



## Gray matter alterations in chronic pain: A network-oriented meta-analytic approach



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### ARTICLE INFO

#### Article history:

Received 23 January 2014

Received in revised form 25 March 2014

Accepted 12 April 2014

#### Keywords:

Chronic pain

Brain networks

Gray matter alterations

Voxel-Based Metaanalysis

### ABSTRACT

Several studies have attempted to characterize morphological brain changes due to chronic pain. Although it has repeatedly been suggested that longstanding pain induces gray matter modifications, there is still some controversy surrounding the direction of the change (increase or decrease in gray matter) and the role of psychological and psychiatric comorbidities. In this study, we propose a novel, network-oriented, meta-analytic approach to characterize morphological changes in chronic pain. We used network decomposition to investigate whether different kinds of chronic pain are associated with a common or specific set of altered networks. Representational similarity techniques, network decomposition and model-based clustering were employed: i) to verify the presence of a core set of brain areas commonly modified by chronic pain; ii) to investigate the involvement of these areas in a large-scale network perspective; iii) to study the relationship between altered networks and; iv) to find out whether chronic pain targets clusters of areas. Our results showed that chronic pain causes both core and pathology-specific gray matter alterations in large-scale networks. Common alterations were observed in the prefrontal regions, in the anterior insula, cingulate cortex, basal ganglia, thalamus, periaqueductal gray, post- and pre-central gyri and inferior parietal lobule. We observed that the salience and attentional networks were targeted in a very similar way by different chronic pain pathologies. Conversely, alterations in the sensorimotor and attention circuits were differentially targeted by chronic pain pathologies. Moreover, model-based clustering revealed that chronic pain, in line with some neurodegenerative diseases, selectively targets some large-scale brain networks. Altogether these findings indicate that chronic pain can be better conceived and studied in a network perspective.

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### 1. Introduction

Chronic pain is defined by the International Association for the Study of Pain as a pain persisting over the healing phase of an injury (Loeser and Treede, 2008). Whether continuous or recurrent, chronic pain must be of sufficient duration and intensity to adversely affect a person's level of function, well-being and quality of life, chronic pain states are generally considered as either neuropathic or nociceptive, although this subdivision has been criticized and less clear-cut subdivisions are proposed (Bennett et al., 2006; Treede et al., 2008).

Converging evidence from animal and human studies indicates that chronic pain induces a dramatic anatomical and functional reorganization of brain structures and networks (Apkarian et al., 2009).

Studies using voxel-based morphometry (VBM), a computational-based technique that measures focal differences in concentrations of brain tissue using a voxel-wise comparison between two groups of subjects (Ashburner and Friston, 2000), have reported conflicting results suggesting that chronic pain can either decrease (Apkarian et al., 2004; Buckalew et al., 2008; Burgmer et al., 2009; Davis et al., 2008; Draganski et al., 2006; Geha et al., 2008; Gerstner et al., 2012; Gustin et al., 2011; Gwilym et al., 2010; Kuchinad et al., 2007; Rocca et al., 2006; Rodriguez-Raecke et al., 2009; Schmidt-Wilcke et al., 2006; Schmidt-Wilcke et al., 2010; Seminowicz et al., 2011; Tu et al., 2010; Unrath et al., 2007; Valet et al., 2009; Valfre et al., 2008; Vartiainen et al., 2009), or increase (Etgen et al., 2005; Garraux et al., 2004; Obermann et al., 2007; Obermann et al., 2009; Schmidt-Wilcke et al., 2006; Schmidt-Wilcke et al., 2007; Schweinhardt et al., 2008; Seminowicz et al., 2011; Tu et al., 2010; Younger et al., 2010) gray matter density. Some authors have even reported a lack of any

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change (Hsu et al., 2009; Rocca et al., 2006; Schmidt-Wilcke et al., 2005; Schmidt-Wilcke et al., 2007) in gray matter volume or density. These discrepancies may be underpinned by the different category of chronic pain considered (e.g. low back pain or migraine), by the different underlying etiology (e.g. nociceptive vs neuropathic) or by other confounding factors such as, for example, concomitant psychiatric comorbidities like depression or anxiety. Many fields of cognitive neuroscience are now moving towards a network approach to capture the dynamics of brain functioning (Bressler and Menon, 2010). New views posit that the elaboration of noxious stimuli and pain perception depend largely on the activity of networks (Cauda et al., 2013; Mayhew et al., 2013). Recent findings by our and other groups have indicated that noxious stimuli trigger the response of different brain networks at different temporal delays from stimulus onset (Cauda et al., 2013; Mayhew et al., 2013). Network dynamics have also been proposed to underpin the process of chronification of pain (Baliki et al., 2012; Farmer et al., 2012; Hashmi et al., 2013). However, no study has so far characterized gray matter alterations in chronic pain using a network approach. In the present study, we performed a meta-analysis of VBM studies investigating structural changes in the gray matter of chronic pain patients using a novel network approach. We addressed three questions: i) is there a core set of brain areas altered in chronic pain?; ii) are different kinds of chronic pain associated with a common or specific set of altered large-scale brain networks?; and iii) when alterations of gray matter are reported together, do they reflect clusters of modified areas that share some relationship or are they casually found together?

## 2. Materials and methods

### 2.1. Selection of studies

Systematic searches using ‘chronic pain’ and ‘voxel-based morphometry’ as keywords were conducted on the Medline, Scopus and Scirus databases. Additional searches were performed for the term ‘voxel-based morphometry’ associated with each disorder indicated by the American Chronic Pain Association (ACPA) as part of the spectrum of chronic pain (<http://www.theacpa.org/7/Conditions.aspx>). Reference lists of the identified papers were examined for studies not found with the database search. As a result we selected 80 papers. Of these, we excluded: a) non-original studies ( $N = 17$ ); b) studies that did not include gray matter location in Talairach/Tournoux or in Montreal Neurological Institute (MNI) coordinates ( $N = 6$ ); c) studies in which the field of view was confined to a restricted region of the cortex ( $N = 13$ ); d) studies in which the comparison between chronic pain patients and healthy subjects was lacking and e) studies with unspecified VBM analysis ( $N = 10$ ). We also tried to identify any instances of multiple reports of single data-sets across articles, to ensure that only one report of a study contributed to the coordinates for the present meta-analysis (see PRISMA, 2009 Flow Diagram of article selection in Supplementary materials for further details).

Following the recommendations provided by Rainville and Duncan (2006), we used tables to collect a detailed description of neuroimaging modalities, VBM techniques and data reporting the number of increased and decreased gray matter foci. We also checked the clinical condition of the experimental samples in terms of adherence to the diagnostic criteria for chronic pain, any comorbidity, medication and the overlap of control groups and experimental samples.

Based on these criteria, 32 papers were included, with a total of 1509 subjects (739 patients and 707 controls). There is a lack of information concerning the gender of the sample for three studies (Schmidt-Wilke et al., 2005; Oberman et al., 2007 Study 1; Buckalew et al., 2008). Given all the others, the patient group comprised 196 men and 553 women. The control group comprised 252 men and 565 women (Table 1).

### 2.2. Anatomical likelihood estimation (ALE)

We used the anatomical likelihood estimation (ALE) procedure to evaluate the presence of a common pattern of gray matter alterations in all types of chronic pain. ALE meta-analysis is a quantitative voxel-based meta-analysis method that can be used to estimate consistent activation (or areas of gray matter increases/reductions) on the basis of foci of interest across different imaging studies that have reported statistically significant peaks of activation (Laird et al., 2005b; Laird et al., 2009). During an ALE analysis, each activation focus is modeled as the center of a Gaussian probability distribution to generate a modeled activation (MA) map for each reported study. These 3D Gaussian distributions are consequently summed to generate a statistical map that estimates the probability of activation for each voxel as determined by the entire set of studies. This map is then thresholded using a permutation test (Laird et al., 2005a; Lancaster et al., 2000; Lancaster et al., 2007).

We used a new ALE algorithm that estimates the spatial uncertainty of each focus taking into account the possible differences among studies related to sample size (Eickhoff et al., 2009; Eickhoff et al., 2012). This algorithm comprises a method to calculate above-chance clustering between experiments (i.e. random effects analysis, RFX), rather than between foci (fixed effects analysis, FFX) (Eickhoff et al., 2009; Eickhoff et al., 2012). In view of this, when we gathered data that were non-Talairach coordinates, we performed an accurate transformation using the most recent and unbiased method (Eickhoff et al., 2009).

ALE maps were computed using a Java-based version of the ALE software named GingerALE (version 2.0.4) and customized Matlab routines at an FDR-corrected threshold of  $p < 0.05$  and a minimum cluster size of  $K > 50 \text{ mm}^3$ .

### 2.3. Jackknife analysis

To rule out the possibility of some activations being driven by the involvement of a small subset of studies, we performed a jackknife analysis. The jackknife is a non-parametric method for estimating the sampling distribution of a statistic (Radua et al., 2011; Radua and Mataix-Cols, 2009). Given a sample data-set and a desired statistic (e.g. the mean), the jackknife works by computing the desired statistic with an element (or a group of elements) deleted. This is done for each element of the data-set. These statistics are used to generate an estimate of the sampling distribution. The results are presented as probability maps where a high probability means that a certain area is led by the majority of the experiments included. By contrast, a low probability means that a certain area is led by few experiments thus indicating the need for caution when interpreting this point.

