E．結論

腰痛経験者は視覚情報によってvirtual low back painと表現できるような腰痛の仮想体験をする。腰痛の仮想体験によって生じる脳神経活動は，腰痛の実体験の脳神経活動と類似していた。

F．健康危険情報

総括報告書に記載

G．研究発表

1．　論文発表

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H．知的財産権の出願・登録状況

（予定を含む。）

1．特許取得

特になし

2．実用新案登録

特になし

3．その他

特になし

厚生労働省科学研究費補助金（長寿科学総合研究事業）
分担研究報告書
腰痛の診断、治療法に関する研究：痛み・しびれの可視化技術の確立並びに
MRIを用いた脊髄投射路および末梢神経イメージング法の確立

慢性腰痛患者に対する疼痛刺激による脳内反応の変化

研究分担者　紺野慎一　福島県立医科大学医学部整形外科学講座　教授

研究要旨：慢性腰痛患者の脳活動を解析するために、を対象とした。腰部を圧迫刺激時に、脳 functional-MRI を撮影し、脳賦活部位を慢性腰痛患者と正常ボランティアの２群間で比較した。慢性腰痛患者の脳賦活部位は、後帯状皮質で認められ、脳結合性の機能障害が示唆される所見が認められた。

A. 研究目的

難治性の非特異的腰痛患者において、心理的・社会的問題の関与がリスク因子として指摘されており、脳の情動的な認知の違いにより個人の感じる疼痛に違いが生じることが知られている。本研究では、脳 **functional-MRI** を用いて、慢性腰痛患者における疼痛関連脳活動の特徴を明らかにすることを目的とした。

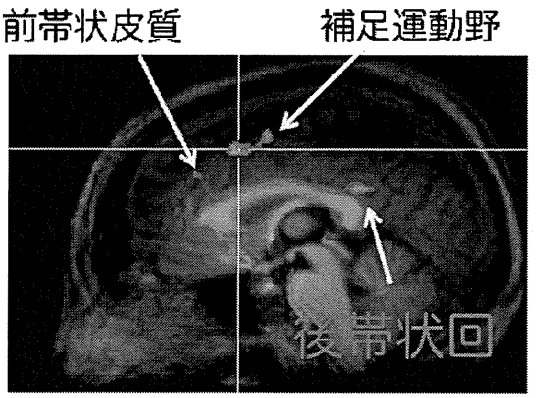
B. 研究方法

慢性腰痛患者８名と正常ボランティア１０名を対象とした。包括席 QOL 尺度である SF-36、腰痛特異的 QOL 尺度（RDQ）と精神医学的問題の簡易質問票（BS-POP）に回答してもらい、得点を算出し２群間を解析した。圧迫部位は、シリーズ１と同様で、圧迫力は、統一した圧迫力（300kPa, 400kPa, 500kPa）に設定し、ブロック型パラダイム法で行った。MRI は、3.0 テスラ高速 MRI スキャナーを使用した。高速エコープランナー法による脳の T2 強調 MRI スキャンを行い、解析ソフトウェア Brain voyager を用いて、血中酸素濃度依存的（BOLD）信号を解析した。

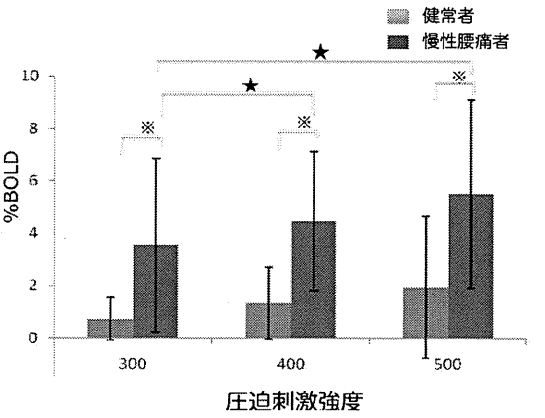
本研究は、当該研究施設の倫理委員会にて承認されている。対象者の人権擁護として、研究の承諾の取り消しはいつでも行うことができる。対象者の不利益を一切被らない。個人情報を保護するために、匿名化したデータで解析を行う。以上の内容を含む研究参加説明書を用いて、研究内容を説明し、研究参加への承諾を得た。

C. 研究結果

対象者の背景として、腰痛患者では、SF-36 のすべての下位尺度で有意に QOL が低下していた。また、腰痛関連 QOL も腰痛患者で低下しており、国民平均値より高得点で、腰痛有訴者のなかでは、本研究の対象者は、より QOL の低かった。腰痛患者の全例で、BS-POP 値が高値で精神学的問題を有していた。疼痛の程度は、圧迫の強さに従って、対象者の感じる疼痛の強さが有意に強くなった。しかし、２群間で差が認められなかった。慢性腰痛患者の後帯状皮質での BOLD 信号は、健常者と比較して、有意に増大した（図１）。



経時的な変化を解析したところ、BOLD 信号が、健常者では後帯状皮質の賦活が低下していたが、腰痛患者では、後帯状皮質の脳賦活が増大し、腰部圧迫刺激に対する反応の乖離が認められた（図２）。



