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Associations of limbic-affective brain activity and severity of ongoing chronic arthritis pain are explained by trait anxiety

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ABSTRACT

Functional magnetic resonance imaging studies (fMRI) have transformed our understanding of central processing of evoked pain but the typically used block and event-related designs are not best suited to the study of ongoing pain. Here we used arterial spin labelling (ASL) for cerebral blood flow mapping to characterise the neural correlates of perceived intensity of osteoarthritis (OA) pain and its interrelation with negative affect. Twenty-six patients with painful knee OA and twenty-seven healthy controls underwent pain phenotyping and ASL MRI at 3T. Intensity of OA pain correlated positively with blood flow in the anterior mid-cingulate cortex (aMCC), subgenual cingulate cortex (sgACC), bilateral hippocampi, bilateral amygdala, left central operculum, mid-insula, putamen and the brainstem. Additional control for trait anxiety scores reduced the pain-CBF association to the aMCC, whilst pain catastrophizing scores only explained some of the limbic correlations. In conclusion, we found that neural correlates of reported intensity of ongoing chronic pain intensity mapped to limbic-affective circuits, and that the association pattern apart from aMCC was explained by trait anxiety thus highlighting the importance of aversiveness in the experience of clinical pain.

1. Introduction

Chronic pain affects approximately 11% of the population, with poor outcomes for current treatment (Harstall and O., 2003). Large surveys across Europe and Canada found that arthritis/osteoarthritis (OA) joint pain was the most common cause of chronic pain, reported by over one third of chronic pain patients (Breivik et al., 2006; Schopflocher et al., 2011). Pain is a primary symptom of OA, a degenerative joint disease, but there is disagreement on how well structural damage (as evidenced by radiographs) concurs with the severity or presence of symptoms including pain (Hannan et al., 2000). Previous studies of chronic OA pain have suggested that the pain experience is not only the result of constant or aberrant nociceptive drive due to joint tissue damage or inflammation (Mease et al., 2011) but is also inclusive of psychological factors such as anxiety and depression (Marks, 2009; Axford et al., 2010; Edwards et al., 2011). Neuroimaging studies have found functional and structural brain changes in chronic pain patients thought to reflect brain plasticity and potentially providing targets for pharmacological and psychological therapies (Davis and Moayedi, 2013).

Despite the increasing interest in neuroimaging studies in chronic pain, findings are often inconsistent not only between different pain aetiologies but also in chronic musculoskeletal pain. The brain response to evoked pain was abnormal in some studies in patients with OA especially in those reporting hyperalgesia, with other studies of OA and chronic lower back pain subjects not reporting differences from controls (Gwilym et al., 2009; Apkarian et al., 2005; Parks et al., 2011; Sofat et al., 2013; Wasan et al., 2011; Hiramatsu et al., 2014). Similar discrepancies between studies were shown for other chronic pain cohorts such as fibromyalgia and chronic regional pain syndrome (Freund et al., 2011; Kamping et al., 2013; Lebel et al., 2008; Pujol et al., 2009). These discrepancies might have arisen from the challenge to induce comparable pain states between patients and controls when using fixed stimulus intensity (Ducreux et al., 2006; Gwilym et al., 2009) rather than comparable perceived pain intensity (Hiramatsu et al., 2014; Gracely et al., 2002).

Moreover, experimentally evoked pain is unlikely to reproduce the full subjective experience of chronic pain with its aversive nature related to individual fears, beliefs and memories. To overcome these limitations, it would be desirable to directly study ongoing arthritis pain with appropriate methods that allow assessment of particular brain states. One such method is positron emission tomography (PET) using radioactive tracers to map cerebral glucose metabolism which revealed marked differences in the glucose metabolic pattern during clinical arthritis pain compared with experimental pain (Kulkarni et al., 2007). Alternatively, MRI based mapping of cerebral blood flow (CBF) using an arterial magnetic spin label (ASL) has shown promise to noninvasively study pain states in post-surgical pain, fibromyalgia, post-herpetic neuralgia,

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chronic low back pain and OA patients (Howard et al., 2011; Howard et al., 2012; Liu et al., 2013; Wasan et al., 2011; Shokouhi et al., 2015). Whole-brain ASL was recently used for covariance analysis of CBF maps with perceived intensity of capsaicin-induced pain in healthy controls (Segerdahl et al., 2015). The experimental approach also differs from earlier BOLD fMRI studies based on correlating perceived pain intensity across stimulation blocks (Boly et al., 2007; Christmann et al., 2007; Moulton et al., 2012; Peyron et al., 2007; Straube et al., 2009) by using an acute noxious stimulus to induce a prolonged pain state similar to Favilla et al. (2014). This whole-brain ASL correlational approach seems ideally suited to investigate clinical ongoing pain, thereby overcoming the experimental challenge to induce clinically relevant pain and the need for defining *a priori* regions of interest (Howard et al., 2012).

There is accumulating evidence linking the presence of chronic pain to increased levels of negative affect, including anxiety and depression (Axford et al., 2010; Marks, 2009), with some theorising that chronic pain and negative mood together form a continuum of aversive learning (Baliki and Apkarian, 2015). It is however unclear how this increase in negative affect relates to changes in brain function in chronic pain, as investigation of their interrelation has not been systematic.

Against this background, we aimed to use ASL to identify and characterise the neural correlates of clinical knee OA pain. Specifically, we hypothesised that brain areas encoding ongoing pain intensity overlap with limbic networks, and that the co-activation pattern can be partly explained by negative affect.

To test these hypotheses, we investigated the covariance pattern of regional CBF, indexing neural activity, with subjective rating of ongoing pain in chronic knee OA patients. We then repeated partial correlation analysis controlling for markers of negative affect that showed associations with pain severity.

