特集　リウマチ性疾患の痛みをやさしく教えます

# 運動器疾患における神経障害性疼痛

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Key Words ■神経障害性疼痛 ■中枢性感作 ■変形性関節症 ■後縦靱帯骨化症 ■プレガバリン

神経障害性疼痛は国際疼痛学会で「体性感覚系に対する損傷や疾患の直接的結果として生じている疼痛」と定義され，痛覚過敏やアロディニアを特徴とする非ステロイド性抗炎症薬抵抗性の痛みである．神経根症など脊椎疾患の多くにみられ，四肢運動器の障害においても生じている可能性がある．

## ■ はじめに―神経障害性疼痛とは？―

現在，痛みは①侵害受容性疼痛，②神経障害性疼痛，③心因性疼痛（または機能性疼痛）に分類される．①の侵害受容性疼痛は，痛み情報が皮膚などの侵害受容器から脊髄後角を経て外側視床路を通る上向路を中心とした，生体へのさまざまな有害な外的侵襲に対する生理的反応である．また，③の心因性疼痛は身体表現性疼痛とほぼ同義で，身体の障害から予測される痛みをはるかに超える痛みがあり，心理的要因が原因の過半であると診断された場合に用いられる．

神経障害性疼痛は知覚神経の障害による痛みであり，痛覚過敏や通常は痛くない程度の刺激を痛みと感じるアロディニア，神経障害で妥当と思われる部位への電撃痛や刺すような痛み，焼けるような痛みなどを特徴とする．末梢から脊髄後角そして脳に至る感覚神経系のさまざまなレベルで生じると想定されており，国際疼痛学会（International Association for the Study of Pain：IASP）において「体性感覚系に対する損傷や疾患の直接的結果として生じている疼痛」[1]と定義されている．診断ではIASPから診断アルゴリズム[2]が提唱され，スクリーニングとして神経障害性疼痛用調査票が各国で作成されている．われわれはpainDETECT[3]を用いている．ただ，臨床上は侵害受容性疼痛と神経障害性疼痛が併発している場合が多い．また痛み刺激は内側脊髄視床路を通り前帯状回や扁桃体に至る痛みの情動系も賦活化するため，抑うつや不安といった情動障害が起こりやすい．すなわち，上記3種類の痛みはほとんどの臨床例でオーバーラップして表出されていることを認識する必要がある．治療の観点からは各種薬剤の効果が異なることが重要であり，侵害受容性疼痛では非ステロイド性抗炎症薬（non-steroidal anti-inflammatory drugs：NSAIDs）が比較的有効であるが，神経障害性疼痛ではNSAIDsの効果はきわめて限定的であり，抗けいれん薬や抗うつ薬が有効である．

神経障害性疼痛用調査票を用いた疫学調査では一般人の7～8%[4]に神経障害性疼痛がある．また，運動器疾患を担当する整形外科の慢性疼痛外来患者の39～43%[5]に

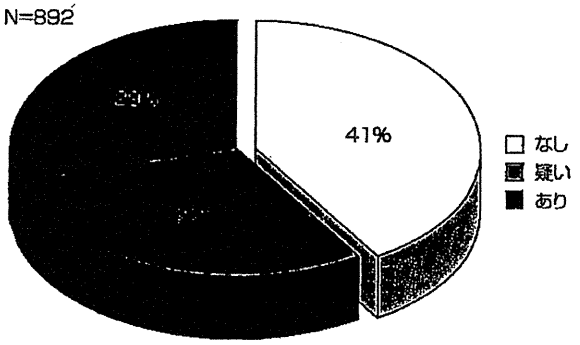
みられるとされる．外傷や腫瘍性疾患などでも神経障害性疼痛の関与はあると思われるが，本稿では脊椎と四肢変性疾患について触れる．