D. 考察

本研究の結果から、慢性腰痛患者では、圧迫刺激に対して、不快感の強い腰痛を感じていることが示唆された。さらに、感じている疼痛の程度が同じであっても、慢性腰痛患者では、脳賦活が増大していることから、fMRIが客観的評価法の１つになりうる可能性が示唆された。また、脳結合性の機能障害が示唆される所見が認められたことから、さらに後帯状皮質を含むネットワークの脳賦活とドーパミンシステムに関連する脳部位を検討する必要がある。

E. 結論

後帯状皮質が、慢性腰痛患者で特異的な脳賦活部位であると考えられる。腰痛の治療による反応性についての検討に有用である。

F. 健康危険情報

総括研究報告書に記載

G. 研究発表

1. 論文発表

なし

2. 学会発表

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H. 知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金（長寿科学総合研究事業）
分担研究報告書

腰痛の診断、治療法に関する研究：
痛み・しびれの可視化技術の確立並びにMRIを用いた脊髄投射路及び抹消神経イメージング法の確立に関する研究

腰椎変性疾患における椎間運動パターンの解明に関する研究

研究分担者　長本行隆　藤森孝人　岩﨑幹季　　大阪大学整形外科

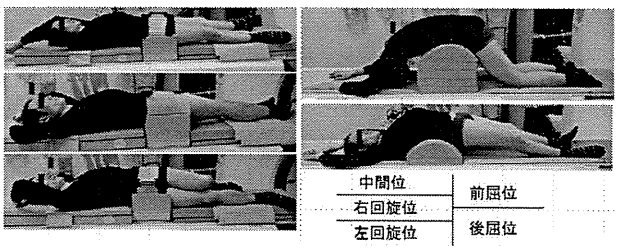
研究要旨:大阪大学整形外科では以前から3D-MRIを用いたボリュームレジストレーション法(以下VR法）を用いて正常頚椎、腰椎の生体内3次元運動解析を報告してきた。本手法では、従来のmodalityでは限界のあった生体腰椎の微細な椎間運動を3次元的かつ高精度で捉えることができる。今回本手法をさらに解析精度の向上が見込めるCTに適応して、腰椎変性疾患の運動解析を行い、正常腰椎との比較により変性腰椎の椎間運動パターンを見出し、腰椎異常可動性の新たな評価や病態の解明、早期診断法の確立を目指す

A. 研究目的

腰椎変性疾患や腰椎手術後などに生じる腰椎椎間異常可動性を高精度な手法で3次元計測し、術前後での比較を行い椎間の3次元動態の変化を捉えること。

B. 研究方法

腰椎変性疾患で固定術を予定している症例を対象とする。臨床評価パラメータとして術前と術後6カ月に神経学的所見、JOAスコア、腰痛、下肢症状の有無について調査する。CT撮影は中間位、最大前後屈位、最大両回旋位の5ポジションで行い、PCソフトウェアによる画像解析処理(VR法)により腰椎椎間運動の3次元解析を行う。



動作解析に関しては、術前の罹患変性椎間や術後の隣接椎間における正常動態との相違に注目する。各評価パラメータと椎間可動域との関連性についても検討を行う。

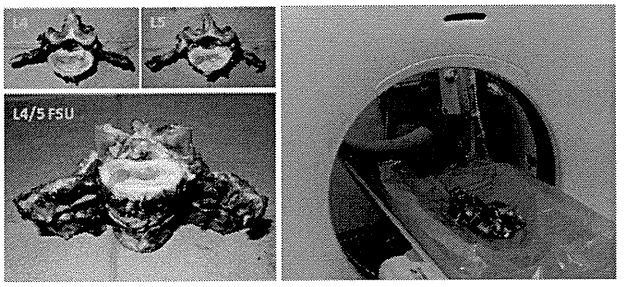
（倫理面への配慮）

①撮影により脊椎由来の症状が悪化する危険性への対策として、全撮影に必ず分担研究者が立会い、症状の変化に注意を払いながら撮影を行うこととし、症状に異変を生じた場合は速やかに撮影を中止する。

②X線被曝の問題。治療上CT撮影の必要な症例のみを対象としており、複数回の撮影でも中間位以外では撮影線量を1/5に低減して全被曝量の増加を抑えるようにしている。

（CTを用いたVR法の動作解析精度）

新鮮凍結ブタの脊椎を用いて動作解析手法の精度を検証した。



ブタ L4, L5 椎体を用いて、各骨内に tantalnum ball を 8 個打ちこみ CT を撮影、marker-based registration により得られた値を正解値として、8 種類の椎間動作を VR 法による測定値と比較し、その誤差を RMSd として算出した。下表の如く非常に高い精度が得られた。

RMSd	Rx	Ry	Rz	Tx	Ty	Tz
	0.07°	0.01°	0.07°	0.02mm	0.06mm	0.13mm

C. 研究結果

最終年度までに 39 例の撮影を終了した。疾患内訳は、変性すべり症 21 例、変性側弯 6 例、分離すべり症 4 例、腰椎固定術後隣接椎間障害 3 例、仙腸関節障害 2 例、腰部脊柱管狭窄症 2 例、L5 形成不全性すべり症 1 例である。さらに、術後 6 カ月時の画像取得まで終了した症例は 18 例である。検討を容易にするため対象を L4 腰椎変性すべり症に限定した。今回中でも L4/5 に PLIF (posterior lumbar interbody fusion)を施行した 6 症例に関して、術前後での 3 次元動態の変化について検討した。椎間可動域変化率は、