2. Material and methods

2.1. Subjects and materials

Ethical approval was granted by Nottingham Research Ethics Committee 2 (Ref: 10/H0408/115). A total of 43 patients (median age 67.0 years, range 45–84 years, range of pain duration 12–456 months, 19 males) with radiographically defined unilateral chronic knee osteoarthritis and 30 healthy controls (median age 64.5 years, age range 43–80 years, 11 males) were included after giving written informed consent. Imaging data was excluded if of poor quality due to movement or imaging artefacts (patients = 8, controls = 3) and also patients reporting no pain on the day were excluded (n = 9). Group demographics after exclusions can be found in Table 1.

Directly before the scan session, all subjects underwent questionnaire assessments studying levels of education (where a score of 1 represents the attainment of a higher degree and 8 represents no educational attainment, adapted from Egerton and Mullan (2008)), pain severity (Visual Analogue Scale, VAS; 0–100), anxiety (State-Trait Anxiety Inventory, STAI), neuropathic-like pain components (PainDETECT – only in the patient cohort), pain catastrophizing (Pain Catastrophizing Scale, PCS) and depression (Beck's Depression Index, BDI-II) (Beck et al., 1996; Spielberger et al., 1983; Freynhagen et al., 2006; Sullivan et al., 1995). As BDI-II and PainDETECT scores show non-parametric properties, these scores were converted following Rasch analysis to allow use in linear analyses (unpublished data; see supplementary material for full details).

2.1.1. MRI data acquisition

Subjects underwent multimodal MRI at 3T (MR750 Discovery, GE Healthcare) using a 32-channel head coil. Only ASL data is reported alongside high-resolution T1-weighted, 3D-FSPGR scan of the whole-brain, used for registration (Flip angle = 12°, echo time [TE] = 3.172 ms, repetition time [TR] = 8.148 ms, inversion time [TI] = 450 ms, field of view [FOV] = 256 mm, slice thickness = 1 mm, matrix = 256 × 256). The ASL sequence combines pulsed-continuous ASL (pCASL) labelling with a 3D spiral read-out (Flip angle = 111°, TE = 10.5 ms, TR = 4632 ms, labelling duration = 1450 ms, post-labelling duration = 1525 ms, FOV = 240 mm, slice thickness = 4 mm, slice gap = 4 mm, number of slices = 36, echo train length = 1, number of excitations = 3, matrix = 128 × 128) (Dai et al., 2008). Background suppression was used and an M_0 image collected for image quantification. T1-weighted images were acquired parallel to the AC-PC line whilst the bottom of the acquired ASL image was positioned just below the cerebellum to allow whole-brain CBF imaging.

Table 1
Patient Demographics and group differences.

Data	Knee OA patients	Healthy controls	P-value
N.	26	27	–
Median age (range)	67.5 (54–84)	65.0 (57–80)	0.076
N. Males	12	9	0.35
Laterality of affected knee	12 left/14 right	–	–
N. Right-handed	24	23	–
Median educational scores	6[b]	3	0.023
VAS 0–100	40.2 (10–80)	–	–
PainDETECT[c]	12.5 (0–25)	–	–
BDI (range)[c]	7.8 (0–19)	2.5 (0−12)	0.0003
STAI-S	31.7 (20–55)[a]	26.4 (20–49)[a]	0.037
STAI-T	41.4 (21–70)[a]	30.7 (20–52)[a]	0.004
PCS	13.6 (1–34)	11.7 (0–29)	0.438
PCS: helplessness	5.6 (1–14)	4.2 (0−13)	0.203
PCS: magnification	2.4 (0–6)	2.3 (0–7)	0.903
PCS: rumination	5.6 (0–15)	5.2 (0−20)	0.749

Displayed are the mean (range) values unless elsewise specified. BDI – Beck's Depression Index, STAI-S – State Anxiety, STAI-T – Trait Anxiety, PCS – Pain Catastrophizing Scale.
[a] 1 subject score missing.
[b] 2 subjects were missing.
[c] Scores reported are the raw questionnaire scores.

2.2. Image processing

Cerebral blood flow (CBF) maps (ml/100 g/min) were generated using an automatic reconstruction script as reported in Zaharchuk et al. (2010). The data was then manually brain-extracted using NeuRoi (http://www.nottingham.ac.uk/scs/divisions/clinicalneurology/software/neuroi.aspx), registered linearly (12 DOF) to MNI-space with FSL-FLIRT v6.0 (FMRIB software library) (Jenkinson et al., 2002) and smoothed to 8 mm FWHM in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). In this study we were focussed only upon grey matter CBF linked to pain perception and hence used a grey matter mask to mitigate the multiple-test correction. For whole grey matter analyses, we used a dual-tissue probability mask (excluding ≤20% grey matter and ≥30% cerebrospinal fluid) based on the modified International Consortium for Brain Mapping (ICBM) tissue-probability maps provided in SPM8 (Rex et al., 2003). Probability thresholds were visually adapted to the 3D ASL dataset to increase grey matter specificity.

2.3. Statistical analyses

To address the main study aim we undertook a whole-brain grey matter correlation with reported VAS scores in OA subjects. Secondary tests included a between group comparison (all OA *vs.* HC), a subgroup comparison of those patients with left- or right-lateralised knee OA, and repeat correlation analyses with pain intensity 1) using data flipped in the x-axis (only data from participants with OA in the left knee were flipped), 2) controlling for any affective scores that correlated with reported pain intensities. All whole grey matter tests were corrected for age and sex, as well as for mean global CBF to control for inter-subject CBF differences of no interest using a GLM approach. Voxel-wise non-parametric permutation testing was carried out using FSL-randomise to correct for multiple comparisons (5000 permutations) and