### 2.4. Network decomposition

In a previous study, Biswal and colleagues used a large cohort of volunteers (1414) who underwent a resting-state fMRI scan to parcellate the brain surface, and found that, with the use of data-driven methods, the resting brain can be clustered into 20 large-scale networks, which are also identifiable when the brain is involved in an active task (Biswal et al., 2010). We applied the same parcellation technique to the selected studies and examined how many voxels of altered gray matter density fell within each network. This allowed us to investigate whether chronic pain is associated with differential modifications of brain structures belonging to different brain networks, such as attentional, thalamic and sensorimotor brain structures.

**Table 1**  
Overview and demographics of the included studies.

	Sample						Healthy control					
	Year	First author	Subjects	Age (Y)	Range (Y)	/	Diagnosis	Duration (Y)	Subjects	Age (Y)	Range (Y)	/
Neuropathic pain	2011	Gerstner	9	25.5 ± 2.5		0/9	Myofascial temporomandibular disease	2.5 ± 2.1	9	24.8 ± 1.4		0/9
	2011	Gustin	21	45.7 ± 2.9	28–70	4/17	Trigeminal neuropathy; trigeminal neuralgia	8.5 ± 2.1	30	53.6 ± 3.2	24–87	6/24
	2010	Younger	14	38 ± 13.7	23–61	0/14	Myofascial temporomandibular disease	4.4 ± 2.9	15	38 ± 13.7	23–61	0/15
	2010	Schmidt-Wilcke	8	52.2 ± 8.9		1/7	Persistent idiopathic facial pain		11	51.3 ± 8.6		2/9
	2009	Vartiainen	8	47	41–53	1/7	Labial or genital herpes	3–20	28	32	22–53	10/18
	2009	Wood	30	42.03 ± 8.43		0/30	Fibromyalgia		20	40.05 ± 10.01		0/20
	2008	Geha	22	40.7 ± 2.3		3/19	Complex regional pain syndrome	3–13.5	22	40.5 ± 2.3		3/19
	2008	Buckalew	8			4/4	Chronic back pain	3 months +	8	69.9 ± 3.9		
	2007	Schmidt-Wilcke	20	53.6 ± 7.7		1/19	Fibromyalgia		22	50.7 ± 7.3		2/20
	2007	Kuchinad	10	52		0/10	Fibromyalgia		10	45		0/10
	2006	Draganski	28	41.9 ± 13.8		20/8	Phantom limb pain	119.3 ± 140 m	28	41.4 ± 13.7		20/8
	2006	Schmidt-Wilcke	18	50.4 ± 6.8	34–59	9/9	Chronic back pain	176 ± 87.60 m	18	49.9 ± 8.7	32–60	9/9
	2004	Apkarian	26			10/16	Musculoskeletal; radiculopathy	11.3 ± 11.4	26	43.3		10/16
	Nociceptive pain	2011	Barnden	25	32	19–46	6/19	Chronic fatigue syndrome	7.4 ± 3.5	25	32.8	20–46
2011		Pantano	19	53.2 ± 11.2		4/15	Primary cervical dystonia	12.7 ± 6.5	28	47.5 ± 15.6		11/17
2010		Seminowicz	56	32.2 ± 12.3		0/56	Irritable bowel syndrome	11.1 ± 7.7	49	31.1 ± 12.3		0/49
2010		Gwilym	16	68		8/8	Primary osteoarthritis		16	68		8/8
2010		Tu	32	23.84 ± 2.99		0/32	Primary dysmenorrhea	10.19 ± 3.25	32	23.81 ± 2.8		0/32
2009		Obermann	7	39.6 ± 15.1	18–65	0/7	Chronic posttraumatic headache	118.1 ± 51.4	30	35 ± 13.7	19–67	13/17
2009		Rodriguez	32	66.8 ± 9		13/19	Primary osteoarthritis	7.35	32	63.9 ± 8.8		13/19
2009		Valet	14	51.1	28–68	0/14	Miscellanea	9.8 ± 7.2	25	51.7	32–60	11/14
2008		Kim	20	33.7 ± 11.3	15–53	3/17	Aura	9.8 ± 6	33	33.8 ± 10.5	15–53	4/29
2008		Schweinhardt	14	25.7 ± 5.1	19–36	0/14	Vulvar vestibulitis syndrome	5 ± 2.9	14	25.6 ± 6		0/14
2008		Valfrè	11	38.9 ± 6.4		2/9	Aura	20.6 ± 8.9	27	34.9 ± 8.6		7/20
2008		Davis	9		30–58	3/6	Irritable bowel syndrome		11		24–50	4/7
2007		Unrath	63	63.7 ± 11.4		18/45	Idiopathic restless legs syndrome	22.3 ± 7.1	40	63.4 ± 9.9		11/29
2007		Obermann Study 1	11	52.6	41–67		Idiopathic blepharospasm	5.5 ± 4.3	11	52.8 ± 11.6		4/7
2007		Obermann Study 2	9	55.9	43–63	2/7	Idiopathic cervical dystonia	10 ± 6.8	9	57.5 ± 8.2		2/7
2006		Rocca	16	42.7	28–58	1/15	Aura	24.8	15	38.6	24–50	2/13
2006		Etgen	16	67.4 ± 4.3		4/12	Primary blepharospasm	6.5 ± 4.9	16	65.3 ± 4.9		4/12
2005		Etgen Study 1	28	53.3 ± 8		7/21	Idiopathic restless legs syndrome	19 ± 14	28	52 ± 8.3		7/21
2005		Etgen Study 2	23	59.3 ± 10		6/17	Idiopathic restless legs syndrome	11.4 ± 11	23	59 ± 10.2		6/17
2005		Schmidt-Wilcke	40	50.85	16–70	12/28	Chronic tension type headache; medication-overuse headache					
2004	Okada	16	34	24–46	10/6	Chronic fatigue syndrome (CFS)	10 ± 244 m	49	34.4	21–47	27/22	
2004	Garraux	36	53 ± 9.7		21/15	Focal hand dystonia (FHD)	13 ± 7	36	52 ± 9.6		21/15	
1999	May	25	47	25–74	23/2	Idiopathic headache		29	33	20–55	29/0	

## 2.5. Distance matrix

We then applied representational similarity techniques (Kriegeskorte et al., 2008) to the results obtained with network decomposition in order to investigate the relationship between networks.

To obtain the visual representation, we first transformed the modeled activation maps of each experiment into a series of vectors containing the number of voxels altered in each network. Next, we constructed a representational similarity matrix by calculating the correlation between each vector ( $r$ ). The distance matrix (or representational dissimilarity matrix) was derived as  $1 - r$ . Lastly, we built a dendrogram of this matrix using a hierarchical clustering algorithm. This clustering approach had the advantage of allowing the visualization of hierarchies within the data.

## 2.6. Model-based clustering

Studies about gray matter modifications often report similar groups of targeted areas. For instance area  $a$  is usually shown to be structurally altered together with area  $b$ . This raises the question of whether such modifications are observed together by chance or constitute a cluster. In this latter case, it may be that the alteration of one area is strictly related to the alteration of another. To investigate this possibility, we applied model-based clustering.

The model-based clustering methodology is based on probability models, such as the Mixture Gaussian Model (Neumann et al., 2008). The idea behind this approach is that since a signal can be represented as a sum of sinusoids, each having its own amplitude, a probability distribution can be explained as a sum of Gaussians, each having its own weight. In mathematical terms, Mixture Gaussian models assume that the data is generated from a set of  $K$  simple Gaussian distributions like:

$$p(x) = \sum_k \pi_k N(\mu_k, \Sigma_k)$$

where  $\pi_k$  are the weights that a sample is drawn from,  $k$  is the mixture component and  $\mu_k$  and  $\Sigma_k$  are the means and covariance matrices of a multivariate normal distribution  $N$ . Given a sample  $D = \{x_1, x_2, x_3, \dots, x_n\}$  the goal is to estimate the parameters of the mixture  $(\pi_k, \mu_k, \Sigma_k)$  for  $k = 1 \dots K$ . In other words, the idea is to find those parameters that best describe the original distribution, in terms of weights, mean and variance. In order to have a measure of how well the reconstructed distribution approximated the original one, we used the maximum likelihood estimation (MLE) approach that uses the logarithm of the likelihood function (L) for estimating parameters:

$$\ln P(D|\pi, \mu, \Sigma) = \sum_i \ln \sum_k p_{\pi}(z_i = k) p_{\mu, \Sigma}(x_i | z_i = k).$$

The MLE was used to identify the number of correct clusters using as measure the Akaike information criterion (AIC) that is defined mathematically as:

$$AIC = 2k - 2\ln(L)$$

where  $k$  is the number of parameters of the model (i.e. the number of clusters). The idea is to test a different number of clusters, (in our case from 1 to 20) and choose the number that minimizes the Akaike information criterion. The Akaike information criterion (AIC) constitutes a measure of the quality of the model and allows model selection. It is used to measure the goodness of fit of the model in relation to its complexity.

