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The dorsolateral prefrontal network is involved in pain perception in knee osteoarthritis patients

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HIGHLIGHTS

- Dorsolateral prefrontal cortex (DLPFC) activity increases significantly in knee OA.
- DLPFC activity is associated with activity in the pain matrix in controls.
- DLPFC activity increases without association with pain matrix activity in OA.
- Chronic pain induces abnormal brain connectivity between DLPFC and pain matrix.

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ABSTRACT

Functional MRI (fMRI) studies have been used to investigate how the brain processes noxious stimuli in osteoarthritis (OA) and to identify the cortical location of pain perception. However, no consensus has been reached regarding brain activity associated with pain-induced conditions in OA patients. We examined cerebral responses using intra-epidermal electrical stimulation of the . knee in knee OA patients. To replicate the pain of knee OA in terms of predictability, acute pain generated by electrical stimulation was provided simultaneously with displayed images in this study. We used fMRI to identify differences in response between healthy subjects and knee OA patients and explored the modulating cortico-subcortical and cortico-cortical pathways using psychophysiological interaction (PPI) analysis. Our results show that chronic pain results in a different brain activation profile in the DLPFC and the pain matrix in knee OA patients. Abnormal brain connectivity between the DLPFC and the pain matrix is induced by chronic pain in knee OA patients.

1. Introduction

Osteoarthritis (OA), the commonest form of arthritis, affects large weight-bearing joints such as the knee and hip and is highly prevalent among the elderly [19]. Chronic pain is the primary complaint, severely impairing both activities of daily life and quality of life for knee OA patients. Local physiological mechanisms of pain involve recruitment of pro-inflammatory mediators, including nerve growth factor, nitric oxide and prostanoids, to the OA joint, causing localized damage such as synovial inflammation, and activating peripheral nociceptors [23].

Characteristic knee OA pain has been attributed to nociceptive pain [4], but chronic knee OA pain also has a neuropathic component [10]. Post-herpetic neuralgia, trigeminal neuralgia, phantom limb pain, and complex regional pain syndrome, which are represented by neuropathic pain, are representative diseases which cause chronic pain, and such pain is experienced even at rest. In contrast, knee OA causes almost no pain at rest and is predictable by the patients themselves, so that the pain profile is different to that of other diseases developing chronic pain.

The pain matrix is often used to understand the neural mechanisms of pain in health and disease. Recently, functional MRI (fMRI) studies have been used to investigate how the brain

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processes noxious stimuli in OA and to identify the cortical location of pain perception. Baliki et al. and Parks et al. tested the effects of mechanical pressure stimulation of the right knee in OA patients, and revealed that activity of many pain-related brain regions was commonly observed in acute pain and there was no significant difference between knee OA patients and controls [1,20]. In contrast, Gwilym et al. used punctate stimulation of the greater trochanter of the right hip and they found significant increases in activation of the anterior cingulate cortex (ACC), right dorsolateral prefrontal cortex (DLPFC), left middle frontal gyrus, and left lateral occipital cortex in hip OA patients compared to controls [8]. Parks et al. investigated brain activity associated with spontaneous pain in knee OA patients and identified increased activity in the prefrontal limbic cortical areas, which is often observed in cases of chronic pain such as chronic low back pain and post-herpetic neuralgia [20]. Knee OA patients who have no pain at rest may have cerebral responses to acute pain solely when the acute pain is administered at rest. However, no consensus has been reached regarding brain activity associated with pain-induced conditions in OA patients.

No fMRI study to date has evaluated brain activity induced by pain stimulation with an intra-epidermal electrode in knee OA patients. The acute pain stimulation we employed was similar to the pain of knee OA in terms of predictability, because electrical stimulation occurred simultaneously with displays of images. Thus, based on the characteristics of the pain of knee OA, we examined cerebral responses in chronic pain patients to acute pain induced by intra-epidermal electrical stimulation of the right knee, and elucidated the difference in pain cognition between the knee OA patients and healthy subjects using fMRI focusing on the pain matrix.

2. Materials and methods

2.1. Participants

Study participants were 12 knee OA patients (9 female, 3 male) and 11 healthy subjects (8 female, 3 male). All subjects provided written informed consent before participation, according to a protocol approved by our institutional ethics committee.

