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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

Table 1
Demographic and psychometric variables of patients and healthy subjects.

	Patients ($n = 12$)	Healthy subjects ($n = 11$)	P value
Demographic variables			
Age	62.7 ± 5.7	56.4 ± 7.3	0.04*
Female/male	9/3	8/3	
Pain duration (months)	113.4 ± 175.6	–	
Rating of clinical pain (NSR)	5.3 ± 2.3	–	
Kellgren–Lawrence Grading Scale			
0	0	–	
1	2	–	
2	7	–	
3	3	–	
4	0	–	
Stimulation intensity (mA)			
NRS 1 (mild discomfort)	0.1 ± 0.07	0.08 ± 0.05	0.56
NRS 4 (moderate pain)	0.64 ± 0.47	0.64 ± 0.49	0.98
Psychometric variables			
SF-MPQ	5.8 ± 4.6	0.5 ± 0.8	<0.01*
Sensory	5.3 ± 3.7	0.5 ± 0.7	<0.01*
Affective	0.4 ± 1.0	0.1 ± 0.3	0.3
PCS	19.9 ± 10.2	5.3 ± 6.5	<0.01*
Rumination	8.3 ± 3.6	2.5 ± 3.3	<0.01*
Magnification	4.0 ± 2.3	0.8 ± 1.3	<0.01*
Helplessness	7.6 ± 5.1	1.7 ± 3.0	<0.01*
SF-36			
Physical functioning	71.3 ± 13.8	87.3 ± 12.9	<0.01*
Role physical	82.3 ± 21.6	96.6 ± 5.8	0.046*
Bodily pain	55.4 ± 15.8	87.3 ± 14.6	<0.01*
General health	59.2 ± 20.1	76.9 ± 16.5	0.03*
Vitality	67.2 ± 25.4	67.4 ± 13.5	0.98
Social functioning	86.5 ± 17.2	92.0 ± 14.0	0.41
Role emotional	88.9 ± 16.8	99.2 ± 2.5	0.06
Mental health	70.0 ± 18.6	84.1 ± 7.7	0.03*

NRS = numerical rating scale; SF-MPQ = short form of the McGill pain questionnaire.
PCS = pain catastrophizing scale; SF-36 = short form-36.
* $P < 0.05$ (two sample t-test).

experimental paradigm [6]. This approach can capture the way in which activity in one brain region modulates activity in another by specifically assessing responses to the active task relative to an informative baseline. In the present context, a significant effect on PPI means that the correlation between the seed and coupled region during pain stimulation differs significantly from that during low level pain stimulation. The extracted individual images were then taken to the second level to perform a random effect analysis, using a two-sample t-test between patients and healthy subjects (statistical threshold of $P < 0.001$, $k > 2$, uncorrected for whole-brain). The analysis method has been described in detail in a previous study [27].

Spearman's correlation analysis was performed using average contrast estimates of voxels within the clusters detected by two sample t-tests, in order to examine whether activation of these regions during pain perception correlated with corresponding pain characteristics and psychometric evaluation scores. The two sample t-test was used to compare the differences in pain characteristics and psychometric evaluation scores between patients and healthy subjects. Spearman's correlation coefficients and two-sample t-tests were calculated using SPSS (Chicago, IL) for Windows (release 21.0 for PC). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Participant characteristics

When the mean stimulus intensity of pain and low level pain stimulation was analyzed, no significant difference was found between groups. Table 1 shows all demographic and psychometric data of patients and healthy subjects.

3.2. fMRI data

3.2.1. Group differences analyzed by two-sample t-test

Areas which were significantly activated in OA patients compared to healthy subjects were the superior frontal cortex, the inferior parietal cortex, and the lingual and occipital areas. The region of pain matrix was revealed as the superior frontal cortex, contained within the dorsolateral prefrontal cortex (DLPFC) (Fig. 1 and Table 2).

3.2.2. Psychophysiological interaction (PPI) analysis

PPI analyses were performed to assess functional connectivity between the bilateral DLPFC [a 6-mm sphere centered at: right: $x = 24$, $y = 22$, $z = 52$ and left: $x = -16$, $y = 44$, $z = 42$] and other areas focusing on the pain matrix. No significant increases in functional connectivity were observed in OA patients compared to normal subjects. In fact, healthy subjects rather than OA patients were found to have functional connectivities within the pain matrix (Table 3). Positive correlation between the superior occipital cortex [a 6-mm sphere centered at: $x = -14$, $y = -96$ $z = 4$] and bilateral DLPFC was not found in any contrasts.