## 1．脊椎変性疾患における神経障害性疼痛

脊椎症において神経障害は以前から脊椎疾患の主たる課題である．ただし運動障害すなわち麻痺に大部分の関心が注がれてきた点は否めない．欧州の腰痛患者に対する調査では25～30%に神経障害性疼痛の関与があると報告されている[9]．われわれが厚生労働省研究班でおこなった2010年の頸椎後縦靱帯骨化症に対する調査では神経障害性疼痛のある患者が29.8%を占め，疑いを含むと6割にみられた（図❶）．また2011年におこなった腰部脊柱管狭窄症に対する調査では神経障害性疼痛のある患者が13.8%，疑いを含むと5割にみられた．

神経障害性疼痛の代表としては腰椎椎間板ヘルニアにみられる腰部神経根症（根性坐骨神経痛）や変形性頸椎症に伴う頸部神経根症がある．いずれも強烈な痛みを起こしうる病態であり，即効的な疼痛緩和には大量ステロイドの短期内服やブロック治療が望ましい．より有害事象の少ない治療として2010年から使用可能となったプレガバリンがよい．ただし，めまいやふらつきが一時的に出現することが多いため，処方開始時からすぐに有効量を投与することはむずかしい．運動障害が高度あるいは進行する例や，上記保存治療で痛みを緩和できない場合には圧迫部位の解除すなわち除圧手術が必要である．プレガバリンはきわめて有効な場合があり，手術が回避できた例がしばしばある．

また，手術で圧迫を解除しても神経障害性疼痛が治癒しない場合も少なくない．われわれが2007年におこなった調査では脊椎手術を受けた患者においても2割程度の患者は日常生活に支障をきたすような痛みが残存していた[10]．また腰部脊柱管狭窄症後の足底部のしびれが残りやすいことが知られており，治療満足度にも影響する[11]．腰椎椎間板ヘルニアの術後にプレガバリンを投与すると残存する痛みが緩和され治療成績が向上した報告があり[12]，手術治療をおこなう患者でも神経障害性疼痛を意識して治療に臨む必要がある．




**図❶ 後縦靱帯骨化症の神経障害性疼痛**

## 2．変形性関節症における神経障害性疼痛

四肢の変形性関節症（osteoarthritis：OA）における痛みの主体は何であろうか？変性は関節軟骨の変性，磨耗からはじまるとされているが，神経終末がないため正常軟骨に痛みが生じることはない．軟骨変性から軟骨下骨の障害，それに引きつづいて生じる骨棘形成や滑膜炎が原因とされる侵害受容性疼痛と考えられており，病期によっては炎症性疼痛が主体となる．しかし近年，侵害受容性疼痛と炎症性疼痛のみではなく，神経障害性疼痛の関与があることがしだいに明らかになってきた．関節組織が障害を受けると，マクロファージやリンパ球などから各種nerve growth factorやサイトカインが放出され，神経終末の刺激に対する閾値を低下させる．こうした，いわゆる末梢性感作が脊髄後角にある痛み伝播を増幅させ修飾させると中枢性感作が生じ[6]，さらに痛みに病的に敏感な状態，すなわち神経障害性疼痛となる．高齢者の膝OAに対する調査票の研究では28%に神経障害性疼痛の要素があったとされる[7]．また，Caチャネル$\alpha_2\delta$サブユニットをブロックするプレガバリンは三環系抗うつ薬とならんで神経障害性疼痛の第一選択薬であるが，人工膝関節手術の術後投与によって痛みが緩和され治療成績が向上したことがランダム比較試験で示されている[8]．このように神経障害性疼痛は四肢関節変性疾患においても重要な病態であると認識されはじめている．

## おわりに

神経障害性疼痛の代表的な疾患は線維筋痛症や複合性

局所疼痛症候群，脊髄障害性疼痛症候群であるが，運動器疾患に広くみられる病態である可能性が高くなっている．今後，運動器疾患の診療においては神経障害性疼痛を念頭に置いてあたる必要があるだろう．

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# 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 |