⊿(%)=(術前-術後)/術前×100

と定義して angulation、translation を算出した。

5. 固定椎間(L4/5)における動態変化

症例		前後屈(°)		回旋(°)	
		術前	術後	術前	術後
1	66 ♀	14	2.4	7.6	2.5
2	58 ♀	12	1.2	6.8	1.4
3	69 ♂	6.1	6.8	8.0	2.4
4	69 ♂	8.2	3.6	0.4	0.9
5	46 ♀	15	0.7	4.0	0.5
6	61 ♂	6.6	0.8	4.7	1.3
平均		10.3	2.5	5.3	1.5

固定椎間では術後概して前後屈、回旋ともに可動域は減少していたが、可動域の残存する症例が少なからず存在した。

2. 固定隣接椎間(L3/4, L5/S)における動態変化

固定隣接上位椎間における術前後可動域変化(angulation)

症例		固定隣接上位椎間変化率			固定隣接下位椎間変化率		
			前後屈	回旋		前後屈	回旋
1	66 ♀	L3/4	-80% -7.5° (9.3°→1.8°)	-6% -0.1° (1.6°→1.5°)	L5/S	-7% -0.9° (11.5°→10.6°)	+100% +0.5° (0.5°→1.0°)
2	58 ♀	L3/4	+72% +13.2° (4.8°→18°)	-4% -0.1° (2.4°→2.3°)	L5/S	-55% -7.9° (14.3°→6.4°)	0% ±0° (0.3°→0.3°)
3	69 ♂	L3/4	-1% -0.1° (9.7°→9.6°)	+14% +0.1° (1.1°→1.2°)	L5/S	+12% +0.7° (8.4°→9.1°)	+100% +0.3° (0.4°→0.7°)
4	69 ♂	L3/4	-46% -3.3° (7.2°→3.9°)	-62% -0.9° (1.5°→0.6°)	L5/S	+68% +3.4° (5.0°→8.4°)	-59% -0.6° (1.1°→0.5°)
5	46 ♀	L3/4	10% +1.1° (10.3°→11.4°)	234% +0.4° (0.2°→0.6°)	L5/S	-12% -1.8° (15.0°→13.2°)	172% +1.2° (0.6°→1.8°)
6	61 ♂	L3/4	5% +0.7° (11.7°→12.4°)	-24% -0.6° (2.5°→1.9°)	L5/S	+156% +7° (4.5°→11.5°)	-7% -0.1° (1.3°→1.2°)
平均			-6.7% +0.68°	+25% -0.2°		+27% +0.08°	+51% +0.22°

固定隣接上下位椎間における術前後可動域変化（translation）

症例		固定隣接上位椎間変化率		固定隣接下位椎間変化率	
			前後屈		前後屈
1	66 ♀	L3/4	+350% +0.7mm (0.2mm→0.9mm)	L5/S	+45% +0.5mm (1.1mm→1.6mm)
2	58 ♀	L3/4	+180% +1.8mm (0.1mm→1.9mm)	L5/S	+62% -1.5mm (2.4mm→0.9mm)
3	69 ♂	L3/4	-73% -2.2mm (3.0mm→0.8mm)	L5/S	+100% +0.1mm (0.1mm→0.2 mm)
4	69 ♂	L3/4	-78% -0.47mm (0.6mm→0.13mm)	L5/S	+30% +0.3mm (1.0mm→1.3mm)
5	46 ♀	L3/4	+63% +0.5mm (0.8mm→1.3mm)	L5/S	+340% +0.68mm (0.02mm→0.7mm)
6	61 ♂	L3/4	+350% +0.7mm (0.2mm→0.9mm)	L5/S	+350% +0.7mm (0.2mm→0.9mm)
平均			+115% +0.17mm		+155% +0.13mm

固定上下隣接椎間では、前後屈運動、回旋運動ともに概して術後には可動域が増加する傾向を認めた。

D. 考察

CTを用いたVR法では非常に高い精度で椎間運動の3次元的動態の計測ができ、かつアニメーションによる動態の可視化により質的評価も可能である。これまで腰椎疾患や腰椎手術例などの病的な椎間に対する生体内3次元動態解析はこれまでほとんどな報告がなく、このような背景において今回初めて腰椎変性疾患に対する治療介入前後の生体内3次元動態変化を捉えることに成功した。