3.2.3. Correlation analysis between DLPFC activation and associated clinical questionnaires

We conducted correlational analysis between clinical manifestations and bilateral DLPFC activation in all subjects. The PCS (magnification) score and SF-MPQ (sensory) score were significantly positively correlated with right DLPFC activation ($r = 0.425$, $P = 0.043$, $r = 0.597$, $P = 0.003$), while SF36 (PF) score was significantly negatively correlated with right DLPFC activation ($r = -0.474$, $P = 0.002$). The SF-MPQ (sensory) score was significantly positively correlated with left DLPFC activation ($r = 0.435$, $P = 0.038$), while the

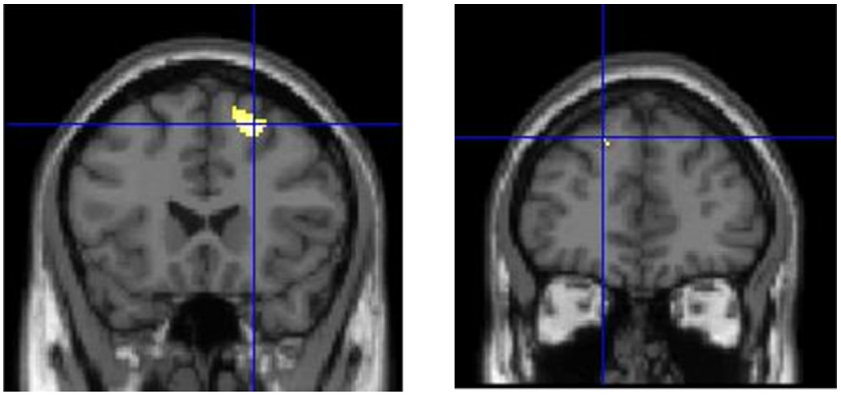

Fig. 1. Area significantly activated in OA patients but not in healthy controls. Brain areas showing increased activation in response to pain in knee arthritis patients versus healthy subjects. The key areas are in the bilateral dorsolateral prefrontal cortex (DLPFC). MNI coordinates of the right DLPFC are $x = 24$, $y = 22$, $z = 52$ and left DLPFC $x = -16$, $y = 44$, $z = 42$. (uncorrected $P < 0.001$)

SF36 (MH) score was significantly negatively correlated with left DLPFC activation ($r = -0.419$, $P = 0.046$).

4. Discussion

Our results suggest that brain activity in the DLPFC increases significantly, becoming more prominent bilaterally in OA patients compared with healthy subjects. Bilateral DLPFC brain activity was associated with activity in the pain matrix (the prefrontal cortex, secondary somatosensory cortex, and thalamus) in healthy subjects, but increased without any association with brain activity in the pain matrix in OA patients.

The function of the DLPFC associated with pain has been elucidated by neuro-imaging and transcranial magnetic stimulation (TMS) studies. Brighina et al. and Fierro et al. reported that pain induced by capsaicin stimulation was alleviated and analgesia was achieved by TMS of the left DLPFC in patients with chronic migraine and in healthy subjects [2,5], while Graff-Guerrero et al. reported that TMS of the right DLPFC selectively increased tolerance to pain in healthy subjects [7]. Lorenz et al. showed that activity in the DLPFC caused an imbalance between the cortex and the subcortical area as well as between the cortices and produced top-down modulation, controlling pain perception [15]. Seminowicz et al. revealed that in cases of moderate pain stimulation, with a trend towards increasing catastrophization, the top-down modulation of pain in the DLPFC was attenuated making pain suppression unlikely, resulting in chronic pain [22]. Krummenacher et al. reported stimulation of DLPFC activity by the placebo effect [13]. Together these results identify pain modulation, placebo analgesia, perceived control of pain, and pain catastrophizing as functions of the DLPFC, and reveal that pain is controlled at the site via the descending pain inhibitory system. Thus the DLPFC is involved in pain suppression not only in healthy subjects but also in patients with chronic pain, and we found that significant increases in activity of the DLPFC in knee OA patients are involved in suppression of chronic pain in our study.

Due to its anatomical location, the DLPFC can adjust to innervate a wide area. The DLPFC is reportedly mutually connected to sites related to motor control (the basal ganglia, premotor cortex, and supplementary motor area), performance and monitoring (cingulate gyrus), and higher-order sensory processing (somatosensory cortices and parietal cortex), as well as to the ventromedial prefrontal cortex which integrates information regarding emotion and memory [17,25]. The adult brain undergoes structural changes in response to the environment. Functional and structural changes and plasticity are known to occur in the central nervous system of patients with chronic pain, and neuroimaging studies have revealed pain matrix abnormality in the cortex and the subcortical area in such patients [3,9]. We investigated the activity in the DLPFC caused by pain and found that it was related to activity in the pain matrix in healthy subjects, but not in knee OA patients, suggesting that the pathogenesis of chronic knee pain in OA involves cerebral cortex remodeling involving changes in cortico-cortical and cortico-subcortical pathways. Our results show that visual areas are more strongly activated in OA patients than healthy subjects. This raises the possibility that this mechanism plays a role in enhanced activation in the DLPFC that receives inputs from secondary or higher sensory areas [26], but PPI analysis in this study revealed no positive connectivity between the DLPFC and the visual cortex. Furthermore, our results revealed that there was a significant difference in brain activity, but not in the intensity of pain stimulation. These results suggest that neural plastic change might potentially occur prior to the change in perception by the nociceptor.