## 2.7. Resting-state connectivity maps

We observed two clusters of gray matter alterations in the anterior insula: one increase and one decrease (see also the Results section). Crucially, these clusters were located in two distinct anatomical positions. We decided to investigate whether these two clusters were characterized by different connectivity patterns, using seed-based resting-state connectivity analysis. After acquiring resting-state data from twenty volunteers, we centered two ROIs in the two insular blobs and calculated their connectivity maps (see next paragraph for details).

## 2.8. Resting-state data: subjects

Twenty healthy right-handed volunteers (10 females, mean age  $32.6 \pm 11.2$ ) free of neurological or psychiatric disorders, not taking any medication known to alter brain activity, and who had no history of drug or alcohol abuse participated in this experiment. Handedness was ascertained with the Edinburgh Inventory (Oldfield, 1971). The

written informed consent of each participant was obtained, in accordance with the Declaration of Helsinki. The study was approved by the institutional committee on ethical use of human subjects at the University of Turin.

## 2.9. Task and image acquisition

Images were acquired during a resting-state scan on a 1.5 Tesla Ingenia™ scanner (Philips Medical Systems). Functional T2\* weighted images were acquired using echo planar (EPI) sequences, with a repetition time (TR) of 2000 ms, an echo time (TE) of 50 ms, and a 90° flip angle. The acquisition matrix was  $64 \times 64$ , with a 200 mm field of view (FoV). A total of 200 volumes were acquired, with each volume consisting of 19 axial slices; slice thickness was 4.5 mm with a 0.5 mm gap; in-plane resolution was 3.1 mm. Two scans were added at the beginning of functional scanning to reach steady-state magnetization before acquiring the experimental data. A set of three-dimensional high-resolution T1-weighted structural images was acquired, using a Fast Field Echo (FFE) sequence, with a 25 ms TR, an ultra-short TE, and a 30° flip angle. The acquisition matrix was  $256 \times 256$ , and the FoV was 256 mm. The set consisted of 160 contiguous sagittal images covering the whole brain.

## 2.10. Data analysis

The data-sets were pre-processed and analyzed using the Brain-Voyager QX software (Brain Innovation, Maastricht, The Netherlands). Functional images were pre-processed as follows to reduce artifacts (Miezin et al., 2000): (i) slice scan time correction was performed using a sinc interpolation algorithm; (ii) 3D motion correction was applied: using a trilinear interpolation algorithm, all volumes were spatially aligned to the first volume by rigid body transformations and the roto-translation information was saved for subsequent elaborations; and (iii) spatial smoothing was performed using a Gaussian kernel of 8 mm FWHM. Several nuisance covariates were regressed out from the time courses to control for the effects of physiological processes (Bandettini and Bullmore, 2008; Birn et al., 2008; Napadow et al., 2008) and motion. Specifically, we included 2 additional covariates from white matter (WM) and cerebrospinal fluid (CSF), as well as 6 motion parameters. The time courses were then temporally filtered in order to keep frequencies between 0.008 and 0.08 Hz only, and normalized. Subsequently, the datasets of each subject were transformed into Talairach space (Talairach and Tournoux, 1988). Two spherical ROIs with a diameter of 8 voxels were placed in the center of mass of the two insular blobs derived from the results of the model-based clusterization. The coordinates of the ROIs of increased gray matter were 31, 11, 4; those of the ROIs of decreases in gray matter were -30, 10, -5. For each subject the time courses of the two ROIs were extracted and normalized. A multi-subject random effect General Linear Model was performed using each subject's time courses as predictors. All maps were thresholded at  $p < 0.05$  and corrected for multiple comparisons using the false discovery rate (FDR).

## 3. Results

### 3.1. Anatomical likelihood estimation

The ALE results showed that chronic pain is associated with a common core set of gray matter decreases in the bilateral medial frontal gyri, bilateral superior frontal gyri, right pre- and post-central gyri (including the primary somatosensory and primary motor cortex), bilateral insula (anterior), right cingulate cortex (dorsal posterior cingulate cortex), basal ganglia, thalamus and periaqueductal gray. Increased gray matter was found in the bilateral post-central gyrus, left inferior parietal lobule, right pre-central gyrus (primary motor cortex), right post-central gyrus, in the dorsal prefrontal areas, in the caudate, thalamus, cerebellum, and pons (see Fig. 1 and also Tables 2–3).

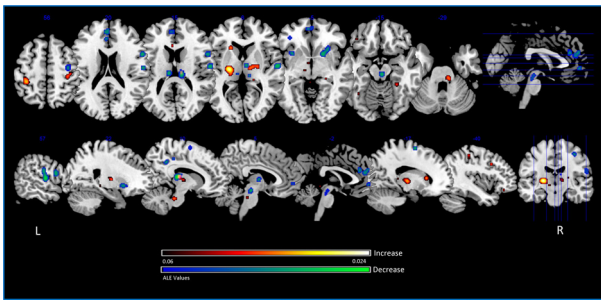
**Table 2**  
Gray matter decreases: activation likelihood estimation results.

Cluster #	Volume (mm <sup>3</sup> )	Weighted center (x, y, z)			x	y	z	Label
1	1368	58.5	−9.51	12.97	60	−8	10	Right precentral gyrus BA 43
					58	−12	22	Right postcentral gyrus BA 3
2	808	11.53	−23.63	11.81	12	−24	12	Right pulvinar
					20	12	−6	Right putamen
3	672	22.77	14.62	−5.36	28	20	−6	Right insula BA 47
					−6	36	28	Left medial frontal gyrus BA 9
4	608	−4.72	36.35	26.03	−6	36	28	Left medial frontal gyrus BA 9
					−6	48	18	Left medial frontal gyrus BA 9
5	560	−2.8	49.06	19.82	0	52	24	Left medial frontal gyrus BA 9
					56	10	18	Right inferior frontal gyrus BA 44
6	504	56.06	10.64	17.95	−10	−22	12	Left medial dorsal nucleus
					4	−22	−14	Periaqueductal gray
7	480	−9.16	−21.31	12	2	54	−2	Right medial frontal gyrus BA 10
					−6	54	−6	Left medial frontal gyrus BA 10
8	400	2.87	−21	−15.15	36	−12	54	Right precentral gyrus BA 4
					14	0	66	Right superior frontal gyrus BA 6
9	328	−1.25	54.28	−3.34	−16	0	64	Left superior frontal gyrus BA 6
					6	−8	6	Right thalamus
10	328	35.43	−12.05	53.27	−10	44	40	Left superior frontal gyrus BA 8
					−32	12	−4	Left insula BA 13
11	240	14.21	0.08	65.15	10	−44	40	Right cingulate gyrus BA 31
					−36	38	−2	Left middle frontal gyrus BA 47
12	224	−16.78	0.01	64.09	6	−8	6	Right thalamus
					−10	44	40	Left superior frontal gyrus BA 8
13	216	6.22	−7.61	6.88	−32	12	−4	Left insula BA 13
					10	−44	40	Right cingulate gyrus BA 31
14	200	−10.41	44.43	39.69	−10	44	40	Left superior frontal gyrus BA 8
					−32	12	−4	Left insula BA 13
15	176	−32.53	12.27	−4.3	−32	12	−4	Left insula BA 13
					10	−44	40	Right cingulate gyrus BA 31
16	168	10	−44.38	39.03	10	−44	40	Right cingulate gyrus BA 31
					−36	38	−2	Left middle frontal gyrus BA 47
17	120	−36.39	37.61	−2.13	−36	38	−2	Left middle frontal gyrus BA 47

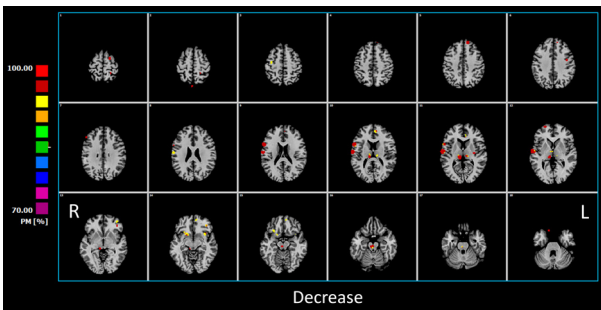
**Table 3**  
Gray matter increases: activation likelihood estimation results.