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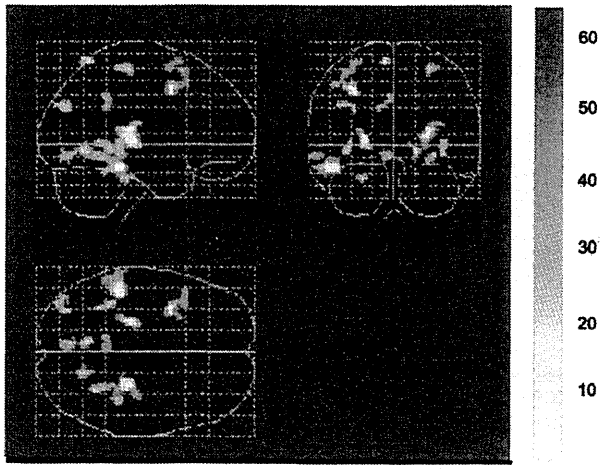


**Figure 1. Areas of cortical activation in the LBP group compared with the non-LBP group in response to virtual LBP stimuli (task – control condition) detected by fMRI($p<0.0005$, Z score>3.4, uncorrected threshold).**
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Fig. 1). The reverse contrast 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.
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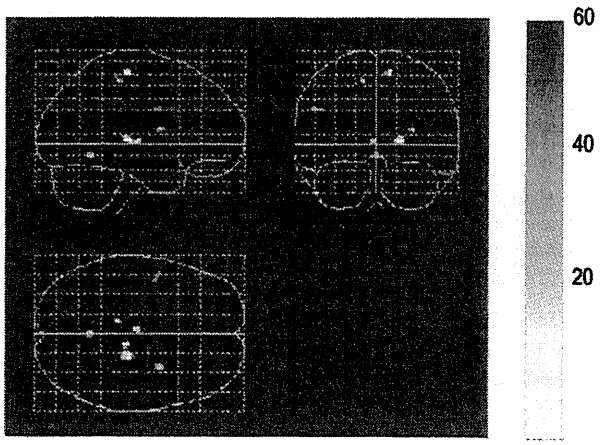


**Figure 2. Areas of cortical activation showing an association with perceived discomfort.**
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## Discussion

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.

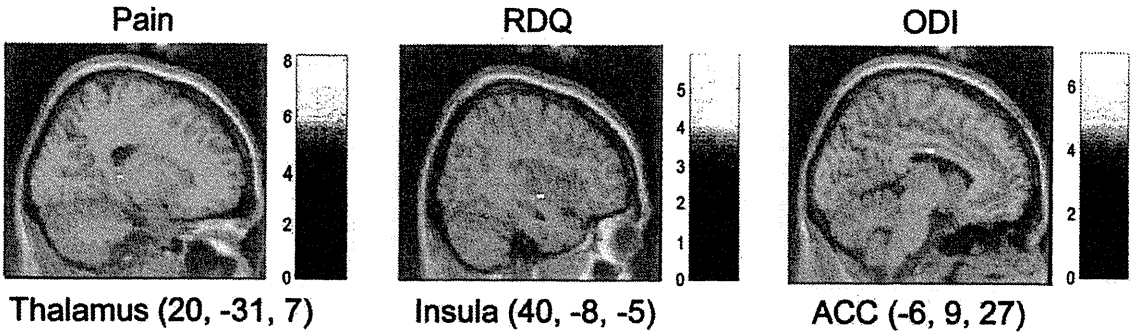


**Figure 3. Sagittal sections showing cortical clusters where activity was linearly correlated with perceived pain, RDQ scores and ODI scores.**
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We found other regions with heightened activity in LBP participants, in areas outside of the classic pain 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 7.4×11.3°. 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

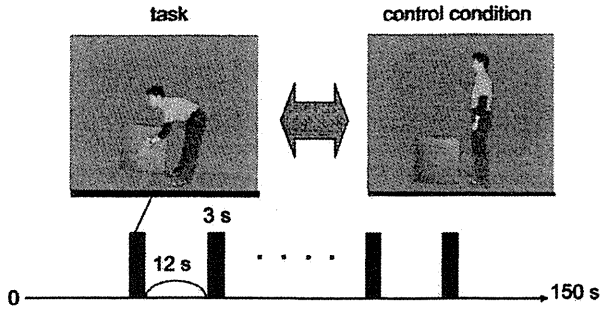


**Figure 4. Experimental design.** Subjects enrolled in the experiment were shown a picture demonstrating a man holding luggage in a half-crouching position (task picture) and a picture demonstrating a man standing in front of luggage, providing the baseline stimulation (control condition picture).
doi:10.1371/journal.pone.0026681.g004

