed pain might be present. In migraines, the nociplastic component predominates. Since, except for migraine, there has been no clinical evaluation to assess the main pain syndromes, the evaluation of these components is limited. Therefore, it is not possible to evaluate whether brain alterations can be generalized to chronic pain in general or certain pain mechanisms, such as nociplastic pain. Although patients using benzodiazepines and opioids to treat pain, were excluded, other conditions, such as anxiety, were not reported and may be confounding factors in the analysis. Also, cognitive assessment or reporting of cognitive changes, described in patients with chronic pain, especially with nociplastic component, could complement the assessment.

AUTHOR CONTRIBUTIONS

Nicola Neumann performed the data analysis and wrote the first draft of the manuscript. Martin Domin did all preprocessing data analyses. Carsten-Oliver Schmidt contributed to data collection. Martin Lotze planned the study and wrote the manuscript. All authors discussed the results and commented on the manuscript.

ACKNOWLEDGEMENTS

This study has been funded by the 'Deutsche Forschungsgemeinschaft' (DFG- LO 795/37-1). The Study of Health in Pomerania (SHIP) is part of the Community Medicine Network of the University Medicine Greifswald, which is supported by the Federal State of Mecklenburg-West Pomerania. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

Deutsche Forschungsgemeinschaft (DFG- LO 795/37-1); The Study of Health in Pomerania (SHIP) is part of the Community Medicine Network of the University Medicine Greifswald, which is supported by the Federal State of Mecklenburg-West Pomerania.

CONFLICT OF INTEREST STATEMENT

The authors report no competing interests.

ORCID

Nicola Neumann https://orcid.org/0000-0001-9055-3714

Martin Lotze https://orcid.org/0000-0003-4519-4956

REFERENCES

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N. J., Habel, U., Schneider, F., & Zilles, K. (2005). Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. *Anatomy and Embryology (Berlin)*, *210*, 343–352.

Baliki, M. N., Geha, P. Y., Fields, H. L., & Apkarian, A. V. (2010). Predicting value of pain and analgesia: Nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron*, *66*, 149–160.

Baliki, M. N., Schnitzer, T. J., Bauer, W. R., & Apkarian, A. V. (2011). Brain morphological signatures for chronic pain. *PLoS One*, *6*, e26010.

Barroso, J., Branco, P., & Apkarian, A. V. (2021). Brain mechanisms of chronic pain: Critical role of translational approach. *Translational Research*, *238*, 76–89.

Behrens, T. E. J., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A. M., Boulby, P. A., Barker, G. J., Sillery, E. L., Sheehan, K., Ciccarelli, O., Thompson, A. J., Brady, J. M., & Matthews, P. M. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience*, *6*, 750–757.

Bilbao, A., Falfán-Melgoza, C., Leixner, S., Becker, R., Singaravelu, S. K., Sack, M., Sartorius, A., Spanagel, R., & Weber-Fahr, W. (2018). Longitudinal structural and functional brain network alterations in a mouse model of neuropathic pain. *Neuroscience*, *387*, 104–115.

Bliss, T. V. P., Collingridge, G. L., Kaang, B.-K., & Zhuo, M. (2016). Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nature Reviews. Neuroscience*, *17*, 485–496.

Bludau, S., Eickhoff, S. B., Mohlberg, H., Caspers, S., Laird, A. R., Fox, P. T., Schleicher, A., Zilles, K., & Amunts, K. (2014). Cytoarchitecture, probability maps and functions of the human frontal pole. *NeuroImage*, *93*(Pt 2), 260–275.

Box, G. E. P., & Tidwell, P. W. (1962). Transformation of the independent variables. *Technometrics*, *4*, 531–550.

Cauda, F., Palermo, S., Costa, T., Torta, R., Duca, S., Vercelli, U., Geminiani, G., & Torta, D. M. E. (2014). Gray matter alterations in chronic pain: A network-oriented meta-analytic approach. *NeuroImage Clin*, *4*, 676–686.

Cauda, F., Torta, D. M.-E., Sacco, K., Geda, E., D'Agata, F., Costa, T., Duca, S., Geminiani, G., & Amanzio, M. (2012). Shared "Core" areas between the pain and other task-related networks. *PLoS One*, *7*, e41929.

Cohen, S. P., & Mao, J. (2014). Neuropathic pain: Mechanisms and their clinical implications. *BMJ*, *348*, f7656.