Cluster #	Volume (mm <sup>3</sup> )	Weighted center (x, y, z)			x	y	z	Label
1	1280	−21.85	−15.35	4.13	−22	−14	4	Left lateral globus pallidus
					−34	−36	56	Left postcentral gyrus BA 40
2	688	−36.11	−33.29	54.52	−42	−30	48	Left inferior parietal lobule BA 40
					10	−20	12	Right medial dorsal nucleus
3	624	15.56	−13.96	8.13	14	−12	6	Right ventral lateral nucleus
					24	−10	6	Right putamen
4	344	27.8	−39.7	−20.7	28	−40	−18	Right culmen
					28	−40	−24	Right culmen
5	320	−19.58	21.2	8.82	−20	22	8	Left caudate body
					34	−26	56	Right precentral gyrus BA 4
6	232	35.8	−26.53	55.92	40	−22	54	Right postcentral gyrus BA 3
					36	−34	58	Right postcentral gyrus BA 40
7	56	−40.84	12.85	35.15	−40	12	36	Left middle frontal gyrus BA 9

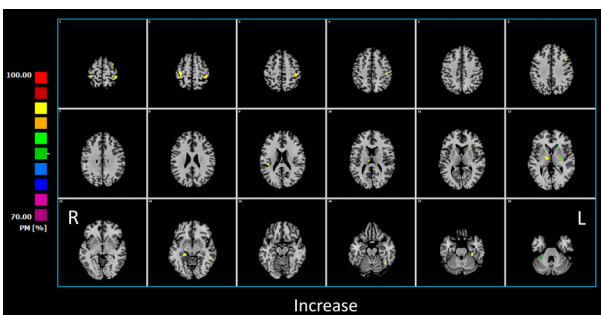




**Fig. 1.** Gray matter anatomical likelihood estimation (ALE) results. This image summarizes the results of all the papers involved in this meta-analysis. Colors from red to yellow show gray matter increases, colors from blue to green show gray matter decreases (two-dimensional ALE maps were computed at a false discovery rate corrected threshold of  $p < 0.05$ , with a minimum cluster size of  $K > 100 \text{ mm}^3$  and visualized using MRIcron). Talairach coordinates of clusters showed in this images are reported in Tables 2 and 3.



**Fig. 2.** Results of the jackknife analysis on the ALE GM decrease results. A high probability (approaching 100%) means that a certain area is led by the majority of the experiments included. By contrast, a lower probability means that a certain area is led by few experiments thus indicating the need to exercise caution in interpreting this point. Talairach coordinates of clusters showed in this images are reported in Table 2.



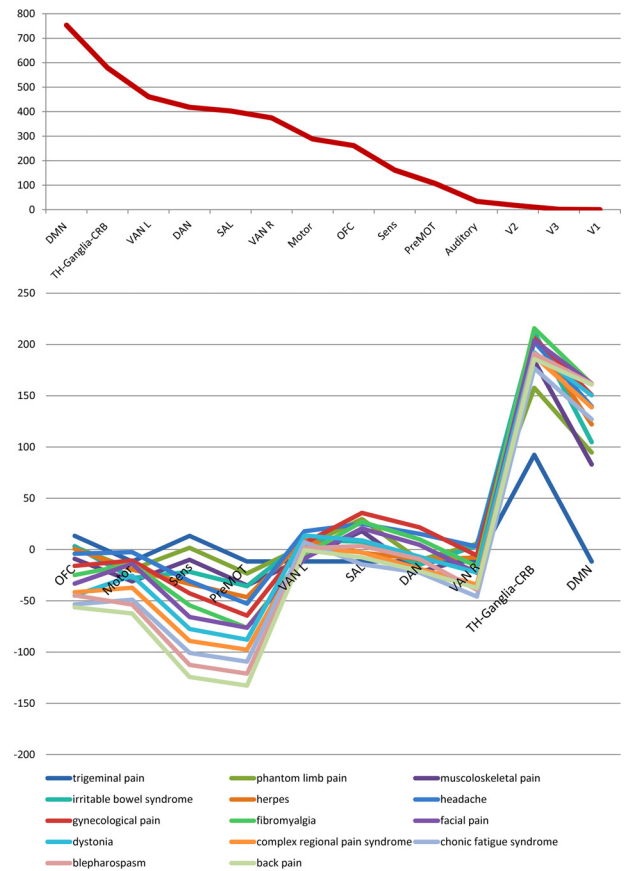
**Fig. 3.** Results of the jackknife analysis on the ALE GM increase results. A high probability (approaching 100%) means that a certain area is led by the majority of the experiments included. By contrast, a lower probability means that a certain area is led by few experiments thus indicating the need to exercise caution in interpreting this point. Talairach coordinates of clusters showed in this images are reported in Table 3.

### 3.2. Jackknife analysis

The jackknife analysis (Tukey, 1958) (Figs. 2 and 3) showed all the areas found in the ALE maps to have very high reliability. Areas with lower (although still very high) reliability were found in the thalamic and ventral prefrontal cortices. Overall the reliability of gray matter increases was 20% lower than that of decreases, probably due to the paucity of papers reporting gray matter increases.

### 3.3. Network decomposition

With the advent of models allowing the investigation of functional integration rather than mere functional segregation (see Friston, 2009

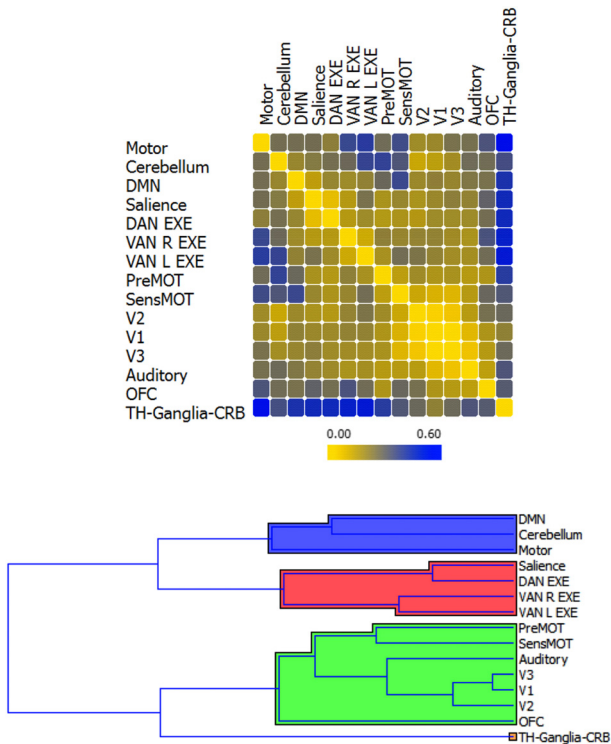


**Fig. 4.** Involvement of the large-scale brain networks in chronic pain-related gray matter alterations. The upper panel shows the global involvement of each large-scale brain network in the pain-related gray matter alterations (the results from all the pathologies are here placed together, the values are expressed in  $\text{mm}^3$  of altered brain volume). All the networks except auditory, V1, V2 and V3 are significantly different from zero. The lower panel shows a cumulative graph depicting the different involvement of the large-scale brain networks in different chronic pain pathologies (the results from all the pathologies are split here, the values are expressed in  $\text{mm}^3$  of altered brain volume). To obtain this graph the data were centered (the mean was subtracted). So higher values represent a greater deviation from the mean.

and also Farmer et al., 2012), researchers have begun to use a ‘network approach’ and study the co-variation of brain activity in response to noxious stimuli in order to unveil the functional significance of brain responses to those stimuli (Farmer et al., 2012). This approach is able to provide new insights in the study of the complex mechanisms underpinning the emergence of pain (Davis, 2011). To investigate which of the large-scale brain networks show GM alterations, we compared the number of increased/reduced voxels in each of the brain networks described by Biswal et al. (2010).

As shown in the upper left panel of Fig. 4, each type of chronic pain shows a different involvement of each large-scale network. To obtain this graph the data were centered (the mean value was subtracted); as a result, lower values represent a small deviation from the mean. The maximal variability was expressed by the thalamic–basal ganglia network (Th–Ba), followed by the DMN and premotor and somatosensory networks. Trigeminal pain showed a reduced involvement of the Th–Ba and DMN networks whereas complex regional pain syndrome, blepharospasm, chronic fatigue syndrome and back pain were characterized by reduced involvement of the somatosensory and premotor networks. Interestingly, the salience and attentional networks were damaged in a very similar way by different chronic pain pathologies.

The lower panel of Fig. 4 shows the mean number of voxels involved for each network. The DMN and Th–Ba, attentional and salience networks are the areas altered most.



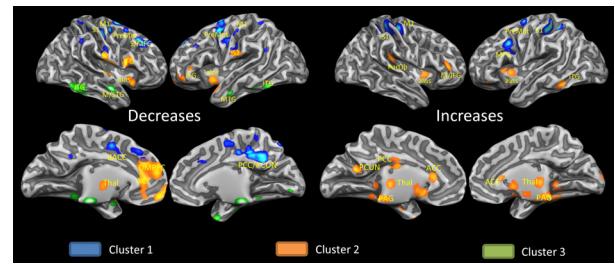
**Fig. 5.** Representation of dissimilarity between each large-scale brain network. The upper panel shows the (dis)similarity between each network. Networks that are involved in the same kind of pathologies are in a closer position. Networks that are involved in different pathologies are placed apart. The dendrogram in the lower part shows the results of a hierarchical clusterization of the large-scale brain networks on the basis of the different involvement of each network. Networks that show a similar involvement in the same kind of pathologies are clustered together.