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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*Review Article*

# The Animal Model of Spinal Cord Injury as an Experimental Pain Model

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Pain, which remains largely unsolved, is one of the most crucial problems for spinal cord injury patients. Due to sensory problems, as well as motor dysfunctions, spinal cord injury research has proven to be complex and difficult. Furthermore, many types of pain are associated with spinal cord injury, such as neuropathic, visceral, and musculoskeletal pain. Many animal models of spinal cord injury exist to emulate clinical situations, which could help to determine common mechanisms of pathology. However, results can be easily misunderstood and falsely interpreted. Therefore, it is important to fully understand the symptoms of human spinal cord injury, as well as the various spinal cord injury models and the possible pathologies. The present paper summarizes results from animal models of spinal cord injury, as well as the most effective use of these models.

## 1. Introduction

Spinal cord injury (SCI) often results in severe motor dysfunction, such as complete paralysis. These patients typically cannot only walk, but also lose bowel, bladder, and sexual functions. Pain impact following SCI has been reported as 37% of higher-level SCI patients with pain and 23% of lower-level SCI patients with pain; given the choice, these patients would trade pain relief for loss of bladder, bowel, or sexual functions [1]. Pain management is, therefore, an important health problem and topic of study.

Pain experiments with human subjects have proven to be practically challenging, fundamentally subjective, and ethically self-limiting. For these reasons, there remains a need for the use of laboratory animal models of pain. Pain is subjective in humans, and interpretation of animal model results requires careful attention. In fact, some have called for the abandonment of animal pain studies in favor of more extensive human testing.

A number of animal models of SCI exist and are primarily used to determine mechanisms of motor dysfunctions [2–4]. Recently, these various SCI animal models have been utilized for pain studies [5]. However, when SCI animal models are used for pain research, special attention should be paid to the concomitant conditions. The present paper discussed the various SCI animal models as models for pain, with an emphasis on the complexities and limitations, as well as strategies for improvement and future use.

## 2. Pain in SCI Patients

*2.1. SCI and the Social Impact.* SCI occurs in most countries at an annual rate of 20–40 individuals per million. SCI is a devastating event that results in motor dysfunction below the level of lesion, as well as development of chronic pain syndromes. Studies have reported the prevalence of pain in SCI patients. A summary of results from 10 studies indicates that an average of 69% of the patients experienced pain, and nearly one-third of patients in pain rated their pain as severe [6]. The stakes are enormous, given the impact of pain on the economy (pain-related treatment costs 1 trillion US dollars

per year in developed countries) [7]. If SCI pain could be eliminated, the quality of life could be greatly improved in patients; they would no longer suffer from pain and could take part in social aspects of life or earn money.

*2.2. Spinal Cord Injury and Chronic Pain.* Following mechanical injury to the spinal cord, a wave of secondary pathological changes occurs and amplifies the extent of initial damage. Apoptosis is critical for triggering collateral damage following primary injury to the spinal cord. Spontaneous and evoked pain is frequent in traumatic or ischemic spinal cord injury.

In complete and partial spinal lesions, chronic pain develops within months following injury [8]. Up to 80% of patients experience clinically significant pain, which is described as burning, stabbing, and/or electric-like [9, 10]. Post-SCI pain results in drastically impaired daily routines and quality of life to a greater extent than motor impairment [11]; it is refractory to clinical treatments, despite a variety of neurosurgical, pharmacological, and behavioral therapeutic strategies [12, 13]. The pain so greatly affects quality of life that depression and suicide frequently result [14, 15].

## 3. Chronic Pain Classification in SCI (Tables 1 and 2)

Siddall and colleagues [16] classified SCI pain from spinal cord injury into two broad types, with three regions of pain.

