Observational Study

Gender Differences in the Association of Brain Gray Matter and Pain-Related Psychosocial Characteristics

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Background: Although the association of gray matter morphology alterations and pain-related psychosocial characteristics with pain intensity and chronification in people with chronic spinal pain is evident, research on their mutual interaction is scarce and does not account for possible gender differences. Gender-based differences are, however, of utmost importance to consider when examining pain neurobiology.

Objectives: To look for gender differences in the association between magnetic resonance imaging- (MRI) derived brain gray matter morphology and self-reported psychosocial characteristics.

Study Design: An explorative, observational study.

Setting: University Hospitals Ghent and Brussels, Belgium.

Methods: Brain gray matter morphology (using MRI) and self-reported psychosocial characteristics were examined in women and men with nonspecific chronic spinal pain. Statistical analyses were performed in SPSS and R to identify differences between men and women regarding brain gray matter, self-reported psychosocial characteristics, as well as gender differences in the association between those outcome measures.

Results: A total of 94 people with chronic spinal pain were studied, including 32 men (15 suffering from neck pain, 17 suffering from low back pain; demographics [mean ± SD] age: 45.00 ± 12.02 years; pain duration: 128.37 ± 110.45 months), and 62 women (36 suffering from neck pain, 26 suffering from low back pain; demographics [mean ± SD] age: 38.78 ± 12.69 years; pain duration: 114.27 ± 92.45 months). Woman showed larger (positive) associations of several central brain areas (paracentral, precentral, postcentral, etc.) with perceived consequences ($P < 0.001$), emotional representations ($P < 0.001$), chronicity ($P < 0.001$), and pain catastrophizing ($P < 0.001$). Men showed larger (both positive and negative) associations of the precuneus cortex, the precentral gyrus, and the insula with perceived personal control ($P < 0.001$) and kinesiophobia ($P < 0.001$).

Limitations: Other factors, such as menstrual cycle and medication can have a certain influence, and were only partly taken into consideration in the present investigation to obtain sufficient power. Another limitation is the observational study design, which hampers the possibility to look for causal or temporal interactions.

Conclusions: Gray matter morphology relates differently to psychosocial characteristics in women and men. These explorative findings provide ideas for further research to investigate if targeting perceived negative consequences of the illness, perceived emotional representations, perceived chronicity, and pain catastrophizing in women, and perceived personal control of the illness and kinesiophobia in men, could contribute to the normalization of brain alterations in people with nonspecific chronic spinal pain.

Key words: Gray matter, brain morphology, central nervous system, illness perceptions, central sensitization

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In the chronic pain field, emerging techniques contributed to a paradigm shift toward modern pain neurosciences (1). The use of magnetic resonance imaging (MRI) increased the understanding that many patients with chronic pain demonstrate alterations within the central nervous system in general and the brain in particular (2-4). These neuroplastic changes in the brain, including alterations in gray matter properties, show a strong association with the persistence of pain, even long after the extinction of the primary nociceptive input (5,6).

Also, in patients with nonspecific chronic spinal pain (nCSP), alterations in brain structure are present (7). These patients experience spinal pain owing to a nonspecific cause (i.e., no specific medical cause can be found to explain the pain). nCSP includes chronic low back pain, failed back surgery syndrome (e.g., >3 years ago, anatomically successful operation without symptom disappearance), chronic whiplash associated disorders, and chronic nontraumatic idiopathic neck pain. Patients with chronic low back pain, for example, demonstrate changes in gray matter volume (2,7-11) and cortical thickness (8,12,13). However, the challenge of these advances in pain neuroscience lies in the translation to clinical practice. Although these brain changes are well established in patients with chronic pain, it remains largely unknown how to reverse them.

Besides the established association between pain chronification and neuroplasticity, maladaptive pain-related psychosocial characteristics are also known to play a cardinal role in the occurrence and persistence of nCSP (14). These pain-related psychosocial characteristics include kinesiophobia, pain catastrophizing, maladaptive illness perceptions (i.e., perceived chronicity, controllability, symptoms, duration, and others), and hypervigilance (15-17). They are identified as important predictors of pain and disability (18,19), and their presence is related to poor treatment outcome in patients with nCSP (20-23). Therefore, the association between brain gray matter changes and these pain-related psychosocial characteristics is important for unravelling the nature behind the established brain gray matter changes in people with nCSP. For example, evidence shows a significant negative association between brain gray matter structure and pain catastrophizing in patients with irritable bowel syndrome (24), but this association has not been considered in people with nCSP nor have gender differences been taken into account.

Gender-based differences are, however, of utmost importance to consider when examining pain neurobiology (25). Although the experience of pain is highly similar in men and women, important gender differences exist at the level of pain processing, pain mechanisms, and behavioral responses to pain (26-28). In patients with chronic pain, in particular, different studies indicate more prominent alterations in the primary sensorimotor cortex, enhanced anterior cingulate structural alterations, and greater amygdala functional responsivity (i.e., greater emotional-arousal responses) in women compared to men (29-32), whereas men show greater insula reactivity (33).

Because these brain regions involved in the emotional-arousal and affective-cognitive processing of pain show different alterations and reactivity in men and women, we presume that gender differences will be present in the association of pain-related psychosocial characteristics and brain gray matter. If present, they might indicate that therapists should address psychosocial characteristics as a key target during therapy differently in men and women. Therefore, this study examined if gender differences can be found in the association of gray matter with pain-related psychosocial characteristics in patients with nCSP.

Methods

Study Design

This cross-sectional observational multicenter study took place in 2 centers: the University Hospitals of Ghent and Brussels. Patients' informed consent was obtained before participation and ethical approval was granted by the medical ethics committees of the University Hospitals of Ghent (2013/1133) and Brussels (2013/385). Patients were recruited and tested between January 2014 and January 2016. Patients filled out a series of questionnaires online in standardized order. All MRI scans were performed at the University Hospital Ghent.

Patients

To optimize external validity of the study findings, right-handed persons with nCSP were recruited through different sources: flyers in the Universities and University Hospitals of Brussels and Ghent, occupational health services and primary care practices, and via social media and adverts. Persons were found eligible for study participation when meeting the following criteria: native Dutch speakers, between ages 18 and 65 years, having nCSP (including chronic low back pain, chronic whiplash associated disorders, and chronic nontraumatic neck pain) for at least 3 months and at

least 3 days per week, not starting a new treatment or medication 6 weeks prior to study participation to obtain a steady state.

Exclusion criteria were: a specific medical diagnosis, possibly related to their pain (e.g., neuropathic pain, chronic fatigue syndrome, fibromyalgia, a history of neck/back surgery in the past 3 years, and others). Additionally, people living > 50 km away from the study location were excluded to avoid cancellation (34).