Cohen, S. P., Vase, L., & Hooten, W. M. (2021). Chronic pain: An update on burden, best practices, and new advances. *The Lancet*, *397*, 2082–2097.

Craig, A. D. (Bud). (2003). Pain mechanisms: Labeled lines versus convergence in central processing. *Annual Review of Neuroscience*, *26*, 1–30.

Dlugosch, G. E., & Krieger, D. (1995). *Fragebogen zur Erfassung des Gesundheitsverhaltens: FEG*. Swets Test Services.

Eickhoff, S. B., Paus, T., Caspers, S., Grosbras, M.-H., Evans, A. C., Zilles, K., & Amunts, K. (2007). Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *NeuroImage*, *36*, 511–521.

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, *25*, 1325–1335.

Fitzcharles, M.-A., Cohen, S. P., Clauw, D. J., Littlejohn, G., Usui, C., & Häuser, W. (2021). Nociplastic pain: Towards an understanding of prevalent pain conditions. *The Lancet*, *397*, 2098–2110.

Henn, A. T., Larsen, B., Frahm, L., Xu, A., Adebimpe, A., Scott, J. C., Linguiti, S., Sharma, V., Basbaum, A. I., Corder, G., Dworkin, R. H., Edwards, R. R., Woolf, C. J., Habel, U., Eickhoff, S. B., Eickhoff, C. R., Wagels, L., & Satterthwaite, T. D. (2023). Structural imaging studies of patients with chronic pain: An anatomical likelihood estimate meta–analysis. *Pain*, *164*(1), e10–e24.

Kohoutová, L., Atlas, L. Y., Büchel, C., Buhle, J. T., Geuter, S., Jepma, M., Koban, L., Krishnan, A., Lee, D. H., Lee, S., Roy, M., Schafer, S. M., Schmidt, L., Wager, T. D., & Woo, C.-W. (2022). Individual variability in brain representations of pain. *Nature Neuroscience*, *25*, 749–759.

Kosek, E., Cohen, M., Baron, R., Gebhart, G. F., Mico, J.-A., Rice, A. S. C., Rief, W., & Sluka, A. K. (2016). Do we need a third mechanistic descriptor for chronic pain states? *Pain*, *157*, 1382–1386.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*, *16*, 606–613.

Kuner, R. (2010). Central mechanisms of pathological pain. *Nature Medicine*, *16*, 1258–1266.

Kuner, R., & Flor, H. (2017). Structural plasticity and reorganisation in chronic pain. *Nature Reviews. Neuroscience*, *18*, 20–30.

Kurth, F., Zilles, K., Fox, P. T., Laird, A. R., & Eickhoff, S. B. (2010). A link between the systems: Functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Structure & Function*, *214*, 519–534.

Lotze, M., Domin, M., Schmidt, C. O., Hosten, N., Grabe, H. J., & Neumann, N. (2020). Income is associated with hippocampal/amygdala and education with cingulate cortex grey matter volume. *Scientific Reports*, *10*, 18786.

Mayr, A., Jahn, P., Stankewitz, A., Deak, B., Winkler, A., Witkovsky, V., Eren, O., Straube, A., & Schulz, E. (2022). Patients with chronic pain exhibit individually unique cortical signatures of pain encoding. *Human Brain Mapping*, *43*, 1676–1693.

McEwen, B. S. (2006). Plasticity of the hippocampus: Adaptation to chronic stress and allostatic load. *Annals of the New York Academy of Sciences*, *933*, 265–277.

McEwen, B. S., Bowles, N. P., Gray, J. D., Hill, M. N., Hunter, R. G., Karatsoreos, I. N., & Nasca, C. (2015). Mechanisms of stress in the brain. *Nature Neuroscience*, *18*, 1353–1363.

Mills, S. E. E., Nicolson, K. P., & Smith, B. H. (2019). Chronic pain: A review of its epidemiology and associated factors in population-based studies. *British Journal of Anaesthesia*, *123*, e273–e283.

Mouraux, A., & Iannetti, G. D. (2018). The search for pain biomarkers in the human brain. *Brain*, *141*, 3290–3307.

Mutso, A. A., Radzicki, D., Baliki, M. N., Huang, L., Banisadr, G., Centeno, M. V., Radulovic, J., Martina, M., Miller, R. J., & Apkarian, A. V. (2012). Abnormalities in hippocampal functioning with persistent pain. *The Journal of Neuroscience*, *32*, 5747–5756.