今回、固定椎間における動態変化の検討では、PLIF術後6か月の時点では、CTで一見骨癒合が認められると判断されるような椎間でも、椎間可動域が残存していることが詳細な可動域計測により判明した。PLIF後の骨癒合に関する報告に関して、大和田ら[1]はCFRP (carbon fiber reinforced polymer) cage併用PLIFでは18例全例に6か月以内で骨癒合が得られたと報告している。しかし我々の動作解析によると、術後6か月の段階では前後屈平均2.5°回旋平均1.5°の可動性は残存しており、骨癒合は不完全と考えられる。固定術後の骨癒合判定はCTを以ってしても困難な場合がある。本法では微小な可動域を計測することが可能であり、今後術後様々な時期のPLIF術後症例複数を対象に横断的に本法による固定椎間の可動域測定値とCT画像上の骨癒合所見との相関を調査することで、将来的にはCT画像上から正確な骨癒合を判断できるような基準を設定したいと考えている。

腰椎固定手術後の隣接椎間障害については多くの報告があり、Parkらのreviewによれば、腰椎固定術後、隣接椎間に変性所見の出現・増強などの画像所見が認められる頻度は5.2%~100%であり、隣接椎間への追加手術の頻度は0~27.5%と報告されている[2]。生体力学的な研究でも、椎間固定による可動椎間減少によりその隣接上下椎間に可動性亢進などの変化をきたすことが示されている[3]。そしてこの可動性の変化は、インストルメントの長さや剛性の高さに比例する[4]と報告されている。本研究でも隣接上下椎間の可動域は概して増加する傾向を認め、今後解析症例を増やして固定椎間の長さの違いによる隣接椎間可動性変化の相違についても検討を加える予定である。またOkudaらはL4/5 PLIFの術後症例において、隣接上位椎体椎弓の傾きや隣接上位椎間関節の関節面角度左右差が大きいことを隣接上位椎間障害の危険因子として明らかにしているが[5,6]、今回隣接上位椎間において回旋、前後屈ともに可動性が増加している症例も認められ、我々は隣接椎間における術後早期の前後屈、回旋各可動域増加が隣接椎間障害発症に関与していると推察している。本件に関しても引き続き症例数を増やして現在検討を続けているところである。

本手法の限界として、①腰椎可動域の再現性の問題：治療介入後の動態変化を捕捉するには、本来ならば一定可動域内における動態を比較することが望ましい。しかし、腰椎では体表からのランドマークが少なく、装具などで腰椎運動を規定しても、腰下肢痛の程度や患者の意欲、装具のフィッティングなどの影響を受け、高い再現性を保ちながら一定可動域を形成することが困難であった。結局本研究ではこの再現性の問題をクリアするために装具作成などにかなりの労力を要した。②撮影範囲の問題：前屈位での撮影では、体幹～頭部がCTの筐体に接触し、上位腰椎の撮影範囲はかなり患者の体格や姿勢により変化してしまったため、今回腰椎可動域の検

討はL3/4高位以遠でしか行えなかった。

E. 結論

VR法により腰椎固定術後の隣接椎間や仙腸関節に生じる生体内3次元動態変化を捉えることに成功した。

F. 健康危険情報

総括研究報告書に記載

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H. 財産権の出願・登録状況

特許取得：未取得

実用新案登録：未取得

その他：特になし

III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Shimo K, Ueno T, Younger J, Nishihara M, Inoue S, Ikemoto T, Taniguchi S, Ushida T.	Visualization of painful experiences believed to trigger the activation of affective and emotional brain regions in subjects with low back pain.	PLoS One	6	e26681	2011
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IV. 研究成果の刊行物・別刷

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PLoS one

Visualization of Painful Experiences Believed to Trigger the Activation of Affective and Emotional Brain Regions in Subjects with Low Back Pain

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Abstract

In the management of clinical low back pain (LBP), actual damage to lower back areas such as muscles, intervertebral discs etc. are normally targeted for therapy. However, LBP may involve not only sensory pain, but also underlying affective pain which may also play an important role overall in painful events. Therefore we hypothesized that visualization of a painful event may trigger painful memories, thus provoking the affective dimension of pain. The present study investigated neural correlates of affect processing in subjects with LBP (n = 11) and subjects without LBP (n = 11) through the use of virtual LBP stimuli. Whole brain functional magnetic resonance imaging (MRI) was performed for all subjects while they were shown a picture of a man carrying luggage in a half-crouching position. All subjects with LBP reported experiencing discomfort and 7 LBP subjects reported experiencing pain. In contrast to subjects without LBP, subjects with LBP displayed activation of the cortical area related to pain and emotions: the insula, supplementary motor area, premotor area, thalamus, pulvinar, posterior cingulate cortex, hippocampus, fusiform, gyrus, and cerebellum. These results suggest that the virtual LBP stimuli caused memory retrieval of unpleasant experiences and therefore may be associated with prolonged chronic LBP conditions.

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Introduction

Psychological factors are known to affect the subjective experience of pain. Pain catastrophizing is one such maladaptive response to pain that is characterized by heightened pain intensity [1], increased disability [2]and difficulty disengaging from pain [3]. Recently, functional neuroimaging techniques have been developed that allow the neural correlates of psychological states to be explored. The blood oxygenation level-dependent contrast (BOLD-fMRI) is currently the most popular tool for mapping human brain activity [4]. Pain-related brain activations which could be considered as psychological factors have been reported in various studies. In healthy volunteers, several brain regions, including the primary and secondary somatosensory cortices, insula, anterior cingulate cortex (ACC), thalamus, and motor cortex, respond to real noxious stimuli and are regarded as part of the "pain matrix" [5,6]. However, it is also known that the expectation of pain can evoke brain activation patterns resembling that of a real pain experience [7].