Pain-Related Psychosocial Characteristics

Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) assesses catastrophic thoughts regarding pain and contains 13 items, scored on a 5-point Likert-scale, that describe different thoughts and feelings that one may experience during pain. The 13 items lead to 3 subscales: rumination (4 items), magnification (3 items), and helplessness (6 items), and a total score. Higher scores indicate more pain catastrophizing (35). The PCS has adequate reliability in various subgroups of musculoskeletal disorders (36), and has good criterion and construct validity (36,37).

Tampa Scale for Kinesiophobia

The Tampa Scale for Kinesiophobia (TSK) assesses fear of movement or (re)injury and contains 17 items, each scored on a 4-point Likert-scale. Total scores range from 17-68 (cut-off score = 37), with higher scores indicating higher fear of movement (38,39). The TSK has a moderate construct validity and excellent test-retest reliability (39,40).

Illness Perception Questionnaire

The revised Illness Perception Questionnaire (IPQr) measures several dimensions of illness perceptions, all scored on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). The "acute/chronic timeline" (5 items) and "cyclical timeline" (4 items) domains assess the patients' beliefs regarding the course of their pain and the time scale of illness symptoms. The "consequences" domain (6 items) refers to beliefs regarding the impact of the illness on quality of life and functional capacity. The "personal control" (6 items) and "treatment control" (5 items) domains measure the perceived influence of own behavior and treatment efficacy. The "emotional representations" domain (6 items) refers to emotional responses generated by the illness. The "illness coherence" (5 items) domain assesses to which degree a participant has a coherent understanding of his or her illness (41,42). The IPQr has a good test-retest reliability, factor structure, and predictive validity in different patient populations (42).

Pain Vigilance and Awareness Questionnaire

The Pain Vigilance and Awareness Questionnaire (PVAQ) measures the patient's awareness of and attention to pain in 16 items. The total score ranges from 0-80, with higher scores indicating a higher degree of pain vigilance and awareness. The questionnaire correlates highly with the construct of general body vigilance (43), it has good internal consistency and test-retest reliability, and is shown valid and reliable in several chronic pain populations (43-45).

Brain MRI

Data Acquisition

MRI images were acquired on a 3T Siemens Magnetom TrioTim system (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel RF head coil. A T1-weighted sequence with a magnetization prepared rapid gradient-echo was used to acquire anatomic images of the brain (256 x 256 matrix, repetition time = 2250 ms, echo time = 4.18 ms, flip angle = 9°, 176 slices, 1 mm slice thickness, voxel-size = 1.00 x 1.00 x 1.00 mm, field of view = 25.6 x 25.6 cm, 5'14" acquisition time). All scans were visually checked for overall quality and motion artefacts.

Data Processing

Anatomic scans were analyzed using FreeSurfer v5.3.0. The structural images were analyzed with the FreeSurfer analysis suite (http://surfer.nmr.mgh.harvard.edu/), using additional computing resources from the high-performance computing TIER1 cluster at the University of Ghent (http://ugent.be/hpc/). Briefly, the following steps were conducted: 1) removal of nonbrain tissue using a hybrid watershed/surface deformation procedure (skull stripping) (46); 2) automated transformation to Talairach space; 3) intensity normalization (47); 4) subject specific segmentation of the subcortical white matter and deep gray matter volumetric structures (48,49); 5) Tessellation of the boundary between gray and white matter, automated topology correction (50,51), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders (52-54); 6) inflation of the individual surfaces (55), and registration to a spherical

atlas based on individual cortical folding patterns to match across-subjects cortical geometry (56); 7) parcellation of the cerebral cortex into units with respect to gyral and sulcal structure according to the Desikan-atlas (49,57); and 8) calculation of spatial maps with estimates for cortical thickness, cortical area, and cortical volume. These maps are created using spatial intensity gradients across tissue classes and are not restricted to the voxel resolution of the original data, and thus, can detect submillimeter differences between groups. These procedures have been validated against histological analysis (58) and manual measurements (59,60). Images of each subject were visually inspected to ensure the accuracy of the skull stripping, segmentation, parcellation, and cortical surface reconstruction. In addition, if the gray matter boundary included dura, the dura was removed manually. If single-subject corrections took > 30 minutes, the data quality of these subjects were labelled as inadequate, which led to the exclusion of the subject.

Statistical Analysis

Using SPSS Version 24.0 (IBM Corporation, Armonk, NY), population characteristics (age, length, weight, duration of spinal pain, diagnosis, and pain-related psychosocial characteristics) were analyzed for differences between men and women using independent t tests, the Mann-Whitney U tests, or the Fisher exact tests depending on the distribution and nature of the specific variable.

All other analyses were performed using statistics department of the University of Auckland, New-Zealand. Associations between brain morphology and pain-related psychosocial characteristics were tested by estimating a general linear model (GLM) at each vertex. Groups were added as fixed factors together with age as a covariate and the questionnaires (PCS, TSK, IPQr and PVAQ) as variables of interest. Models were estimated for each variable of interest, using cortical thickness, surface area, and volume as dependent variables in the different models. The GLM estimated both main effects and interactions using the build-in DODS (different onsets, different slopes) option in FreeSurfer. Thereafter, t-contrasts were applied to test for significant gender variables of interest interactions at each vertex at a significance level $\kappa < 0.05$.

Data were Bonferroni-corrected for analysis in both hemispheres to keep the family-wise error rate < 0.05 and subjected to cluster-wise correction for multiple comparison at a cluster-based significance level of < 0.05 using a Z Monte Carlo simulation with 5,000 iterations. For each cluster, the *P* value resembles the probability of seeing a maximum cluster of that particular size or larger during the simulation. Information on cluster-wise *P* values with its corresponding 90% confidence intervals were reported.

Results

Patients Characteristics

One-hundred thirteen persons with nCSP were included in the present study and were subjected to the MRI scan and self-reported questionnaires. After analysis of the MRI data in FreeSurfer, a total of 19 patients (5 women; 14 men) were excluded from the final analyses owing to errors of the gray and white matter borders because of excessive head motion. Therefore, 94 patients were included in the analysis, comprising 32 men and 62 women. Details on patient characteristics can be found in Table 1.