*3.1. Nociceptive Pain.* It is crucial for a pain clinician to distinguish between nociceptive or neuropathic pain, because the clinical approach for each is different. The first choice for nociceptive pain treatment following SCI is often a nonsteroidal, anti-inflammatory drug, or opiate, which often results in sufficient pain control.

*3.1.1. Musculoskeletal Pain.* Musculoskeletal pain is very common in SCI patients. In chronic states, secondary overuse or abnormal use of structures, such as the arm and shoulder, occurs [17]. Muscle spasm pain is a commonly observed type of musculoskeletal pain and is refractory for treatment of common musculoskeletal pain; analgesics are sometimes helpful, but antispasticity treatment may be needed in many cases [18].

*3.1.2. Visceral Pain.* Pathology in visceral structures, such as urinary tract infection, bowel impaction, and renal calculi, generally results in nociceptive pain. Visceral pain usually exhibits a delayed onset following SCI, which could be due to normal afferent input *via* sympathetic or vagal nerves in paraplegics or *via* the vagus nerve in tetraplegics [19, 20]. Patients with upper thoracic injury or cervical SCI may present with autonomic dysreflexia headache, because of bowel impaction or bladder distension.

*3.2. Neuropathic Pain.* SCI often results in neuropathic pain, which is difficult to treat and exhibits various patterns due to its pathology.

TABLE 1: Classification of the Spinal Cord Injury Pain Task Force of the International Association of the Study of Pain.

| Broad type | Broad system | Affected structures/Pathologies |
|---|---|---|
| Nociceptive | Musculoskeletal | Bone, joint, muscle trauma, or inflammation |
| | | Mechanical instability |
| | | Muscle spasm |
| | | Secondary overuse |
| | Visceral | Renal calculus (kidney stones) |
| | | Bowel and sphincter dysfunctions |
| | | Headache by autonomic dysreflexia |
| Neuropathic | Above-level | Compression mononeuropathy |
| | | Complex Regional Pain Syndrome |
| | At-level | Nerve root compression (cauda equine) |
| | | Syringomyelia |
| | | Spinal cord trauma/ischemia |
| | | Dual-level cord and root trauma (double-lesion syndrome) |
| | Below-level | Spinal cord trauma/ischemia |

TABLE 2: SCI pain classification by Bryce and Ragnarsson.

| Location | | Type | Etiologic subtypes |
|---|---|---|---|
| Above-level | nociceptive | 1 | Mechanical and musculoskeletal |
| | | 2 | Autonomic dysreflexia headache |
| | | 3 | Others |
| | neuropathic | 4 | Compressive neuropathy |
| | | 5 | Others |
| At-level | nociceptive | 6 | Mechanical and musculoskeletal |
| | | 7 | Visceral |
| | neuropathic | 8 | Central |
| | | 9 | Radiculopathy |
| | | 10 | Compressive neuropathy |
| | | 11 | Complex Regional Pain Syndrome |
| Below-level | nociceptive | 12 | Mechanical and musculoskeletal |
| | | 13 | Visceral |
| | neuropathic | 14 | Central |
| | | 15 | Other |

*3.2.1. At-Level Pain.* At-level pain occurs in dermatomes near the spinal injury and develops shortly after the injury. The pain is often characterized as stabbing or stimulus-independent and is accompanied by allodynia [21, 22].

*3.2.2. Below-Level Pain.* Below-level pain is localized to dermatomes distal to the injury site and develops more gradually than at level pain; it is often classified as a stimulus-independent, continuous, burning pain [21, 22].

*3.2.3. Above-level Pain.* Above-level pain occurs at dermatomes cranial to the injury site [21, 22].

*3.3. Other Classification of SCI Pain (Table 2).* Bryce et al. classified SCI pain by location of the pain [23]. In terms of animal behavior, this classification helps to provide a better understanding of pain pathology. In basic pain research, pain is defined as neuropathic or nociceptive. Similarly, SCI pain is complex and the pathology should be taken into consideration at the same time. It is important to understand the pathologies in each model.