In a previous study [8,9], Ogino reported that the imagination of pain even without physical injury engages the cortical representations of the pain-related neural network. Also, we reported that prior pain experiences can strongly affect pain anticipation and associated brain activations. We have also found that the anticipation of painful stimuli can cause the activation of cortical areas underlying pain-related affect in chronic neuropathic pain patients [10]. Activation in the brain during the visualization of a painful experience was found in the ACC and the medial prefrontalcortex (MPFC), which are regions known to be areas associated with pain and affect processing. Similar activations were found to be correlated with pain catastrophizing in individuals with fibromyalgia [11]. In that study, pain catastrophizing was associated with greater activity in the dorsolateral prefrontal cortex, rostral ACC, and MPFC, regions implicated in pain vigilance, attention and awareness [12,13,14,15]. These results suggest that pain-related neuronal activities might reflect the development and maintenance of chronic pain syndromes.

Low back pain (LBP) is one of the most common chronic pain syndromes. A recent fMRI study in humans reported actual LBP-related cerebral substrates [16]. Abnormal activations were identified in the prefrontal cortex, insula, thalamus, posterior cingulate cortex (PCC), supplementary motor area (SMA), and premotor areas (PMA) – predominantly in the right hemisphere.

Table 1. Evaluations of task-related discomfort and pain.

	LBP group (n = 11)	non-LBP group(n = 11)
Experiences evoked by tasks		
Discomfort (range)	3.5 (1–6)	0
Pain (range)	2.1 (0–6)	0
RDQ (mean ± SD)	3.1±3.1	0
ODI (mean ± SD)	19.8±7.8%	0

RDQ, Roland-Morris Disability Questionnaire; ODI, Oswestry Disability Index 2.0.
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We hypothesized that visualization of a painful experience would provoke unpleasant emotions, and these emotions might have a role in the maintenance of chronic pain syndromes. The present study investigated neural correlates of affect processing in subjects with nonspecific LBP and subjects without LBP by using virtual visual stimuli.

Results

Self-reported discomfort and pain (Table 1)

All subjects in the LBP group reported discomfort associated with viewing the simulated back pain (mean NRS score, 3.5; range, 1–6). 7 of the 11 subjects in the LBP group described pain associated with the task. However, no subjects in the non-LBP group reported any discomfort or pain resulting from viewing the picture of back pain.

fMRI results

Compared with the non-LBP group, the LBP group demonstrated significantly more activation in the left fusiform, as well as left inferior temporal gyrus, bilateral precentral gyrus, left middle frontal gyrus, left superior frontal gyrus, bilateral thalamus, bilateral caudate, right insula, left postcentral gyrus, bilateral lingual gyrus, bilateral parahippocampal gyrus, right superior temporal gyrus, left angular gyrus, left superior occipital gyrus, left precuneus, left middle temporal gyrus, left posterior cingulate cortex (PCC), and left cerebellum (Table 2,

Table 2. Talairach coordinates and Broadmann's areas for regions of statistically significant activation ($p<0.0005$ at voxel level uncorrected threshold) in response to virtual LBP stimulation (task – control condition).

Anatomical region	Side	Coordinate	Broadmann area	Z score
LBP group as compared to non-LBP group				
Fusiform gyrus	Lt	−46, −34, −13	Area 20	4.53
Inferior temporal gyrus	Lt	−57, −43, −15	Area 37	3.60
Precentral gyrus	Lt	−32, 8, 38	Area 9	4.38
	Rt	28, −24, 56	Area 4	4.03
Middle frontal gyrus	Lt	−46, 20, 43	Area 8	3.68
		−32, 11, 60	Area 6	3.50
Superior frontal gyrus	Lt	−40, 16, 53	Area 8	3.56
Thalamus	Lt	−24, −25, 7	-	4.34
	Rt	24, −27, 0	-	3.40
Caudate	Lt	−28, −32, 13	-	3.57
	Rt	38, −35, −3	-	3.91
Insula	Rt	28, −27, 12	Area 13	4.30
	Rt	34, −20, 18	Area 13	3.50
Postcentral gyrus	Lt	−8, −55, 64	Area 7	4.07
Lingual gyrus	Rt	18, −62, 0	Area 19	3.99
	Lt	−6, −72, −5	Area 18	3.81
Parahippocampal gyrus	Lt	−36, −43, 0	Area 19	3.96
	Rt	32, −53, −4	Area 19	3.91
	Rt	28, −41, −10	Area 36	3.62
Superior temporal gyrus	Rt	40, −35, 4	Area 41	3.78
Angular gyrus	Lt	−32, −74, 30	Area 39	3.88
Superior occipital gyrus	Lt	−38, −80, 33	Area 19	3.78
Precuneus	Lt	−42, −72, 35	Area 19	3.42
Middle temporal gyrus	Lt	−60, −35, −5	Area 21	3.62
Posterior cingulate gyrus	Lt	−10, −41, 30	Area 31	3.61
	Lt	−4, −43, 37	Area 31	3.55
Cerebellum	Lt	−24, −30, −20	-	3.88
non-LBP group as compared to LBP group				
Caudate	Rt	22, −34, 20	-	3.61