### 3.4. Distance matrix

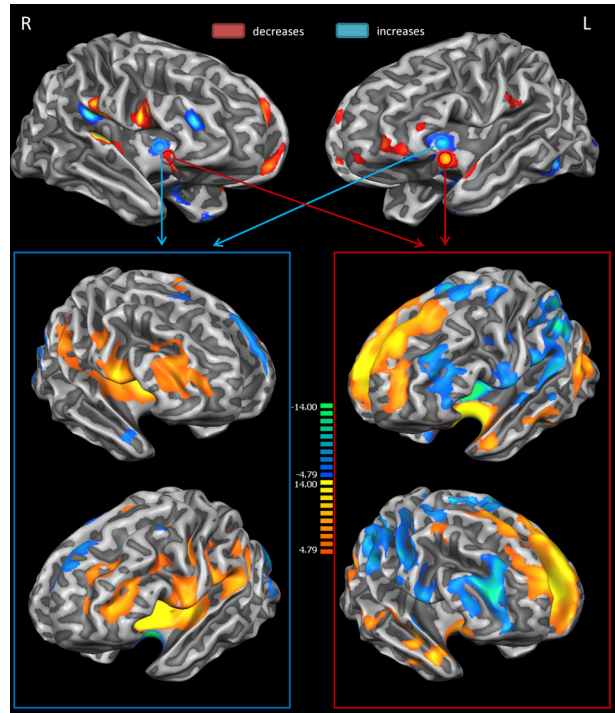
The (dis)similarity representation analysis (Fig. 5) showed that with the exception of the thalamus–basal ganglia network, the other networks could be clustered into three groups showing a similar involvement in chronic pain pathologies: a first group was composed of the DMN and cerebellar and motor networks; a second group of the salience and attentional networks; and a third group of the OFC, premotor, sensorimotor, auditory and visual networks.

### 3.5. Model-based clustering

The optimal number of clusters was calculated by minimizing the Akaike information criterion. This method showed an optimal cluster number of three for gray matter decreases and two for gray matter increases. The left panel of Fig. 6 shows the three clusters into which the gray matter decreases were decomposed. The first cluster was found to involve the fronto-parietal and medial wall areas, the second included the operculo-insular, cingulate, posterior thalamic and medial prefrontal areas, and the third comprised the temporal and pontine areas. The right panel of Fig. 6 shows the three clusters into which the gray matter increases were decomposed. The first included the somatomotor and somatosensory, premotor and parietal areas and the second the operculo-insular, basal ganglia, pontine and dorso-ventral prefrontal areas. Interestingly both decreases and increases were observed in the anterior insula, but in different portions of the region (see Fig. 7).



**Fig. 6.** Results of the model-based clusterization. The images on the left show the three clusters into which the gray matter decreases were parcellated. The images on the right show the two clusters into which the gray matter increases were parcellated.



**Fig. 7.** Resting-state seed voxel functional connectivity of the two anterior insular gray matter alterations: decrease-related and increase-related. The lower left panel shows the areas functionally connected to the “increase seed”. The lower right panel shows the areas functionally connected to the “decrease seed”.

### 3.6. Resting-state connectivity maps

We performed a resting-state connectivity experiment to explore whether the two anterior insular clusters derived from the decomposition of gray matter increases and decreases belong to different networks. As shown by Fig. 7, the two insular clusters presented a very different functional connectivity pattern. The increase cluster had a strong connectivity to the salience detection network with anticorrelations with a series of medial, dorsal prefrontal and parietal areas of the default mode network (DMN). The decrease cluster showed a connectivity with areas anticorrelated with the increase cluster. These areas were mainly constituted by the anterior part of the DMN. The decrease cluster showed anticorrelation with the salience detection network. These results suggested that the functional connectivity profile of the two ROIs is coherent with the gray matter modifications. The opposite alteration (increase or decrease) was mirrored in the opposite functional connectivity of these two ROIs: while the “increase” ROI showed a correlation with the salience network and an anticorrelation with the DMN, the “decrease” ROI presented an anticorrelation with the salience network and a correlation with the DMN.

## 4. Discussion

This study was designed to: i) verify the presence of a core set of brain areas commonly modified by chronic pain; ii) investigate the involvement of these areas in a large-scale network perspective; iii) study the relationship between altered networks and; iv) find out whether chronic pain targets clusters of areas. Our results show that: i) gray matter alterations in single areas should be better conceived in a framework of large-scale brain networks and ii) large-scale brain networks present both pathology-unspecific and pathology-specific involvements.

### 4.1. Network approach for the study of gray matter modifications induced by chronic pain

It has been demonstrated that the presence of long-lasting ongoing pain can modify the structure of the brain, inducing local morphological changes in the brain parenchyma (Farmer et al., 2012; May, 2008, 2011; Woolf and Salter, 2000). Indeed, in the last decade, the application of neuroimaging techniques, such as voxel-based morphometry (VBM), has provided considerable insight into structural brain reorganization in subjects suffering from chronic pain syndromes. The results of previous VBM studies have converged in concluding that chronic pain induces gray matter structural changes, often related to the duration of pain (Apkarian et al., 2009). However, these studies have not always obtained homogeneous results as to the areas affected by chronic pain and the amount of overall reorganization. In the present study we characterized gray matter modifications under a novel perspective which took into account networks rather than single areas. Our choice was motivated by recent theoretical frameworks which underline the importance of large-scale networks in the elaboration of noxious stimuli (Cauda et al., 2013; Mayhew et al., 2013), in the transition from acute to chronic pain (Baliki et al., 2012; Hashmi et al., 2013) and in the maintenance of chronic pain (Farmer et al., 2012). Indeed, it is now widely accepted that brain regions work in synergy and that their correlated or anticorrelated activity can be grouped into several large-scale networks (Fox et al., 2005; Mesmoudi et al., 2013). Besides, single areas can belong to more than one network and be functionally linked to different regions depending on the task (Cauda et al., 2012; Torta et al., 2013). This network approach may help to explain why previous studies on gray matter alterations in chronic pain have reported inconsistent results at the level of single areas.

### 4.2. Shared and specific alterations in large-scale brain networks induced by chronic pain

Our results revealed that chronic pain can induce both common and pathology-specific changes in large-scale networks. Gray matter alterations were almost always found to be present, regardless of the chronic pain syndrome, in the DMN and the thalamus–basal ganglia circuit and attention networks. In contrast, sensory networks were seldom and variably targeted by chronic pain. Trigeminal, musculoskeletal, phantom limb pain and irritable bowel syndrome were characterized by a minor involvement of the DMN and basal ganglia networks, but by greater alterations of the somatosensory and premotor networks. Conversely, blepharospasm, complex regional pain syndrome and chronic low back pain were characterized by a greater involvement of the DMN and basal ganglia networks, with a more marginal contribution of the somatosensory and premotor networks. Baliki et al. (2011) have recently investigated gray matter alterations in chronic back pain, osteoarthritis and complex regional pain syndrome considering gray matter alterations under an area and network perspective. The authors compared the three groups and a healthy control group in terms of total neocortical volume reduction and evidenced that only the chronic back pain group differed significantly

from the others. In addition, by performing a voxel based morphometry analysis, the authors observed common and specific reductions in gray matter for the three pain conditions. All groups showed decreases in the insula. The chronic back pain group had reductions in somatosensory areas, pre- and post-central gyri, the hippocampus and temporal lobes; the osteoarthritis group in the cingulate cortex, hippocampus and inferior temporal cortex; and the complex regional pain syndrome group in the orbitofrontal cortex. Moreover the authors parceled the cortex into 82 ROIs and observed that secondary somatosensory cortices, bilateral insulae and dorsal and orbital frontal regions, besides the hippocampus were those that better differentiated between groups. In order to study gray matter alterations in an inter-relation between areas, the authors correlated the gray matter decreases between each pair of ROI: they observed specific alterations in pain patients as compared to healthy subjects. Specifically, whereas healthy controls showed greater correlations between neighboring voxels (i.e. anatomically contiguous areas were more likely to have similar gray matter density), pain patients presented strengthened long distance correlations. These alterations were specific enough to be able to classify the group correctly.

Ours is however the first report that, by covering a wide spectrum of chronic pain syndromes, is able to specify that chronic pain targets large-scale brain networks. This is in line with the network degeneration hypothesis characterized in degenerative syndromes that posits that atrophy (here conceived as gray matter decreases) recapitulates healthy brain functional networks (Seeley et al., 2009). In this view, the pathology targets specific large-scale networks, which, in the healthy brain, feature the perceptual or cognitive function that is altered in the disease.

Notably, our findings show that attention circuits (the salience, ventral and dorsal attentional networks) are similarly affected in all pain syndromes and their involvement is not subject to change in relation to the pathology under examination. This finding can substantiate the idea that attention networks are always targeted by chronic pain, regardless of its etiology and regardless of the attention network (see Cauda et al., 2010). Indeed, we found gray matter decreases to affect both the ventral exogenous attention network, usually linked to bottom-up processing, and the dorsal endogenous attention network, linked to top-down processing. We also observed that the DMN was targeted by all chronic pain pathologies. The DMN is thought to be implicated in self-referential cognitive processing, self-awareness and self-monitoring. It is plausible to hypothesize that a long-lasting and intruding disorder like chronic pain alters interoceptive functions per se, regardless of the etiology of the disease.

The thalamic–basal ganglia networks were also always targeted. Thalamic–cortical dysrhythmia has often been proposed as a mechanism that underlies chronic pain states (Llinas et al., 1999). The observation of increased levels of power spectrum in various pain states measured by EEG (Saab, 2012; Sarnthein et al., 2006; Stern et al., 2006) has led to the suggestion that altered brain oscillation may constitute a characteristic of dysfunctional thalamo–cortical loops. Recently, it has been shown that, in chronic neuropathic pain, the thalamus is characterized by significant volume loss and reduced inhibitory neurotransmitter content (Henderson et al., 2013).