Gender Differences in the Association Between Gray Matter Properties and Pain-Related Psychosocial Characteristics

Details on significant associations and gender differences can be found in Table 2. There was a gender difference in association present in 21 brain areas (mostly found in gray matter area and volume). Significant gender differences in the association between gray matter metrics and pain-related psychosocial characteristics were found in the postcentral gyrus, the paracentral lobule, the precentral gyrus, the precuneus gyrus, the lateral orbitofrontal cortex, and the insula. The (positive) associations of these brain areas with perceived consequences, emotional representations, chronicity, and pain catastrophizing were larger in woman compared to men. However, men showed larger associations between several of these brain areas and perceived personal control or self-reported kinesiophobia. These greater associations in men compared to women were mostly negative (except for the association between perceived personal control and precuneus gray matter morphology). Visualization of the significant clusters can be found in Fig. 1. Visualization of the magnitude of gender differences can be found in Fig. 2.

Discussion

General Discussion

The aim of this study was to examine if gender dif-

Table 1. *Demographic characteristics of patients with nCSP (n = 94; 32 men and 62 women).*

		Mean	Median	SD	Range (min-max)	IQR	Gender Differences *P* value
Age (yrs)[a]	Men	45.00	47.00	12.02	21.00-65.00	20.00	0.072
	Women	38.78	38.50	12.69	19.00-65.00	25.00	
Body height (cm)[a]	Men	179.72	180.00	6.68	167.00-197.00	9.00	< 0.001
	Women	166.40	167.00	5.94	153.00-181.00	7.75	
Body weight (kg)[a]	Men	81.53	80.00	12.45	60.00-108.00	18.00	< 0.001
	Women	63.30	63.00	10.70	46.00-95.00	14.75	
Spinal pain duration (mos)[b]	Men	128.37	96.00	110.45	14.00-420.00	146.00	0.575
	Women	114.27	75.00	92.45	6.00-348.00	156.80	
		Frequencies					
Pain problem n (%)[c] Neck pain; low back pain	Men	15 (46.9); 17 (53.1)					0.383
	Women	36 (58.1); 26 (41.9)					
		Mean	**Median**	**SD**	**Range (min-max)**	**IQR**	
Pain Catastrophizing Scale – Total[b] (/52)	Men	16.97	12.50	12.22	2.00-48.00	21.00	0.696
	Women	16.61	15.00	8.57	3.00-39.00	13.00	
Pain Catastrophizing Scale–Rumination[a] (/16)	Men	6.00	5.00	4.60	0.00-16.00	9.00	0.482
	Women	6.65	6.00	3.78	0.00-14.00	6.00	
Pain Catastrophizing Scale–Magnification[b] (/12)	Men	2.97	2.00	2.73	0.00-10.00	4.00	0.544
	Women	2.34	2.00	1.72	0.00-7.00	2.00	
Pain Catastrophizing Scale–Helplessness[a] (/24)	Men	8.00	6.00	5.79	0.00-22.00	9.00	0.671
	Women	7.63	6.00	4.51	1.00-21.00	7.00	
Tampa Scale for Kinesiophobia[a] (/68)	Men	36.66	36.50	6.26	28.00-50.00	11.00	0.300
	Women	35.24	34.00	7.28	21.00-61.00	8.00	
Illness Perception Questionnaire–Timeline[a] (/25)	Men	24.69	24.50	3.69	18.00-30.00	7.00	0.057
	Women	23.06	23.00	4.03	11.00-30.00	5.00	
Illness Perception Questionnaire–Timeline Cyclical[a] (/20)	Men	13.34	14.00	3.56	5.00-20.00	4.00	0.327
	Women	12.61	13.00	3.08	5.00-20.00	4.00	
Illness Perception Questionnaire–Consequences[a] (/30)	Men	17.34	17.00	4.32	10.00-29.00	5.00	0.309
	Women	16.40	16.00	4.69	8.00-28.00	7.00	
Illness Perception Questionnaire–Personal Control[a] (/30)	Men	20.75	20.50	3.72	13.00-27.00	6.00	0.298
	Women	19.95	21.00	4.33	6.00-30.00	6.00	
Illness Perception Questionnaire–Treatment Control[a] (/25)	Men	16.66	16.00	2.54	11.00-21.00	4.00	0.574
	Women	17.00	17.00	2.92	7.00-25.00	4.00	
Illness Perception Questionnaire–Emotional Representations[a] (/30)	Men	14.25	14.00	5.28	7.00-30.00	9.00	0.624
	Women	14.87	14.50	4.10	6.00-25.00	4.00	
Illness Perception Questionnaire–Illness Coherence[a] (/25)	Men	16.34	17.00	2.80	11.00-21.00	4.00	0.530
	Women	16.69	17.00	2.41	9.00-21.00	3.00	
Pain Vigilance and Awareness Questionnaire[a] (/80)	Men	38.75	37.00	13.60	14.00-69.00	23.00	0.335
	Women	36.40	36.50	11.09	16.00-70.00	17.00	

The distribution of the continuous data within each group were assessed by histograms, QQ-plots, and the Shapiro-Wilk test. Significant differences are presented in bold.
[a]Data that were assumed to be normally distributed and with equally distributed variances across groups were analyzed with the independent samples t test; [b]Data that were not normally distributed and subsequent group differences were analyzed using the Mann-Whitney U Test; [c]Categorical data were analyzed by performing the Fisher exact test or the chi-square test.
Abbreviations: IQR, interquartile range; SD, standard deviation.

ferences can be found in the association of gray matter morphology with pain-related psychosocial characteristics in patients with nCSP. The results indicate that in women reduced gray matter area and volume of several central brain regions (i.e., paracentral, postcentral, precentral, and supramarginal) associate to a bigger extent with perceived negative consequences of the illness, perceived emotional representations, and pain catastrophizing compared to men. Also, the more women perceive chronicity, the less gray matter thickness in the lateral orbitofrontal cortex. In men with nCSP, gray matter precentral area and insula volume relate more negatively to perceived personal control of the illness. Also, gray matter area and volume of the precuneus cortex relates more positively with perceived personal control and more negatively with kinesiophobia in men compared to women. Finally, perceived symptom fluctuations are more negatively associated to precentral volume in men, whereas they are more positively associated to lingual thickness in women.

It is interesting to see that—besides the results regarding the IPQr timeline cyclical (i.e., perceived symptoms fluctuations)—all results are very straightforward, with a clear distinction in self-reported psychosocial characteristics that related more to certain brain regions in women compared to men, and vice versa. Also, all brain regions with a significant different association between men and women are located closely to each other (i.e., paracentral, precentral, postcentral, supra-marginal, precuneus) except for the lateral orbitofrontal cortex, the lingual cortex, and the insula (Fig. 1). Remarkably, when the association is larger in women compared to men, the respective associations were positive, implying that the higher the scores on the questionnaires (= the more maladaptive pain-related psychosocial characteristics are present), the bigger the gray matter area, volume, or thickness. However, when the association is larger in men compared to women, the direction of the association was less straightforward.