All participants were right handed. Patient selection criteria included secondary and primary OA of the knee, presence of right-sided knee pain, pain lasting longer than 3 months, and pain magnitude of at least 3/10 on a numerical rating scale (NRS). Patients were selected after screening for other chronic pain conditions, diabetes, and neurologic or psychiatric disorders. Healthy subjects were selected after screening for previous history of arthritis, chronic pain conditions, diabetes, and neurologic or psychiatric disorders.

2.2. Clinical assessment

2.2.1. Experimental paradigm and stimuli

Electrical stimulation has been used as a pain stimulus method. It has been reported that electrical stimulation induces not only pain perception (nociceptive A-delta and C fibers) but also tactile sensation (A-beta fibers) [21]. However, intra-epidermal stimulation was used to induce minor pain at the superficial skin level, based on a slight modification of a previously reported method to provide greater selectivity for the activation of A-delta fibers [12,18]. We used a stainless steel concentric bipolar needle electrode (Nihon Kohden, Tokyo, Japan) for intra-epidermal stimulation. This needle electrode permitted the selective stimulation of cutaneous A-delta fibers. The electrical stimuli were 50 Hz current constant double pulses 0.5 ms in duration. The constant current stimulator (SEN-8203; Nihon Kohden) and isolator (SS-403J; Nihon Kohden) were located outside the MRI room, and the electrode was connected to the isolator via a magnet-compatible extension cable.

We stimulated the medial aspect of the participants' right knee using two needle electrodes, one producing painful stimulation, and the other low level pain stimulation. Participants rated the pain stimulus intensity on an NRS from 0 (no pain) to 10 (worst pain) outside the MRI room before imaging was conducted, and a current intensity corresponding to a rating of 4 (moderate pain) was used for pain stimulation while a rating of 1 (mild discomfort) was used for low level pain stimulation during the subsequent imaging phase. Painful and low level pain stimulation was performed according to the method described in a previous report [28].

During fMRI recording, participants were instructed to concentrate on the pain when an image appeared on the screen inside the MRI room. An MR-compatible back projection screen (Silent Vision SV-6011; Avotec Inc., Stuart, FL) was used. Participants' electrical stimulation occurred simultaneously with displays of different images. The duration of stimulation was 16 s (we provided pain stimulation 16 times per 16 s period, with each stimulus having a duration of between 0.3–1 seconds), evaluation was 8 s with a random break. Participants experienced stimulation a total of 12 times with pain stimulation alternated with low level pain stimulation.

2.2.2. Pain characteristics and psychometric evaluation

All participants completed the Short-Form McGill Pain Questionnaire (SF-MPQ), pain catastrophizing scale (PCS), and MOS 36-Item Short-Form Health Survey (SF-36). The SF-MPQ and PCS were used to assess pain characteristics [16,24].

2.2.3. fMRI data acquisition

Imaging data were acquired using a GE 3.0 T scanner (General Electric, Milwaukee, WI). A time-course series of 208 volumes per participant (including pre- and post-task periods) was acquired axially using echo planar imaging (EPI) sequences (TR = 2000 ms, TE = 27 ms, FA = 90 deg, matrix size = 64 × 64, FOV = 256 mm, 4 mm slice thickness, 32 slice, no gap). Functional scans lasted 6 min 56 s. After functional scanning, structural scans were acquired using T1-weighted gradient echo pulse sequences (TR = 7 ms, TE = 1.9 ms, FA = 20 deg, matrix size = 256 × 256, FOV = 256 mm, 1 mm slice thickness, 184 slice).

2.2.4. fMRI analysis

Data were analyzed using the statistical parametric mapping software package, SPM8 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7.12.0 (Mathworks, Sherborn, MA). The first 4 volumes of the fMRI run were discarded to ensure a steady-state MR signal, and the remaining 204 volumes were used for statistical analysis. Each set of functional volumes was realigned to the first volume to remove head motion, spatially normalized to a standard template based upon the Montreal Neurological Institute (MNI) reference brain with the EPI template via their corresponding mean image, and finally smoothed using an 8-mm full width at half-maximum (FWHM) Gaussian kernel. For each individual, task-related activity was identified by convolving a vector of the stimulus onset times with a synthetic hemodynamic response.

We modeled two contrasts for each individual, using a general linear model (GLM) that included painful and low level pain stimulation conditions, and compared the two. OA patients were compared with healthy subjects using the two-sample *t*-test. Brain regions with significant BOLD changes were yielded based on a voxel-level height threshold of $P < 0.001$ (uncorrected).

We conducted psychophysiological interaction (PPI) analysis to identify interactions between brain regions in relation to an