### 4.3. Investigating how chronic pain affects large-scale brain networks

By applying representational similarity techniques to the results of the network decomposition we observed a parcellation into three clusters (Fig. 5 lower panel), where the first cluster was composed of the DMN, cerebellum and motor areas, the second of the salience/attention networks and the third of the sensory networks. The thalamic–basal ganglia network remained isolated.

These results substantiate our previous conclusion: that the attention and sensory networks are differentially affected by chronic pain pathologies: the attentional networks show pathology-unspecific



changes, whereas in the sensory networks strong damage variability is observed for different chronic pain categories.

To obtain true data-driven confirmation as to whether chronic pain specifically targets some large-scale brain networks we performed a model-based clusterization of our data-set. In this analysis we investigated increases and decreases in gray matter separately.

Our analyses confirmed the network-based results, indeed this new data-driven analysis highlighted three clusters of decreases and two of increases. Increases were observed not only in the somatosensory and somatomotor areas, as previously reported (Schweinhardt et al., 2008), but also in the operculo-insular cortex. Decreases were observed in the fronto-parietal regions, temporal and pontine regions and, again, in the anterior insula. The fact that decreases and increases tap on differential networks is important. As already suggested by previous studies on chronic pain and now supported by data on experimental pain, it is highly likely that differential networks respond to noxious and painful stimuli in a different manner and with different temporal envelopes (Cauda et al., 2013; Mayhew et al., 2013; Moulton et al., 2012). These networks may thus undergo selective alterations by the pathology.

#### 4.4. Role of the insular cortex in gray matter alterations

Our findings indicate that both increases and decreases in gray matter can be found in the insula. Crucially, increases and decreases did not occur in the same region of the anterior insula: increases were observed in the dorsal anterior insula, whereas decreases were detected in the ventral anterior insula. These two areas, as revealed by resting-state functional connectivity, are correlated with different networks. The ventral anterior insula (gray matter increases) was correlated with the salience network and anticorrelated with the DMN. Conversely, the dorsal anterior insula was correlated with anterior parts of the DMN and anticorrelated with the salience network. These data offer another possible explanation for the increase/decrease pattern that has so far been explained in terms of duration of the pathology (Apkarian et al., 2004). Our results suggest that increases and decreases occur in two anticorrelated networks: increased activity in one network leads to decreased activity in the other. This view in which different areas of the brain that are related to different and somewhat opposite functions exert an opposite (anticorrelated) connectivity pattern and are attacked in an opposite way by pathologies opens novel perspectives (Mesmoudi et al., 2013).

A possible explanation for the pattern of decrease/increase in the insula may be that the salience network and sensory regions are over-excited by greater weights attributed to external stimuli such as pain. This functional over-recruitment may promote a structural reorganization of the areas in the network (such as the somatosensory areas and ventral anterior insula) and induce an increase in gray matter. The excessive activation of the salience network may, in turn, cause de-activation of the anticorrelated circuit (DMN), which, as a consequence, undergoes a reduction in volume. This explanation implies a tight link between functional and structural modifications, which has yet to be fully characterized in chronic pain. However, at least two lines of reasoning support this view. First, it is difficult to conceive that functional and structural alterations are not related to one another since functional and structural networks are (Kelly et al., 2012; Pernice et al., 2011; Zhang et al., 2011). Numerous fMRI studies have already demonstrated that chronic pain alters the normal functioning of brain networks (Balenzuela et al., 2010; Cauda et al., 2009a, 2010). For instance, it has been shown that chronic pain disrupts thalamo-cortical connections (Cauda et al., 2010; Jensen et al., 2012), default mode network dynamics (Baliki et al., 2008; Napadow et al., 2012) and the functional connectivity of the dorsal and ventral attentional networks (Cauda et al., 2010; Napadow et al., 2010). Second, it has been shown that synchronous neuronal firing promotes synaptogenesis (Bi and Poo, 1999; Katz and Shatz, 1996) and that intrinsic functional

connectivity and structural covariance converge (Seeley et al., 2009).

Many areas of decreases in gray matter that we found in our data belong to the descending inhibitory circuits. Therefore, another possible conclusion is that the unbalance between anticorrelated networks in favor of increased salience towards external stimuli hampers the physiological inhibition of potentially dangerous stimuli. This mechanism may be another candidate for the maintenance of chronic pain states. This explanation is supported by theoretical models which suggest a less efficient top-down modulation of pain in chronic pain patients. In this sense, chronic pain patients may be more prone to attentional processing of pain-related information (see Van Damme et al., 2010 for a critical review on attentional-related aspects of pain processing) and might have difficulties in disengaging attention from pain (Van Damme et al., 2004).

#### 4.5. Limitations and future perspectives

As our analyses relied on data provided by previous studies, we were not able to control for factors that could have intervened in altering gray matter and that had not been tested in the original research. This is important, as chronic pain patients frequently have several comorbid conditions, for example anxiety and mood disorders, altered life-styles and drug use that might directly contribute to morphological changes. These aspects have not always been considered in previous VBM studies. In particular, the presence of chronic anxiety, depressed mood and chronic stress leads to activation of the hypothalamic–pituitary–adrenal (HPA) axis that, by increasing stress hormones (cortisol in humans), induces neuronal loss in several brain areas. This loss is related to several factors such as an increase in pro-inflammatory cytokines, a reduction in neurotrophic factors and a rise in neurotoxic glutamate (Swaab et al., 2005; Tata and Anderson, 2010). Chronic pain shares several of these mechanisms (increase in cytokine and glutamate release) that may induce a vicious cycle in perpetuating the comorbidity between pain and emotional disorders and between the latter and neuronal loss (Torta and Munari, 2010). It has been observed that, in fibromyalgia patients, the volume decrease in regions that process emotional states is related to the patient's affective state and not to the presence of pain per se (Hsu et al., 2009). What is more, the chronic use of opioids produces neuroplastic changes in animals and also in humans, as confirmed by gray matter dose-related volumetric changes (Younger et al., 2011). In line with this, the use of antidepressants in chronic pain can offer protection against neuronal suffering, by preventing the enhancement of glutamate release induced by stress (Musazzi et al., 2011).

In conclusion, our results showed that chronic pain selectively alters large-scale brain networks. Some of these networks are altered in a very similar way but others are altered differentially by chronic pain pathologies. This adds to a picture in which some common areas represent a “core group” of regions altered by almost all the chronic pain pathologies and some other areas that are differentially damaged and that may represent the specific damage of each pathology. Indeed as already proposed by Baliki et al. (2011), each syndrome also has a specific and discriminable pattern of alterations. Future studies including a larger sample will help to establish the validity of such suggestions.

#### Funding sources

This research was supported by a grant from the ‘Fondazione Carlo Molo’, Turin.

#### Appendix A. Supplementary materials

Supplementary material associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.nicl.2014.04.007>.