For pain catastrophizing, the positive association with several central cortices (paracentral lobule, the postcentral gyrus, the precentral gyrus, and the supramarginal gyrus) was stronger in women compared to men. The association between pain catastrophizing and gray matter metrics has been investigated before, but evidence remains inconsistent: there is moderate evidence for an association between pain catastrophizing and alterations in gray matter morphology in the dorsolateral prefrontal cortex, but the direction of this relation remains unknown (61), and there is some evidence for a negative association of pain catastrophizing and gray matter volume in brain areas involved in somatosensory, motor and pain processing (60,61). However, none of these studies took gender differences into account and included only women (24,62), or both genders in the analysis (63).

Similar results were found for the perceived negative consequences of the illness, the perceived emotional representations, and the perceived chronicity: the association with central brain areas (paracentral lobule and lateral orbitofrontal gyrus) was positive and larger in women with nCSP compared to men. To the best of our knowledge, the association between illness perceptions and gray matter metrics (or the possible gender difference therein) has not been investigated in the literature so far. Nevertheless, like pain catastrophizing, these aspects of illness perceptions seem to be stronger associated with gray matter metrics in women with nCSP. In the paracentral, postcentral, and precentral brain areas, which include the primary motor and somatosensory cortex (64,65), gray matter is known to be altered more prominently in women with chronic pain (25). This might explain why the women in this study show a greater positive association between gray matter metrics in these areas and psychosocial factors, as pain catastrophizing and negative perceptions affect perceived pain intensity and chronification in a negative way (66-68); and the longer or more intense the pain exists, the more the brain changes (5,6).

However, some associations were found more prominent in men compared to women, that is, the association of the precuneus cortex with kinesiophobia; and the association of the perceived personal control with the precuneus cortex (positive correlation), the precentral gyrus (negative correlation), and the insula (negative correlation). The less men feel in control of the symptoms, the smaller the precuneus area and volume, and the larger the precentral area and the insula volume. The more men report kinesiophobia, the smaller the gray matter in the precuneus is. This suggests that perceived personal control might be an important issue to target in men with nCSP, to normalize gray matter alterations. Still, such extrapolations from cross-sectional study findings require experimental testing.

More specifically, the results show that decreased gray matter of the precuneus cortex is associated with more negative psychosocial characteristics in men (= less perceived personal control and more kinesiopho-

Table 2. *Gender differences in the association between gray matter metrics and pain-related psychosocial characteristics in patients with nCSP (n = 94).*

Annotations	Morphologic Measure	Cluster Size (mm^2)	Talairach Coordinates			CWP (90% CI)	Gender Difference◊	*P* value	Association	
			MNIX	MNIY	MNIZ					
Illness Perception Questionnaire revised: 'Consequences'										
Paracentral (lh)	Volume	1,039.96	−7.20	−19.90	72.50	0.020 (0.017; 0.022)	−0.037	< 0.001	+	NS
Illness Perception Questionnaire revised: 'Emotional Representations'										
Paracentral (lh)	Volume	1,628.78	−6.20	−25.80	71.90	2.00E-04 (0; 4.00E-04)	−0.032	< 0.001	+	NS
Illness Perception Questionnaire revised: 'Personal Control'										
Precuneus (lh)	Area	2,472.26	−14.80	−58.80	12.40	6.00E-04 (2.00E-04; 0.001)	0.014	< 0.001	+	NS
Precuneus (rh)	Area	3,344.24	16.40	−55.40	12.20	2.00E-04 (0; 4.00E-04)	0.017	< 0.001	+	NS
Precuneus (lh)	Volume	1,622.16	−17.90	−58.50	14.80	2.00E-04 (0; 4.00E-04)	0.059	< 0.001	+	NS
Precuneus (rh)	Volume	2,978.59	17.90	−55.40	15.10	2.00E-04 (0; 4.00E-04)	0.044	< 0.001	+	NS
Precentral (rh)	Area	1,895.23	41.00	−1.30	17.10	0.005 (0.004; 0.007)	0.014	< 0.001	-	NS
Insula (rh)	Volume	1,554.13	35.90	−7.00	−3.30	8.00E-04 (4.00E-04; 0.001)	0.042	< 0.001	-	NS
Illness Perception Questionnaire revised: 'Timeline'										
Lateral orbitofrontal (rh)	Thickness	1,169.64	29.20	29.60	−11.80	0.005 (0.003; 0.006)	−0.040	< 0.001	+	NS
Illness Perception Questionnaire revised: 'Timeline Cyclical'										
Lingual (lh)	Thickness	1,080.40	−4.80	−83.00	−3.90	0.007 (0.006; 0.009)	−0.040	< 0.001	+	S
Precentral (lh)	Volume	1,527.31	−55.80	−3.10	34.80	2.00E-04 (0; 4.00E-04)	0.046	< 0.001	-	S
Pain Catastrophizing Scale: Total Score										
Postcentral (lh)	Area	1,373.43	−18.50	−32.50	56.60	0.049 (0.045; 0.053)	−0.004	< 0.001	+	NS
Precentral (lh)	Volume	1,316.77	−15.20	−32.00	57.10	0.003 (0.002; 0.004)	−0.012	< 0.001	+	S
Pain Catastrophizing Scale: Helplessness										
Precentral (lh)	Volume	1,367.33	−7.20	−28.40	72.40	0.002 (0.001; 0.003)	−0.023	< 0.001	+	S
Pain Catastrophizing Scale: Magnification										
Postcentral (lh)	Area	1,823.58	−26.10	−30.60	56.80	0.008 (0.006; 0.010)	−0.018	< 0.001	+	S
Supramarginal (lh)	Area	1,836.68	−52.90	−29.10	33.30	0.008 (0.006; 0.009)	−0.023	< 0.001	+	S
Pain Catastrophizing Scale: Rumination										
Precentral (lh)	Volume	941.00	−15.60	−32.50	57.20	0.038 (0.035; 0.041)	−0.024	< 0.001	+	S
Tampa Scale for Kinesiophobia										
Precuneus (lh)	Area	1,376.83	−9.40	−68.50	34.60	0.048 (0.044; 0.052)	0.010	0.003	-	NS

◊Gender differences: Derived from statistical analysis in R; a negative value represents a smaller association between gray matter metrics and pain-related psychosocial characteristics in men compared to women. Significant *P* values (of gender differences) are listed in bold. Overall association (without taking gender into account) presented as + (positive) or – (negative) and NS (not significant) or S (significant).
Abbreviations: CI, confidence interval; CWP, cluster-wise *P* value with 90% confidence interval; lh, left hemisphere; rh, right hemisphere.