Table 2
Areas significantly activated in OA Group patients compared to healthy subjects.

Brain region	L/R	MNI coordinates			*Z*-score	Cluster extent
		X	*Y*	*Z*		
Superior frontal cortex	R	24	22	52	4.04	123
	R	20	6	44	3.13	3
	L	−16	44	42	3.13	3
Inferior parietal cortex	L	−26	−86	46	3.41	63
Lingual gyrus	R	30	−74	2	3.13	2
Superior occipital cortex	L	−14	−96	4	3.97	223
Middle occipital cortex	L	−38	−80	32	3.15	4

Brain regions represented as MNI coordinates with activation maxima of experimentally induced *P*, thresholded at uncorrected $P < 0.001$.
The pain matrix region is the frontal superior area.

Table 3
Area of functional connections in Bilateral DLPFC within the pain matrix in healthy subjects.

Pain-Related Regions	L/R	MNI cordinates			Z-score	Cluster extent
		X	Y	Z		
Functional connectivity between the right DLPFC and pain matrix						
PFC						
Middle frontal cortex	L	-30	60	2	4.29	114
	L	-48	14	50	3.50	12
	L	-32	12	62	3.24	3
Superior frontal cortex	R	20	68	8	3.71	63
	R	20	16	44	3.66	30
	R	20	4	72	3.15	3
S2						
Postcentral gyrus	R	64	-8	22	3.44	4
Inferior parietal cortex	R	52	-40	52	3.45	14
Functional connectivity between the left DLPFC and pain matrix						
PFC						
Middle frontal cortex	R	32	22	54	4.60	626
	L	-46	36	32	3.91	23
Superior frontal cortex	R	32	58	8	3.91	97
	R	16	38	32	3.86	71
	L	-22	-2	46	3.77	123
Superior medial frontal cortex	L	-4	42	46	3.70	97
	L	-12	62	28	3.28	6
	L	-2	30	54	3.22	17
S2						
Inferior parietal cortex	R	38	-52	54	3.79	146
	R	48	-44	44	3.28	2
	R	40	-56	40	3.10	2
	L	-38	-56	42	3.53	136
	L	-52	-42	42	3.34	9
	L	-46	-42	46	3.26	10
Postcentral gyrus	R	48	-28	50	3.58	173
	R	38	-36	40	3.49	12
Th						
	R	8	-12	4	3.31	31
	L	-4	-28	6	3.35	5
	L	-6	-6	4	3.19	14

Brain regions represented as MNI coordinates with activation maxima of experimentally induced *P*, thresholded at uncorrected $P < 0.001$.
PFC = prefrontal cortex; S2 = secondary somatosensory cortex; Th = thalamus.

Correlation analysis with multi-aspect clinical evaluation revealed that DLPFC activity was higher in those with lower mental health scores who felt pain more severely with magnification. However, this analysis is a result of including all subjects; it may not be the specific result in knee OA patients. When pain stimulation was administered, pain was recognized as more harmful in the knee OA patients than in the healthy subjects, and it was considered that in these individuals attention was paid to pain to suppress it. Recently, the pain matrix has been shown to be activated not only by nociceptive stimuli but also by various emotional factors, and it is estimated that the network of pain matrix may acts as a defensive system signaling potentially damaging threats for the body [11,14]. Thus, the resulting independent increase in DLPFC activity without any association with activity in the pain matrix suggests that the function of the DLPFC in suppressing pain failed to work properly, influencing the pathogenesis of chronic pain. Further investigation is necessary to elucidate the precise mechanisms of chronic changes in pain and pain suppression by focusing on DLPFC function in patients with chronic pain.

5. Conclusion

Pain induced by intra-epidermal stimulation of the knee increased bilateral DLPFC activity significantly more in knee OA patients than in healthy subjects. Unlike healthy subjects, activity in the DLPFC had no correlation with activity in the pain matrix, and was increased independently. We conclude that abnormal brain connectivity between the DLPFC and the pain matrix occurs in response to chronic pain in knee OA patients.

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The authors report no conflict of interest related to this work.

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