## References

- Apkarian, A.V., Baliki, M.N., Geha, P.Y., 2009. Towards a theory of chronic pain. *Progress in Neurobiology* 87, 81–97. <http://dx.doi.org/10.1016/j.pneurobio.2008.09.018>, 18952143.
- Apkarian, A.V., Sosa, Y., Sonty, S., Levy, R.M., Harden, R.N., Parrish, T.B. et al., 2004. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *Journal of Neuroscience: the Official Journal of the Society for Neuroscience* 24, 10410–15. <http://dx.doi.org/10.1523/JNEUROSCI.2541-04.2004>, 15548656.
- Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry—the methods. *Neuroimage* 11, 805–21. <http://dx.doi.org/10.1006/nimg.2000.0582>, 10860804.
- Balenzuela, P., Chernomoretz, A., Fraiman, D., Cifre, I., Sitges, C., Montoya, P. et al., 2010. Modular organization of brain resting state networks in chronic back pain patients. *Frontiers in Neuroinformatics* 4, 116, 21206760.
- Baliki, M.N., Geha, P.Y., Apkarian, A.V., Chialvo, D.R., 2008. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *Journal of Neuroscience: the Official Journal of the Society for Neuroscience* 28, 1398–403. <http://dx.doi.org/10.1523/JNEUROSCI.4123-07.2008>, 18256259.
- Baliki, M.N., Petre, B., Torbey, S., Herrmann, K.M., Huang, L., Schnitzer, T.J. et al., 2012. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature Neuroscience* 15, 1117–19. <http://dx.doi.org/10.1038/nn.3153>, 22751038.
- Baliki, M.N., Schnitzer, T.J., Bauer, W.R., Apkarian, A.V., 2011. Brain morphological signatures for chronic pain. *PLoS One* 6, e26010. <http://dx.doi.org/10.1371/journal.pone.0026010>, 22022493.
- Bandettini, P.A., Bullmore, E., 2008. Endogenous oscillations and networks in functional magnetic resonance imaging. *Human Brain Mapping* 29, 737–9. <http://dx.doi.org/10.1002/hbm.20607>, 18465798.
- Bennett, M.I., Smith, B.H., Torrance, N., Lee, A.J., 2006. Can pain be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians. *Pain* 122, 289–94. <http://dx.doi.org/10.1016/j.pain.2006.02.002>, 16540249.
- Bi, G., Poo, M., 1999. Distributed synaptic modification in neural networks induced by patterned stimulation. *Nature* 401, 792–6. <http://dx.doi.org/10.1038/44573>, 10548104.
- Birn, R.M., Murphy, K., Bandettini, P.A., 2008. The effect of respiration variations on independent component analysis results of resting state functional connectivity. *Human Brain Mapping* 29, 740–50. <http://dx.doi.org/10.1002/hbm.20577>, 18438886.
- Biswal, B.B., Mennes, M., Zuo, X.N., Gohel, S., Kelly, C., Smith, S.M. et al., 2010. Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences of the United States of America* 107, 4734–9. 20176931.
- Bressler, S.L., Menon, V., 2010. Large-scale brain networks in cognition: emerging methods and principles. *Trends in Cognitive Sciences* 14, 277–90, 20493761.
- Buckalew, N., Haut, M.W., Morrow, L., Weiner, D., 2008. Chronic pain is associated with brain volume loss in older adults: preliminary evidence. *Pain Medicine (Malden, Mass.)* 9, 240–8, 18298708.
- Burgmer, M., Gaubitz, M., Konrad, C., Wrenger, M., Hilgart, S., Heuft, G. et al., 2009. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. *Psychosomatic Medicine* 71, 566–73, 19414621.
- Cauda, F., D'Agata, F., Sacco, K., Duca, S., Cocito, D., Paolasso, I. et al., 2010. Altered resting state attentional networks in diabetic neuropathic pain. *Journal of Neurology, Neurosurgery, and Psychiatry* 81, 806–11, 19955113.
- Cauda, F., Costa, T., Diano, M., Sacco, K., Duca, S., Geminiani, G. et al., 2013. Massive modulation of brain areas after mechanical pain stimulation: a time-resolved fMRI study. *Cerebral Cortex (New York, N.Y.: 1991)*, 23796948.
- Cauda, F., Sacco, K., D'Agata, F., Duca, S., Cocito, D., Geminiani, G. et al., 2009. Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in diabetic neuropathic pain. *BMC Neuroscience* 10, 138, 19941658.
- Cauda, F., Sacco, K., Duca, S., Cocito, D., D'Agata, F., Geminiani, G.C. et al., 2009. Altered resting state in diabetic neuropathic pain. *PLoS One* 4, e4542.
- Cauda, F., Torta, D.M., Sacco, K., Geda, E., D'Agata, F., Costa, T. et al., 2012. Shared “core” areas between the pain and other task-related networks. *PLoS One* 7, e41929, 22900003.
- Davis, B.R., Vitale, M., Lecompte, M., Vitale, D., Vitale, G.C., 2008. An objective study of pain relief in chronic pancreatitis from bilateral thoracoscopic splanchnicectomy. *American Surgeon* 74, 510–14, [Discussion 514–515] 18556993.
- Davis, K.D., 2011. Neuroimaging of pain: what does it tell us? *Current Opinion in Supportive and Palliative Care* 5, 116–21, 21415755.
- Draganski, B., Moser, T., Lummel, N., Ganssbauer, S., Bogdahn, U., Haas, F. et al., 2006. Decrease of thalamic gray matter following limb amputation. *Neuroimage* 31, 951–7, 16520065.
- Eickhoff, S.B., Bzdok, D., Laird, A.R., Kurth, F., Fox, P.T., 2012. Activation likelihood estimation meta-analysis revisited. *Neuroimage* 59, 2349–61, 21963913.
- Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping* 30, 2907–26, 19172646.
- Etgen, T., Draganski, B., Ilg, C., Schroder, M., Geisler, P., Hajak, G. et al., 2005. Bilateral thalamic gray matter changes in patients with restless legs syndrome. *Neuroimage* 24, 1242–7, 15670702.
- Farmer, M.A., Baliki, M.N., Apkarian, A.V., 2012. A dynamic network perspective of chronic pain. *Neuroscience Letters* 520 (2), 197–203. <http://dx.doi.org/10.1016/j.neulet.2012.05.001>, 22579823.
- Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America* 102, 9673–8, 15976020.
- Friston, K.J., 2009. Modalities, modes, and models in functional neuroimaging. *Science (New York, N.Y.)* 326, 399–403, 19833961.
- Garraux, G., Bauer, A., Hanakawa, T., Wu, T., Kansaku, K., Hallett, M., 2004. Changes in brain anatomy in focal hand dystonia. *Annals of Neurology* 55, 736–9, 15122716.
- Geha, P.Y., Baliki, M.N., Harden, R.N., Bauer, W.R., Parrish, T.B., Apkarian, A.V., 2008. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. *Neuron* 60, 570–81, 19038215.
- Gerstner, G.E., Gracely, R.H., Deebajah, A., Ichesco, E., Quintero, A., Clauw, D.J. et al., 2012. Posterior insular molecular changes in myofascial pain. *Journal of Dental Research* 91, 485–90, 22451533.
- Gustin, S.M., Peck, C.C., Wilcox, S.L., Nash, P.G., Murray, G.M., Henderson, L.A., 2011. Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. *Journal of Neuroscience: the Official Journal of the Society for Neuroscience* 31, 5956–64, 21508220.
- Gwilym, S.E., Filippini, N., Douaud, G., Carr, A.J., Tracey, I., 2010. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. *Arthritis and Rheumatism* 62, 2930–40, 20518076.
- Hashmi, J.A., Baliki, M.N., Huang, L., Baria, A.T., Torbey, S., Hermann, K.M. et al., 2013. Shape shifting pain: chronicification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain: a Journal of Neurology* 136, 2751–68, 23983029.
- Henderson, L.A., Peck, C.C., Petersen, E.T., Rae, C.D., Youssef, A.M., Reeves, J.M. et al., 2013. Chronic pain: lost inhibition? *Journal of Neuroscience: the Official Journal of the Society for Neuroscience* 33, 7574–82, 23616562.
- Hsu, M.C., Harris, R.E., Sundgren, P.C., Welsh, R.C., Fernandes, C.R., Clauw, D.J. et al., 2009. No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder. *Pain* 143, 262–7, 19375224.
- Jensen, K.B., Loitole, R., Kosek, E., Petzke, F., Carville, S., Fransson, P. et al., 2012. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. *Molecular Pain* 8, 32, 22537768.
- Katz, L.C., Shatz, C.J., 1996. Synaptic activity and the construction of cortical circuits. *Science (New York, N.Y.)* 274, 1133–8, 8895456.
- Kelly, C., Toro, R., Di Martino, A., Cox, C.L., Bellec, P., Castellanos, F.X. et al., 2012. A convergent functional architecture of the insula emerges across imaging modalities. *Neuroimage* 61, 1129–42, 22440648.
- Kriegeskorte, N., Mur, M., Bandettini, P., 2008. Representational similarity analysis—connecting the branches of systems neuroscience. *Frontiers in Systems Neuroscience* 2, 4–5, 19104670.
- Kuchinad, A., Schweinhardt, P., Seminowicz, D.A., Wood, P.B., Chizh, B.A., Bushnell, M.C., 2007. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *Journal of Neuroscience: the Official Journal of the Society for Neuroscience* 27, 4004–7. <http://dx.doi.org/10.1523/JNEUROSCI.0098-07.2007>, 17428976.
- Laird, A.R., Eickhoff, S.B., Kurth, F., Fox, P.M., Uecker, A.M., Turner, J.A. et al., 2009. ALE meta-analysis workflows via the BrainMap database: progress towards a probabilistic functional brain atlas. *Frontiers in Neuroinformatics* 3, 23, 19636392.
- Laird, A.R., Fox, P.M., Price, C.J., Glahn, D.C., Uecker, A.M., Lancaster, J.L. et al., 2005. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping* 25, 155–64, 15846811.
- Laird, A.R., Lancaster, J.L., Fox, P.T., 2005. BrainMap: the social evolution of a human brain mapping database. *Neuroinformatics* 3, 65–78, 15897617.
- Lancaster, J.L., Tordesillas-Gutierrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K. et al., 2007. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping* 28, 1194–205, 17266101.
- Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L. et al., 2000. Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping* 10, 120–31, 10912591.
- Llinas, R.R., Ribary, U., Jeanmonod, D., Kronberg, E., Mitra, P.P., 1999. Thalamic cortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proceedings of the National Academy of Sciences of the United States of America* 96, 15222–7, 10611366.
- Loeser, J.D., Treede, R.D., 2008. The Kyoto protocol of IASP basic pain terminology. *Pain* 137, 473–7, 18583048.
- May, A., 2008. Chronic pain may change the structure of the brain. *Pain* 137, 7–15, 18410991.
- May, A., 2011. Structural brain imaging: a window into chronic pain. *Neuroscientist: a Review Journal Bringing Neurobiology, Neurology and Psychiatry* 17, 209–20, 21489967.
- Mayhew, S.D., Hylands-White, N., Porcaro, C., Derbyshire, S.W., Bagshaw, A.P., 2013. Intrinsic variability in the human response to pain is assembled from multiple, dynamic brain processes. *Neuroimage* 75, 68–78, 23485593.
- Mesmoudi, S., Perlberg, V., Rudrauf, D., Messe, A., Pinsard, B., Hasboun, D. et al., 2013. Resting state networks' corticotomy: the dual intertwined rings architecture. *PLoS One* 8, e67444, 23894288.
- Miezin, F.M., Maccotta, L., Ollinger, J.M., Petersen, S.E., Buckner, R.L., 2000. Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage* 11, 735–59, 10860799.
- Moulton, E.A., Pende, G., Becerra, L.R., Borsook, D., 2012. BOLD responses in somatosensory cortices better reflect heat sensation than pain. *Journal of Neuroscience: the Official Journal of the Society for Neuroscience* 32, 6024–31, 22539862.