doi:10.1371/journal.pone.0026681.t002

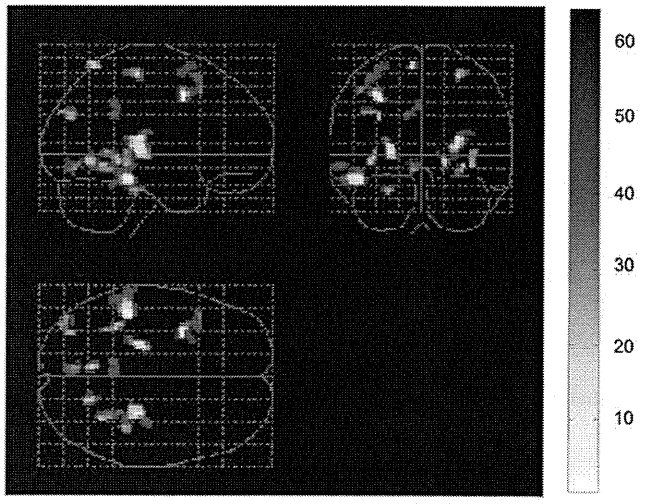

Figure 1. Areas of cortical activation in the LBP group compared with the non-LBP group in response to virtual LBP stimuli (task – control condition) detected by fMRI($p<0.0005$, Z score>3.4, uncorrected threshold).
doi:10.1371/journal.pone.0026681.g001

Fig. 1). The reverse contrast showed that the LBP group had lower activations than the non-LBP group in a single cluster in right caudate (Table 2).

In the LBP group, activations related to discomfort were found in the bilateral thalamus, bilateral medial frontal gyrus, right claustrum, left cerebellum (Table 3, Fig. 2). Activations associated with self-reported pain were found in the right thalamus and right lingual gyrus. RDQ scores were associated with activation in the left ACC, and ODI scores were associated with activations in the right insula (Table 3, Fig. 3).

Table 3. Cortial areas showing a linear signal increase with the discomfort rating, pain rating, RDQ scores and ODI scores.

Anatomical region	Side	Coordinate	Broadmann area	Z score
Discomfort				
Thalamus	Rt	20, −23, 5	-	4.19
	Lt	−4, −17, 3	-	3.78
Medial frontal gyrus	Rt	10, −22, 58	Area 6	3.85
	Lt	−12, −28, 53	Area 6	3.70
	Lt	−50, 1, 28	Area 6	3.38
Claustrum	Rt	30, 3, 13	-	3.75
Cerebellum	Lt	0, −53, −6	-	3.57
Pain				
Thalamus	Rt	20, −31, 7	-	4.27
Lingual gyrus	Rt	8, −86, −11	Area 18	3.62
RDQ				
Anterior cingulate gyrus	Lt	−6, 9, 27	Area 24	3.99
ODI				
Insula	Rt	40, −8, −5	Area 13	3.67

RDQ, Roland-Morris Disability Questionaire; ODI, Oswestry Disability Index 2.0.
doi:10.1371/journal.pone.0026681.t003

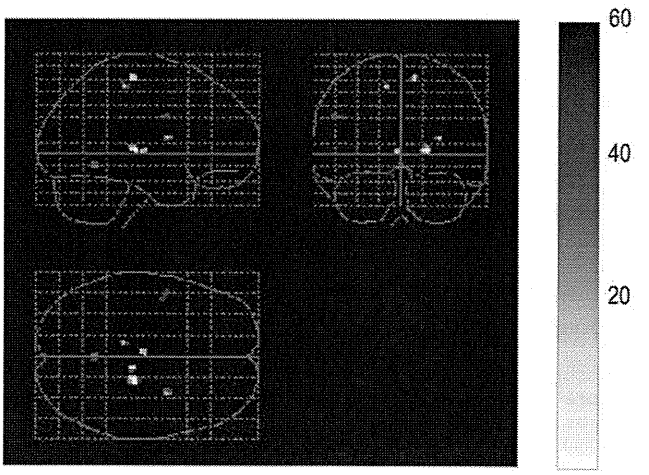

Figure 2. Areas of cortical activation showing an association with perceived discomfort.
doi:10.1371/journal.pone.0026681.g002

Discussion

Our results demonstrate that viewing images of simulated back pain evoke unpleasant feelings, and specific brain activations in individuals with LBP. According to the International Association for the Study of Pain, pain is defined as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". As this definition suggests, both real pain stimuli and virtual pain experiences such as the visual stimuli in our study may play an important role in pain recognition and interpretation in the brain.