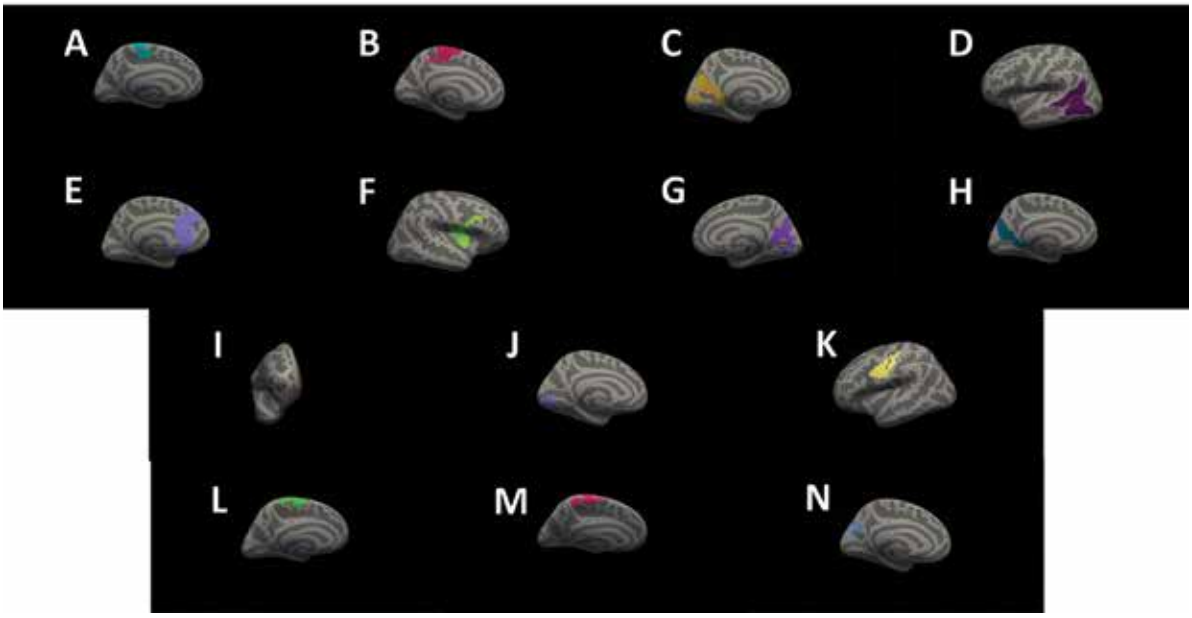

Fig. 1. Visualization of the clusters with a significant gender-difference in the association with pain-related psychosocial characteristics. (A) This paracentral cluster (volume, left hemisphere) shows a greater positive association with perceived negative consequences of the illness (IPQr consequences) in women compared to men. (B) This paracentral cluster (volume, left hemisphere) shows a greater positive association with perceived emotional representations of the illness (IPQr emotional representations) in women compared to men. (C) This precuneus cluster (area, left hemisphere) shows a greater positive association with perceived personal control of the illness (IPQr personal control) in men compared to women. (D) This precuneus cluster (area, right hemisphere) shows a greater positive association with perceived personal control of the illness (IPQr personal control) in men compared to women. (E) This precentral cluster (area, right hemisphere) shows a greater positive association with perceived personal control of the illness (IPQr personal control) in men compared to women. (F) This insula cluster (volume, right hemisphere) shows a greater negative association with perceived personal control of the illness (IPQr personal control) in men compared to women. (G) This precuneus cluster (volume, right hemisphere) shows a greater positive association with perceived personal control of the illness (IPQr personal control) in men compared to women. (H) This precuneus cluster (volume, left hemisphere) shows a greater positive association with perceived personal control of the illness (IPQr personal control) in men compared to women. (I) This lateral orbitofrontal cluster (thickness, right hemisphere) shows a greater positive association with perceived chronicity of the illness (IPQr timeline) in women compared to men. (J) This lingual cluster (thickness, left hemisphere) shows a greater positive association with perceived symptom fluctuations of the illness (IPQr timeline cyclical) in women compared to men. (K) This precentral cluster (volume, left hemisphere) shows a greater negative association with perceived symptom fluctuations of the illness (IPQr timeline cyclical) in men compared to women. (L) This precentral cluster (volume, left hemisphere) shows a greater positive association with pain catastrophizing (PCS) in women compared to men. (M) This postcentral cluster (area, left hemisphere) shows a greater positive association with pain catastrophizing (PCS) in women compared to men. (N) This precuneus cluster (area, left hemisphere) shows a greater negative association with kinesiophobia (TSK) in men compared to women.

bia). The precuneus is a part of the superior parietal lobule, and plays a role in itch and pain sensations and their brain processing (69). Although the exact role of the precuneus in somatosensory processing remains unclear, some suggest an association with empathy for pain and pain modulation by hypnosis (69). For men having nCSP, increasing the perceived personal control during therapy could therefore have a positive impact on gray matter morphology of the precuneus, and therefore impact pain processing. Regarding gray matter of the precentral gyrus and the insula, results indicate that people with nCSP display increased gray matter with more prominent negative psychosocial characteristics. Insula pain-related responses appear to be enhanced to a greater extent in men with chronic pain compared to women with