Nees, F., Ruttorf, M., Fuchs, X., Rance, M., & Beyer, N. (2020). Brain-behaviour correlates of habitual motivation in chronic back pain. *Scientific Reports*, *10*, 11090.

Palomero-Gallagher, N., Eickhoff, S. B., Hoffstaedter, F., Schleicher, A., Mohlberg, H., Vogt, B. A., Amunts, K., & Zilles, K. (2015). Functional organization of human subgenual cortical areas: Relationship between architectonical segregation and connectional heterogeneity. *NeuroImage*, *115*, 177–190.

Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., Keefe, F. J., Mogil, J. S., Ringkamp, M., Sluka, K. A., Song, X.-J., Stevens, B., Sullivan, M. D., Tutelman, P. R., Ushida, T., & Vader, K. (2020). The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. *Pain*, *161*, 1976–1982.

Reckziegel, D., Abdullah, T., Wu, B., Wu, B., Huang, L., Schnitzer, T. J., & Apkarian, A. V. (2021). Hippocampus shape deformation: A potential diagnostic biomarker for chronic back pain in women. *Pain*, *162*, 1457–1467.

Reckziegel, D., Vachon-Presseau, E., Petre, B., Schnitzer, T. J., Baliki, M. N., & Apkarian, A. V. (2019). Deconstructing biomarkers for chronic pain: Context- and hypothesis-dependent biomarker types in relation to chronic pain. *Pain*, *160*, S37–S48.

Rodriguez-Raecke, R., Niemeier, A., Ihle, K., Ruether, W., & May, A. (2009). Brain Gray matter decrease in chronic pain is the consequence and not the cause of pain. *The Journal of Neuroscience*, *29*, 13746–13750.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience*, *27*, 2349–2356.

Seminowicz, D. A., Laferriere, A. L., Millecamps, M., Yu, J. S. C., Coderre, T. J., & Bushnell, M. C. (2009). MRI structural brain changes associated with sensory and emotional function in a rat model of long-term neuropathic pain. *NeuroImage*, *47*, 1007–1014.

Tabachnick, B. G., & Fidell, L. S. (2018). *Using multivariate statistics*. Pearson Education.

Tagliaferri, S. D., Fitzgibbon, B. M., Owen, P. J., Miller, C. T., Bowe, S. J., & Belavy, D. L. (2022). Brain structure, psychosocial, and physical health in acute and chronic back pain: A UK biobank study. *Pain*, *163*, 1277–1290.

Tziortzi, A. C., Searle, G. E., Tzimopoulou, S., Salinas, C., Beaver, J. D., Jenkinson, M., Laruelle, M., Rabiner, E. A., & Gunn, R. N. (2011). Imaging dopamine receptors in humans with [11C]-(+)-PHNO: Dissection of D3 signal and anatomy. *NeuroImage*, *54*, 264–277.

Vachon-Presseau, E., Roy, M., Martel, M.-O., Caron, E., Marin, M.-F., Chen, J., Albouy, G., Plante, I., Sullivan, M. J., Lupien, S. J., & Rainville, P. (2013). The stress model of chronic pain: Evidence from basal cortisol and hippocampal structure and function in humans. *Brain*, *136*, 815–827.

Völzke, H., Alte, D., Schmidt, C. O., Radke, D., Lorbeer, R., Friedrich, N., Aumann, N., Lau, K., Piontek, M., Born, G., Havemann, C., Ittermann, T., Schipf, S., Haring, R., Baumeister, S. E., Wallaschofski, H., Nauck, M., Frick, S., Arnold, A., … Hoffmann, W. (2011). Cohort profile: The study of health in Pomerania. *International Journal of Epidemiology*, *40*, 294–307.

Wiech, K., Lin, C., Brodersen, K. H., Bingel, U., Ploner, M., & Tracey, I. (2010). Anterior insula integrates information about salience into perceptual decisions about pain. *The Journal of Neuroscience*, *30*, 16324–16331.

Zhuo, M. (2020). Cortical plasticity as synaptic mechanism for chronic pain. *Journal of Neural Transmission*, *127*, 567–573.

How to cite this article: Neumann, N., Domin, M., Schmidt, C.-O., & Lotze, M. (2023). Chronic pain is associated with less grey matter volume in the anterior cingulum, anterior and posterior insula and hippocampus across three different chronic pain conditions. *European Journal of Pain*, *27*, 1239–1248. https://doi.org/10.1002/ejp.2153