- Musazzi, L., Racagni, G., Popoli, M., 2011. Stress, glucocorticoids and glutamate release: effects of antidepressant drugs. *Neurochemistry international* 59, 138–49, [21689704](#).
- Napadow, V., Dhond, R., Conti, G., Makris, N., Brown, E.N., Barbieri, R., 2008. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. *Neuroimage* 42, 169–77, [18524629](#).
- Napadow, V., Kim, J., Clauw, D.J., Harris, R.E., 2012. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. *Arthritis and Rheumatism* 64, 2398–403, [22294427](#).
- Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D.J., Harris, R.E., 2010. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis and Rheumatism* 62, 2545–55, [20506181](#).
- Neumann, J., von Cramon, D.Y., Lohmann, G., 2008. Model-based clustering of meta-analytic functional imaging data. *Human Brain Mapping* 29, 177–92, [17390315](#).
- Obermann, M., Nebel, K., Schumann, C., Holle, D., Gizewski, E.R., Maschke, M. et al., 2009. Gray matter changes related to chronic posttraumatic headache. *Neurology* 73, 978–83, [19770474](#).
- Obermann, M., Yaldizli, O., De, Greiff A., Lachenmayer, M.L., Buhl, A.R., Tumczak, F. et al., 2007. Morphometric changes of sensorimotor structures in focal dystonia. *Movement Disorders: Official Journal of the Movement Disorder Society* 22, 1117–23, [17443700](#).
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113, [5146491](#).
- Pernice, V., Staude, B., Cardanobile, S., Rotter, S., 2011. How structure determines correlations in neuronal networks. *PLoS Computational Biology* 7, [21625580](#).
- Radua, J., Mataix-Cols, D., 2009. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry: the Journal of Mental Science* 195, 393–402, [19880927](#).
- Radua, J., Via, E., Catani, M., Mataix-Cols, D., 2011. Voxel-based meta-analysis of regional white-matter volume differences in autism spectrum disorder versus healthy controls. *Psychological Medicine* 41, 1539–50, [21078227](#).
- Rainville, P., Duncan, G.H., 2006. Functional brain imaging of placebo analgesia: methodological challenges and recommendations. *Pain* 121, 177–80, [16513275](#).
- Rocca, M.A., Ceccarelli, A., Falini, A., Colombo, B., Tortorella, P., Bernasconi, L. et al., 2006. Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. *Stroke: a Journal of Cerebral Circulation* 37, 1765–70, [16728687](#).
- 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. *Journal of Neuroscience: the Official Journal of the Society for Neuroscience* 29, 13746–50, [19889986](#).
- Saab, C.Y., 2012. Pain-related changes in the brain: diagnostic and therapeutic potentials. *Trends in Neurosciences* 35, 629–37, [22763295](#).
- Sarnthein, J., Stern, J., Aufenberg, C., Rousson, V., Jeanmonod, D., 2006. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain: a Journal of Neurology* 129, 55–64, [16183660](#).
- Schmidt-Wilcke, T., Hiertlmeier, S., Leinisch, E., 2010. Altered regional brain morphology in patients with chronic facial pain. *Headache* 50, 1278–85, [20236343](#).
- Schmidt-Wilcke, T., Leinisch, E., Ganssbauer, S., Draganski, B., Bogdahn, U., Altmepfen, J. et al., 2006. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. *Pain* 125, 89–97, [16750298](#).
- Schmidt-Wilcke, T., Leinisch, E., Straube, A., Kampfe, N., Draganski, B., Diener, H.C. et al., 2005. Gray matter decrease in patients with chronic tension type headache. *Neurology* 65, 1483–6, [16275843](#).
- Schmidt-Wilcke, T., Lueding, R., Weigand, T., Jurgens, T., Schuierer, G., Leinisch, E. et al., 2007. Striatal grey matter increase in patients suffering from fibromyalgia—a voxel-based morphometry study. *Pain* 132 (Suppl. 1), S109–S116, [17587497](#).
- Schweinhardt, P., Kuchinad, A., Pukall, C.F., Bushnell, M.C., 2008. Increased gray matter density in young women with chronic vulvar pain. *Pain* 140, 411–19, [18930351](#).
- Seeley, W.W., Crawford, R.K., Zhou, J., Miller, B.L., Greicius, M.D., 2009. Neurodegenerative diseases target large-scale human brain networks. *Neuron* 62, 42–52, [19376066](#).
- Seminowicz, D.A., Wideman, T.H., Naso, L., Hatami-Khoroushahi, Z., Fallatah, S., Ware, M.A. et al., 2011. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *Journal of Neuroscience: the Official Journal of the Society for Neuroscience* 31, 7540–50, [21593339](#).
- Stern, J., Jeanmonod, D., Sarnthein, J., 2006. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. *Neuroimage* 31, 721–31, [16527493](#).
- Swaab, D.F., Bao, A.M., Lucassen, P.J., 2005. The stress system in the human brain in depression and neurodegeneration. *Ageing Research Reviews* 4, 141–94. <http://dx.doi.org/10.1016/j.arr.2005.03.003>, [15996533](#).
- Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging. Thieme.
- Tata, D.A., Anderson, B.J., 2010. The effects of chronic glucocorticoid exposure on dendritic length, synapse numbers and glial volume in animal models: implications for hippocampal volume reductions in depression. *Physiology & Behavior* 99, 186–93, [19786041](#).
- Torta, D.M., Costa, T., Duca, S., Fox, P.T., Cauda, F., 2013. Parcellation of the cingulate cortex at rest and during tasks: a meta-analytic clustering and experimental study. *Frontiers in Human Neuroscience* 7, 275, [23785324](#).
- Torta, R.G., Munari, J., 2010. Symptom cluster: depression and pain. *Surgical Oncology* 19, 155–9, [20106657](#).
- Treede, R.D., Jensen, T.S., Campbell, J.N., Cruccu, G., Dostrovsky, J.O., Griffin, J.W. et al., 2008. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 70, 1630–5, [18003941](#).
- Tu, C.H., Niddam, D.M., Chao, H.T., Chen, L.F., Chen, Y.S., Wu, Y.T. et al., 2010. Brain morphological changes associated with cyclic menstrual pain. *Pain* 150, 462–8, [20705214](#).
- Tukey, J.W., 1958. Bias and confidence in not quite large samples. *Annals of Mathematical Statistics* 29, 614.
- Unrath, A., Juengling, F.D., Schork, M., Kassubek, J., 2007. Cortical grey matter alterations in idiopathic restless legs syndrome: an optimized voxel-based morphometry study. *Movement Disorders: Official Journal of the Movement Disorder Society* 22, 1751–6, [17566123](#).
- Valet, M., Gundel, H., Sprenger, T., Sorg, C., Muhlau, M., Zimmer, C. et al., 2009. Patients with pain disorder show gray-matter loss in pain-processing structures: a voxel-based morphometric study. *Psychosomatic Medicine* 71, 49–56, [19073757](#).
- Valfre, W., Rainero, I., Bergui, M., Pinessi, L., 2008. Voxel-based morphometry reveals gray matter abnormalities in migraine. *Headache* 48, 109–17, [18184293](#).
- Van Damme, S., Crombez, G., Eccleston, C., 2004. Disengagement from pain: the role of catastrophic thinking about pain. *Pain* 107, 70–6, [14715391](#).
- Van Damme, S., Legrain, V., Vogt, J., Crombez, G., 2010. Keeping pain in mind: a motivational account of attention to pain. *Neuroscience and Biobehavioral Reviews* 34, 204–13, [19896002](#).
- Vartiainen, N., Kirveskari, E., Kallio-Laine, K., Kalso, E., Forss, N., 2009. Cortical reorganization in primary somatosensory cortex in patients with unilateral chronic pain. *Journal of Pain: Official Journal of the American Pain Society* 10, 854–9, [19638329](#).
- Woolf, C.J., Salter, M.W., 2000. Neuronal plasticity: increasing the gain in pain. *Science (New York, N.Y.)* 288, 1765–9, [10846153](#).
- Younger, J.W., Chu, L.F., D'Arcy, N.T., Trotter, K.E., Jastrzab, L.E., Mackey, S.C., 2011. Prescription opioid analgesics rapidly change the human brain. *Pain* 152, 1803–10, [21531077](#).
- Younger, J.W., Shen, Y.F., Goddard, G., Mackey, S.C., 2010. Chronic myofascial temporomandibular pain is associated with neural abnormalities in the trigeminal and limbic systems. *Pain* 149, 222–8, [20236763](#).
- Zhang, Z., Liao, W., Zuo, X.N., Wang, Z., Yuan, C., Jiao, Q. et al., 2011. Resting-state brain organization revealed by functional covariance networks. *PLoS One* 6, e28817, [22174905](#).