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

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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.

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 $K > 50\ mm^3$.

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.