Functional MRI results showed that many of the areas described as being part of the "pain matrix" are also active during virtual pain. These results suggest that previous experiences of low back pain can sensitize an individual to pain anticipation. Activation in the insular cortex is associated with pain discrimination [17,18,19]. Additionally, the posterior insular cortex also plays a role in directing appropriate motor behaviors [20]. Furthermore, the insular cortex has projections to the SMA [21,22]. The SMA and PMA are commonly activated by pain [19,23], and usually associated with motor preparation. Activation in those areas might be associated with preparation for protective behavior against pain. In addition, we found virtual LBP stimuli led to increased activation in cerebellum. Activity in the cerebellum is frequently found in pain neuroimaging studies. Cerebellar activation is considered to be primarily associated with motor responses [13]. The need for temporally precise information may also be relevant for brain areas involved in initiating, propagating, and executing defensive motor responses to noxious stimuli [11,13,24,25].

The thalamus and the pulvinar are heavily interconnected with the visual and parietal cortices. Neuroimaging studies suggest responses in the pulvinar have a spatiotopic organization that are modulated by visual attention [26,27,28]. These results suggest that low back pain experiences may make individuals pay more attention to pain-related visual stimuli.

Many reports identify a role of the PCC in negative emotion [29,30,31,32,33,34], visuospatial orientation, and assessment of self-relevant sensation [35]. Exaggerated cerebral activation by pain stimuli may also be associated with pathologic pain states such as allodynia [36,37]. Together with its possible role in inflammatory pain [38], PCC activation could possibly reflect the negative emotion and the pathologic state of pain.

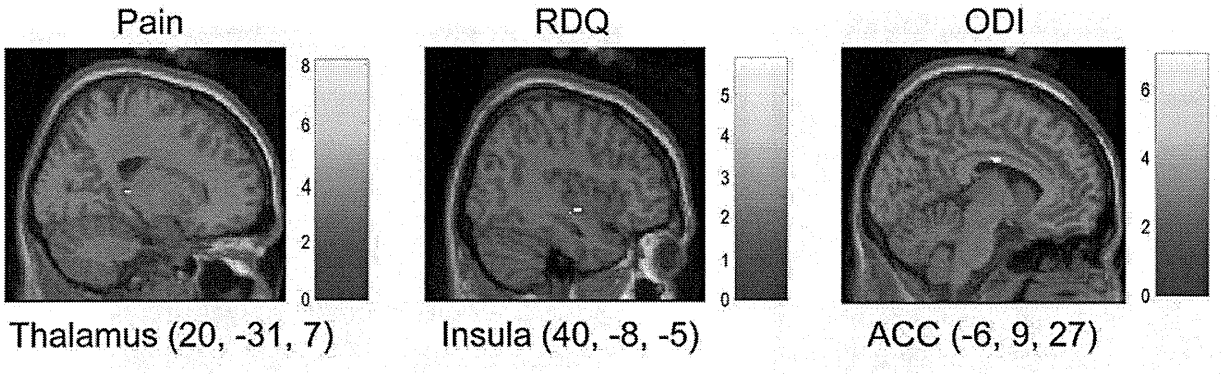

Figure 3. Sagittal sections showing cortical clusters where activity was linearly correlated with perceived pain, RDQ scores and ODI scores.
doi:10.1371/journal.pone.0026681.g003

We found other regions with heightened activity in LBP participants, in areas outside of the classic pain matrix. Those regions included the hippocampus, fusiform gyrus and angular gyrus. While not typically considered a nociceptive processing region, activation in the hippocampus has been previously reported to be activated in response to painful heat [14,39] and laser stimulation [40]. The hippocampus has been traditionally associated with recent memory consolidation [41], spatial memory [42], and fear-initiated avoidance behavior [43]. The hippocampus might also play a role in memorizing the pain stimulation and preparing fear-initiated avoidance. The fusiform gyrus is often associated with facial recognition [44]. It is conceivable, therefore, that our visual stimuli (which included a human face) may have been responsible for observed activations in the fusiform gyrus. However, our visual stimuli included a human facewithout any faical expression. This might suggest that the fusiform gyrus plays another important role in the cognitive neuroscience field. The angular gyrus is associated with empathy and 'theory of mind' [45]. Visual stimuli may cause subjects in the LBP group to imagine self pain or feel empathy towards the individual in pain in the picture.

Via parametric analyses in the LBP group, we identified several regional activations that were associated with discomfort rating, pain rating, RDQ scores and ODI scores. The SMA and PMA were related to the discomfort rating. As indicated previously, the SMA and PMA are involved in motor preparation. Activation in those areas might therefore be associated with preparation of protective behaviors against discomfort and pain. Thalamic activation was associated with both discomfort and pain ratings. Greater insula activation was associated with higher ODI scores. The thalamus and insula are considered part of the sensory component of pain processing [46]. But, a recent study suggests that imagining oneself in painful situations is sufficient to trigger some pain sensory regions [47]. The ACC was associated with RDQ scores. The ACC is an important part of affective pain processing [48,49] and can be activated in tasks of pain empathy [47,50,51,52,53,54,55]. It is unknown, therefore, whether the ACC activations, which were observed in the LBP group, were due to imagined self pain, or empathetic pain for the individual in the picture.

In this study, we showed that pain-related visual stimuli can activate several regions of the pain matrix in LBP patients, but not normal volunteers. Moreover, the pain questionnaire scores in the LBP patients were associated with greater activation of pain-processing brain regions. Functional MRI and the virtual visual tasks are non-invasive methods for probing pain-related fear and catastrophizing. These results might be applied to the evaluation of chronic pain syndromes, such as low back pain, in the future.