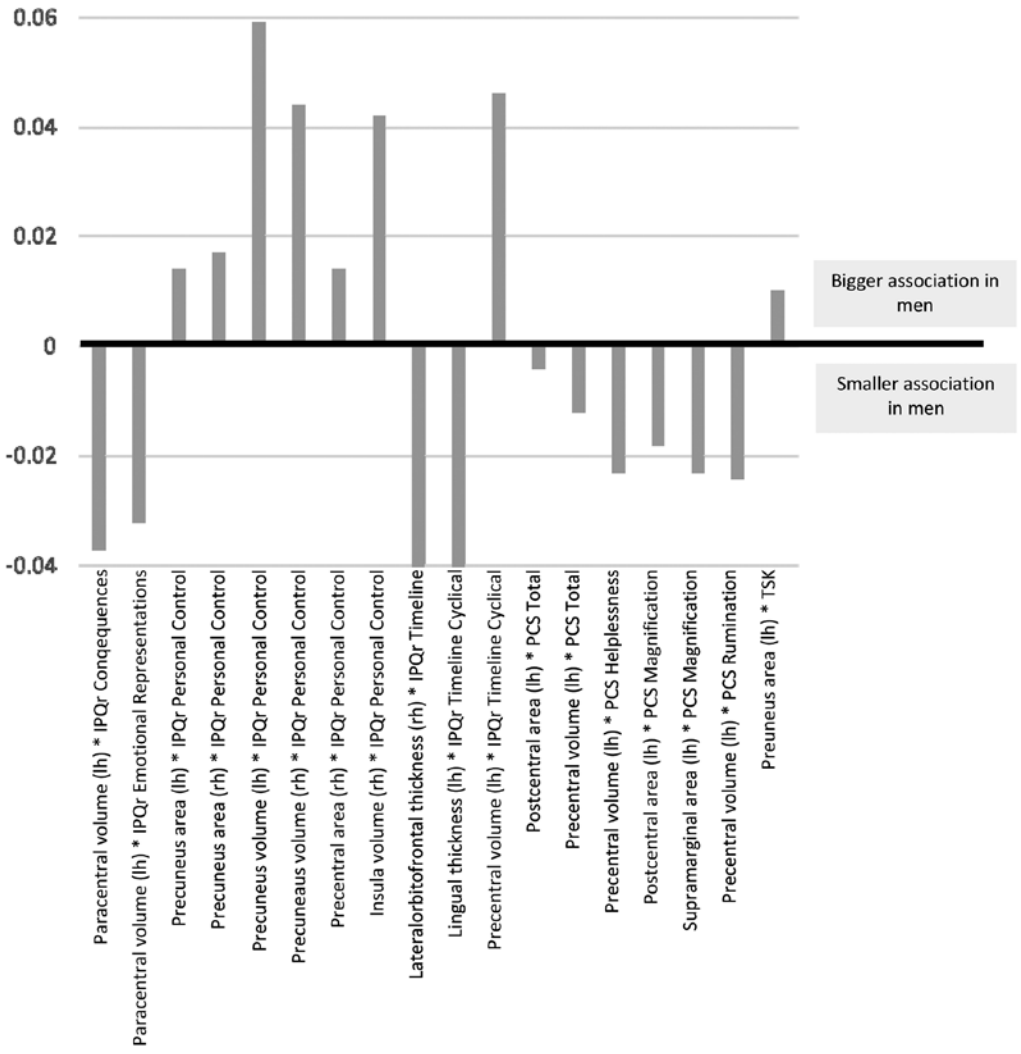

Fig. 2. *Gender differences in the association between gray matter metrics and pain-related psychosocial characteristics in patients with nCSP (n = 94). Derived from statistical analysis in R. Each line represents a specific association for which a gender difference was found. A negative value represents a smaller association between gray matter metrics and pain-related psychosocial characteristics in men compared to women. To illustrate the interpretation, the first line represents the following: the association between the paracentral volume (left hemisphere) and perceived negative consequences was significantly smaller in men compared to women. The direction of the association can be found in Table 2.*

nCSP. The insula is involved in pain-related perceptual, affective, and cognitive responses (70). As the insula is more altered in men, and its function comprises perceptual responses to pain, it does not come as a surprise that perceived personal control is more related to insular gray matter in men compared to women.

In general, these results indicate that the brain signature (i.e., gray matter metrics) for pain-related psychosocial characteristics is different for men and women with nCSP. The brain areas where gender differences were found are known as key areas where neuroplastic changes occur in chronic pain and play a role in the chronification of pain (71). This knowledge

should be taken into consideration when treating a patient with nCSP in clinical practice, although it is impossible to draw conclusions regarding causality of these associations (because of the cross-sectional nature of this study). Together with other evidence (25), these results indicate once more that men and women differ in pain neurobiology and behavioral responses to pain. These results imply the possibility that pain catastrophizing, perceived negative consequences, perceived chronicity, and perceived emotional representations contribute more to the chronic spinal pain problem in women compared to men, and should therefore receive more attention when treating women. The same way of thinking can apply to men with nCSP regarding perceived personal control and kinesiophobia.

Strengths and Limitations

Age, laterality, and gender are not the only factors that should be considered in brain imaging research. Other factors, such as menstrual cycle and medication can have a certain influence, and were only partly taken into consideration in the present investigation to obtain sufficient power. Patients were asked not to change their usual medication or initiate new treatments to obtain a steady state and to account for medication use in the analysis. Of course, it would have been better to implement medication use as confounding factor within the statistical analysis. However, we deliberately chose not to do so to preserve the power of the statistical model.

Another limitation of this study lies in its observational nature. Therefore, causal or temporal interactions could not be investigated. Although this was not the focus of this article, it might be interesting to see if changing maladaptive pain cognitions, perceptions, and ideas lead to changes and/or normalization in certain pain-related brain areas in people with nCSP. The limitations of this study present interesting challenges to further unravel these underlying mechanisms in chronic pain.

The large sample size of this study is a considerable strength, as many brain imaging studies in the field of chronic pain are limited by small sample sizes. Additionally, the use of whole brain analysis and FreeSurfer in the processing of MRI data are strengths worth mentioning. FreeSurfer has some advantages over voxel-based morphometry, including better matching of homologous cortical regions and the possibility to generate gray matter thickness and surface area—2 separate components of volume that do not necessarily track one another (surfer.nmr.mgh.harvard.edu) (72,73).

Conclusions

Brain gray matter metrics relate differently to psychosocial characteristics in women and men with nCSP. In woman with nCSP, reduced gray matter area and volume of several central brain regions (i.e., paracentral, postcentral, precentral, and supramarginal) associate to a bigger extent with perceived negative consequences of the illness, perceived emotional representations, and pain catastrophizing compared to men. Also, the more women perceive chronicity, the less gray matter thickness in the lateral orbitofrontal cortex. In men with nCSP, gray matter precentral area and insula volume relate more negatively to perceived personal control of the illness. Also, in men compared to women, gray matter area and volume of the precuneus cortex relates more positively with perceived personal control and more negatively with kinesiophobia. These results indicate that the brain signature (gray matter metrics) for pain-related psychosocial characteristics is different for men and women with nCSP and confirm the suggested gender differences in pain neurobiology and behavioral responses to pain in people with nCSP. These findings suggest that gender differences should be considered when treating patients with nCSP, but trials are needed to confirm this assumption. Targeting perceived negative consequences of the illness, perceived emotional representations, perceived chronicity, and pain catastrophizing in women; and perceived personal control of the illness and kinesiophobia in men, could contribute to the normalization of brain alterations in people with nCSP.