Materials and Methods

We recruited subjects with nonspecific LBP (LBP group) (n = 11, 6 male, 5 female, mean age 20.4 years) and subjects without LBP (non-LBP group) (n = 11, 5 male, 6 female, mean age 21.5 years). All participants were right-handed, had no history of cerebrovascular disease, and were free from any medication within 24 hours of the study. Scores for the Roland-Morris Disability Questionnaire (RDQ) and Oswestry Disability Index 2.0 (ODI) were obtained for all participants. Participants in the LBP group reported low back pain, and a RDQ or ODI score greater than zero. Participants in the non-LBP group had never experienced low back pain lasting longer than 1 week, and their RDQ and ODI scores were zero. No participants in either group displayed any evidence of structural abnormality in the lumbar spine on MRI, or any neurologic symptoms. None reported having a history of psychiatric disorders, or currently using any psychoactive medications.

We used virtual LBP stimuli depicting a man who is carrying luggage in a half-crouching position (Fig. 4). This picture represents an action that would likely cause pain in an individual with low back pain, and may therefore cause pain anticipation in the LBP group. Participants were also shown a picture depicting a man standing in front of luggage, providing the baseline stimulation (control condition) (Fig. 4). Participants in the LBP group had painful experiences in the half-crouching posture but did not have any pain in the standing posture. In addition, the participants in the LBP group currently feel little pain in daily life. During the fMRI session, trials were presented in a fixed block design. The distance between the participants' eyes and the screen was 12.5 cm, with a visual angle of $7.4 \times 11.3°$. The trials were applied eight times in each series, with each trial presentation lasting 3 seconds. The entire functional experiment lasted 150 seconds (see details of the experimental paradigm in Fig. 4). Self-reported discomfort and pain measures were collected using a numerical rating scale after the experimental session.

Images of the entire brain were acquired using GE SIGNA 3.0 Tesla scanner. Blood oxygenation level-dependent (BOLD) signals were collected with a T2-weighted, multi-slice, gradient echo-planar imaging (EPI) sequence (TE = 35 ms, TR = 3000 ms, flip angle = 90°, slice width = 4 mm, gap = 0 mm, 36 axial slices). Participants were scanned in the supine position, with the head

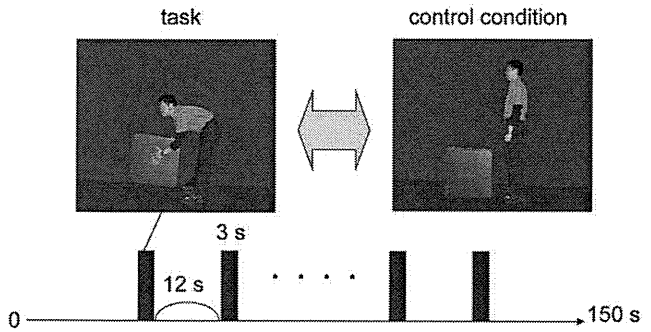

Figure 4. Experimental design. Subjects enrolled in the experiment were shown a picture demonstrating a man holding luggage in a half-crouching position (task picture) and a picture demonstrating a man standing in front of luggage, providing the baseline stimulation (control condition picture).
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fixed to minimize movement artifact. During the experiment, participants were simply instructed to observe the picture on screen.

The study was approved by the Ethical Committee of Kochi Medical School. All participants were informed of the study purpose beforehand and provided written consent to participate.

Results were analyzed on a Unix workstation using SPM2 (Statistical Parametric Mapping) software; Wellcome Department of Cognitive Neurology, Institute of Neurology, London: http://www.fil.ion.ucl.ac.uk/spm). The acquired images were realigned, spatially normalized to a standard EPI template and finally smoothed with an isotropic Gaussian kernel of 6 mm FWHM (full width at half maximum). Significance was assessed using the box car approach, convolved with the canonical hemodynamic response function. Activation maps represent t-test contrasts between the different experimental conditions. To identify the neural substrates for the virtual pain task, we contrasted the task condition and control condition in the LBP and non-LBP groups. Thresholds for activation were set at $p<0.0005$ for the voxel level of activation, and were further corrected for multiple comparisons at the cluster extent threshold of $p<0.05$. The Talairach atlas was used to anatomically localize foci of significant activation [56]. Brain activation between the LBP group and the non-LBP group was statistically compared to identify the neural processing specific to the LBP group ($p<0.05$, corrected, one-way ANOVA).

For the LBP group only, parametric analyses were also performed to determine associations between brain activity and perceived discomfort, perceived pain, RDQ score and ODI score. Normalized ratings were introduced at the subject level, taking into account only trials from the LBP group.

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Author Contributions

Conceived and designed the experiments: KS T. Ushida. Performed the experiments: KS T. Ushida. Analyzed the data: KS T. Ueno JY MN SI T. Ushida. Contributed reagents/materials/analysis tools: TI ST. Wrote the paper: KS T. Ueno JY T. Ushida.

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