References

1. Schmidt-Wilcke T. Neuroimaging of chronic pain. *Best Pract Res Clin Rheumatol* 2015; 29:29-41.
2. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004; 24:10410-10415.
3. Tang L, Zheng H, Chen L, Zhou S, Huang W, Li Y, Wu X. Gray matter volumes in patients with chronic fatigue syndrome. *Evid Based Complement Alternat Med* 2015; 2015:380615.
4. Wood PB. Variations in brain gray matter associated with chronic pain. *Curr Rheumatol Rep* 2010; 12:462-469.
5. Obermann M, Rodriguez-Raecke R, Naegel S, Holle D, Mueller D, Yoon M-S, Theysohn N, Blex S, Diener H-C, Katsarava Z. Gray matter volume reduction reflects chronic pain in trigeminal neuralgia. *Neuroimage* 2013; 74:352-358.
6. Yu R, Gollub RL, Spaeth R, Napadow V, Wasan A, Kong J. Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. *NeuroImage Clin* 2014; 6:100-108.
7. Kregel J, Meeus M, Malfliet A, Dolphens M, Danneels L, Nijs J, Cagnie B. Structural and functional brain abnormalities in chronic low back pain: A systematic review. *Semin Arthritis Rheum* 2015; 45:229-237.
8. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci* 2011; 31:7540-7550.
9. Schmidt-Wilcke T, Leinisch E, Ganssbauer S, Draganski B, Bogdahn U, Altmeppen J, May A. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. *Pain* 2006; 125:89-97.
10. Buckalew N, Haut MW, Morrow L, Weiner D. Chronic pain is associated with brain volume loss in older adults: Preliminary evidence. *Pain Med* 2008; 9:240-248.
11. Ung H, Brown JE, Johnson KA, Younger J, Hush J, Mackey S. Multivariate classification of structural MRI data detects chronic low back pain. *Cereb Cortex* 2014; 24:1037-1044.
12. Sowell ER, Peterson BS, Kan E, Woods RP, Yoshii J, Bansal R, Xu D, Zhu H, Thompson PM, Toga AW. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cereb Cortex* 2007; 17:1550-1560.
13. Yang Q, Wang Z, Yang L, Xu Y, Chen LM. Cortical thickness and functional connectivity abnormality in chronic headache and low back pain patients. *Hum Brain Mapp* 2017; 38:1815-1832.
14. Leeuw M, Goossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *J Behav Med* 2007; 30:77-94.
15. Apkarian A V, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005; 9:463-484.
16. Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. *Trends Cogn Sci* 2008; 12:306-313.
17. Wiech K, Tracey I. The influence of negative emotions on pain: Behavioral effects and neural mechanisms. *Neuroimage* 2009; 47:987-994.
18. Picavet HSJ, Vlaeyen JWS, Schouten JSAG. Pain catastrophizing and kinesiophobia: Predictors of chronic low back pain. *Am J Epidemiol* 2002; 156:1028-1034.
19. Burton AK, Tillotson KM, Main CJ, Hollis S. Psychosocial predictors of outcome in acute and subchronic low back trouble. *Spine (Phila Pa 1976)* 1995; 20:722-728.
20. Smith AD, Jull GA, Schneider GM, Frizzell B, Hooper RA, Sterling MM. Low pain catastrophization and disability predict successful outcome to radiofrequency neurotomy in individuals with chronic whiplash. *Pain Pract* 2016; 16:311-319.
21. Farin E. The reciprocal effect of pain catastrophizing and satisfaction with participation in the multidisciplinary treatment of patients with chronic back pain. *Health Qual Life Outcomes* 2015; 13:163.
22. Boonstra AM, Reneman MF, Waaksma BR, Schiphorst Preuper HR, Stewart RE. Predictors of multidisciplinary treatment outcome in patients with chronic musculoskeletal pain. *Disabil Rehabil* 2015; 37:1242-1250.
23. Glattacker M, Heyduck K, Meffert C. Illness beliefs and treatment beliefs as predictors of short-term and medium-term outcome in chronic back pain. *J Rehabil Med* 2013; 45:268-276.
24. Blankstein U, Chen J, Diamant NE, Davis KD. Altered brain structure in irritable bowel syndrome: Potential contributions of pre-existing and disease-driven factors. *Gastroenterology* 2010; 138:1783-1789.
25. Gupta A, Mayer EA, Fling C, Labus JS, Naliboff BD, Hong J-Y, Kilpatrick LA. Sex-based differences in brain alterations across chronic pain conditions. *J Neurosci Res* 2017; 95:604-616.
26. Berkley KJ. Sex differences in pain. *Behav Brain Sci* 1997; 20:371-380.
27. Cahill L. Why sex matters for neuroscience. *Nat Rev Neurosci* 2006; 7:477-484.
28. Bartley EJ, Fillingim RB. Sex differences in pain: A brief review of clinical and experimental findings. *Br J Anaesth* 2013; 111:52-58.
29. Woodworth D, Mayer E, Leu K, Ashe-McNalley C, Naliboff BD, Labus JS, Tillisch K, Kutch JJ, Farmer MA, Apkarian AV, Johnson KA, Mackey SC, Ness TJ, Landis JR, Deutsch G, Harris RE, Clauw DJ, Mullins C, Ellingson BM. Unique microstructural changes in the brain associated with urological chronic pelvic pain syndrome (UCPPS) revealed by diffusion tensor MRI, super-resolution track density imaging, and statistical parameter mapping: A MAPP network neuroimaging study. *PLoS One* 2015; 10:e0140250.
30. Jiang Z, Dinov ID, Labus J, Shi Y, Zamanyan A, Gupta A, Ashe-McNalley C, Hong J-Y, Tillisch K, Toga AW, Mayer EA. Sex-related differences of cortical thickness in patients with chronic abdominal pain. *PLoS One* 2013;8:e73932.
31. Naliboff BD, Berman S, Chang L, Derbyshire SWG, Suyenobu B, Vogt BA, Mandelkern M, Mayer EA. Sex-related differences in IBS patients: Central processing of visceral stimuli. *Gastroenterology* 2003; 124:1738-1747.
32. Labus JS, Naliboff BN, Fallon J, Berman SM, Suyenobu B, Bueller JA, Mandelkern M, Mayer EA. Sex differences in brain activity during aversive visceral stimulation and its expectation in patients with chronic abdominal pain: A network analysis. *Neuroimage* 2008; 41:1032-1043.
33. Berman S, Munakata J, Naliboff BD, Chang L, Mandelkern M, Silverman D, Kovalik E, Mayer EA. Gender differences in regional brain response to visceral pressure in IBS patients. *Eur J Pain* 2000; 4:157-172.
34. Walders-Abramson N, Anderson B, Larkin ME, Chang N, Venditti E, Bzdick S, Tryggestad JB, Tan K, Geffner ME, Hirst

K. Benefits and barriers to participating in longitudinal research of youth-onset type 2 diabetes: Results from the TODAY retention survey. *Clin Trials* 2016; 13:240-243.

35. Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: Development and validation. *Psychol Assess* 1995; 7:524-532.
36. Severeijns R, Vlaeyen JWS, van den Hout MA, Picavet HSJ. Pain catastrophizing is associated with health indices in musculoskeletal pain: A cross-sectional study in the Dutch community. *Heal Psychol* 2004; 23:49-57.
37. Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med* 1997; 20:589-605.
38. Damsgard E, Fors T, Anke A, Roe C. The Tampa Scale of Kinesiophobia: A Rasch analysis of its properties in subjects with low back and more widespread pain. *J Rehabil Med* 2007; 39:672-678.
39. Roelofs J, Goubert L, Peters ML, Vlaeyen JWS, Crombez G. The Tampa Scale for Kinesiophobia: Further examination of psychometric properties in patients with chronic low back pain and fibromyalgia. *Eur J Pain* 2004; 8:495-502.
40. Roelofs J, Sluiter JK, Frings-Dresen MHW, Goossens M, Thibault P, Boersma K, Vlaeyen JWS. Fear of movement and (re)injury in chronic musculoskeletal pain: Evidence for an invariant two-factor model of the Tampa Scale for Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain* 2007; 131:181-190.
41. Weinman J. The Illness Perception Questionnaire: A new method for assessing the cognitive representation of illness. *Psychol Health* 1996; 11:431-445.
42. Leysen M, Nijs J, Meeus M, Paul van Wilgen C, Struyf F, Vermandel A, Kuppens K, Roussel NA. Clinimetric properties of illness perception questionnaire revised (IPQ-R) and brief illness perception questionnaire (Brief IPQ) in patients with musculoskeletal disorders: A systematic review. *Man Ther* 2015; 20:10-17.
43. Moss-Morris R, Weinman J, Petrie KJ, Horne R, Cameron LD, Buick D. The revised Illness Perception Questionnaire (IPQ-R). *Psychol Health* 2002; 17:1-16.
44. Roelofs J, Peters ML, Muris P, Vlaeyen JWS. Dutch version of the Pain Vigilance and Awareness Questionnaire: Validity and reliability in a pain-free population. *Behav Res Ther* 2002; 40:1081-1090.
45. Roelofs J, Peters ML, McCracken L, Vlaeyen JWS. The Pain Vigilance and Awareness Questionnaire (PVAQ): Further psychometric evaluation in fibromyalgia and other chronic pain syndromes. *Pain* 2003; 101:299-306.
46. Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, Fischl B. A hybrid approach to the skull stripping problem in MRI. *Neuroimage* 2004; 22:1060-1075.
47. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* 1998; 17:87-97.
48. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002; 33:341-355.
49. Fischl B, Salat DH, van der Kouwe AJW, Makris N, Segonne F, Quinn BT, Dale AM. Sequence-independent segmentation of magnetic resonance images. *Neuroimage* 2004; 23(Suppl 1):S69-84.
50. Fischl B, Liu A, Dale AM. Automated manifold surgery: Constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging* 2001; 20:70-80.
51. Segonne F, Pacheco J, Fischl B. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging* 2007; 26:518-529.
52. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999; 9:179-194.
53. Dale AM, Sereno MI. Improved localizadon of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: A linear approach. *J Cogn Neurosci* 1993; 5:162-176.
54. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA* 2000; 97:11050-11055.
55. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* 1999; 9:195-207.
56. Fischl B, Sereno MI, Tootell RB, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* 1999; 8:272-284.
57. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006; 31:968-980.
58. Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, Van Der KA, Jenkins BG, Dale AM, Fischl B. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 2002; 58:695-701.
59. Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SCR, van der Kouwe AJW, Salat DH, Dale AM, Fischl B. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 2003; 60:878-888.
60. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B. Thinning of the cerebral cortex in aging. *Cereb Cortex* 2004; 14:721-730.
61. Malfliet A, Coppieters I, Van Wilgen P, Kregel J, De Pauw R, Dolphens M, Ickmans K. Brain changes associated with cognitive and emotional factors in chronic pain: A systematic review. *Eur J Pain* 2017; 21:769-786.
62. Ceko M, Bushnell MC, Fitzcharles M-A, Schweinhardt P. Fibromyalgia interacts with age to change the brain. *NeuroImage Clin* 2013; 3:249-260.
63. Seminowicz DA, Shpaner M, Keaser ML, Krauthamer GM, Mantegna J, Dumas JA, Newhouse PA, Filippi CG, Keefe FJ, Naylor MR. Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. *J Pain* 2013; 14:1573-1584.
64. Brouwer GJ, Arnedo V, Offen S, Heeger DJ, Grant AC. Normalization in human somatosensory cortex. *J Neurophysiol* 2015; 114:2588-2599.
65. Kovac S, Scott CA, Maglajlija V, Rodionov R, McEvoy AW, Diehl B. Extraoperative electrical cortical stimulation: Characteristics of motor responses and correlation with precentral gyrus. *J Clin Neurophysiol* 2011; 28:618-624.

66. Meeus M, Nijs J, Van Mol E, Truijen S, De Meirleir K. Role of psychological aspects in both chronic pain and in daily functioning in chronic fatigue syndrome: A prospective longitudinal study. *Clin Rheumatol* 2012; 31:921-929.
67. Vase L, Nikolajsen L, Christensen B, Egsgaard LL, Arendt-Nielsen L, Svensson P, Staehelin Jensen T. Cognitive-emotional sensitization contributes to wind-up-like pain in phantom limb pain patients. *Pain* 2011; 152:157-162.
68. Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: Fact or myth? *Clin J Pain* 2013; 29:625-638.
69. Mochizuki H, Kakigi R. Itch and brain. *J Dermatol* 2015; 42:761-767.
70. Menon V, Uddin LQ. Saliency, switching, attention and control: A network model of insula function. *Brain Struct Funct* 2010; 214:655-667.
71. Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. *J Neuroimmune Pharmacol* 2013; 8:518-534.
72. Clarkson MJ, Cardoso MJ, Ridgway GR, Modat M, Leung KK, Rohrer JD, Fox NC, Ourselin S. A comparison of voxel and surface based cortical thickness estimation methods. *Neuroimage* 2011; 57:856-865.
73. Tustison NJ, Cook PA, Klein A, Song G, Das SR, Duda JT, Kandel BM, van Strien N, Stone JR, Gee JC, Avants BB. Large-scale evaluation of ANTs and FreeSurfer cortical thickness measurements. *Neuroimage* 2014; 99:166-179.