## 4. The Role of Animal Model

Human self-ratings of pain, using questionnaires and scales, are reliable, accurate, and versatile for measuring experimental and clinical pain [24]. Nonetheless, the subjectivity of these measures has led to a decade-long search for surrogate biomarkers. To date, an objective surrogate with acceptable high sensitivity and specificity has not been identified. However, individual function-imaging scans could provide a reliable and objective measurement of subjective pain perception [25]. In addition, genetic biomarkers could prove to be useful. However, it is likely that too many genes are involved [26]. Moreover, genomic DNA variants could predict trait sensitivity to pain rather than ongoing levels of pain. Only a small percentage of injuries, infections, or others causes that results in chronic pain syndrome actually develop chronic pain. Therefore, in human studies, it will be difficult to determine the correlation between genetic background and pain severity. Furthermore, common clinical pain conditions, such as back pain, are too polygenic to be effectively modeled and genetically understood.

Animal models cannot self-report. In response to noxious stimuli, behaviors can be reliably and objectively scored, although these simple reflexes or innate responses (such as licking an inflamed paw) seem to lack clinical validity. Indeed, experiments with behavioral measurements of pain in animal models have become more common. According to studies published in flagship journals, pain studies comprise approximately 25% of total studies, more than any other field of study [27].

The animal model of pain plays a central role in analgesic drug development and the fundamental mechanisms that drive it. Despite the development of human imaging studies, such as functional MRI, the use of animal models of pain is a continuing necessity [5].

## 5. Spinal Cord Injury Dynamics and Procedures

Several models of neuropathic pain due to spinal cord injury have been simulated in rats. These studies have primarily focused on spinal cord injury caused by contusion or weight dropping, spinal cord compression, excitatory neurotoxins, photochemical-induced ischemia, spinal cord transaction, or crushing of the spinal cord. These models have also been adapted for mice [28–31]. The development of reliable neurotrauma mouse models provides great promise for evaluating overexpression or inactivation of certain genes on lesion pathophysiology and functional outcome. However, more attention should be focused on motor recovery while evaluating pain behavior, because of the delayed motor recovery in mice compared with rats [32, 33]. The utility for each model summarizes in Table 3.

*5.1. Contusive or Hemicontusive Models.* Spinal contusion is the oldest and most widely used animal model. In addition to motor dysfunction, this injury elicits sensory dysfunction, including neuropathic pain, tactile allodynia, and thermal hyperalgesia [34, 35]. Cervical contusion is rarely reported, because life-threatening adverse effects could occur. Therefore, cervical hemicontusion, following hemilaminectomy, is used to analyze the unilateral spinal cord contusion model. Because motor dysfunction appears in the forelimbs, pain-related behavior is difficult to estimate, and for this reason, cervical contusion is often utilized for motor functional analysis [2, 3]. The thoracic spinal cord contusion model is the most popular pain research model and is induced with impactors, such as the weight-drop impactor [36]. In brief, the exposed spinal cord is injured by dropping a 10.0-g rod from specified heights [37, 38]. After 2 or 3 weeks, motor dysfunction is recovered and pain behavior can be analyzed. The impact of the injury tends to vary. Therefore, especially in short distances from the rod to spinal cord, pain behavior does not always appear. It is difficult to bilaterally drop the rod onto the spinal cord. Following injury, motor function analysis is needed to exclude unilateral paralysis and the possibility of unilateral contusion. Abnormal sensations due to mechanical, thermal, or cold stimuli are observed for several weeks or longer [32, 33, 39–52], and all regions (at-, above-, below-level) of allodynia are analyzed [53–56].

*5.2. Transection or Hemisection Models.* The complete spinal transection injury model reflects symptoms of complete SCI patients. Following laminectomy, spinal cord transection is performed with spring scissors. Occasionally, to attach the two ends for regeneration, a sterile, gel foam is placed between the two resected spinal cord ends. At-level and below-level neuropathic pains are then analyzed [57, 58]. Many studies have reported muscle spasms in the spinal complete transection model [18, 59, 60], and musculoskeletal pain pathology during spasticity could help to clarify the use of this model.

The partial spinal transection injury model (hemisection) has become popular in neuropathic pain studies [61–78]. Motor dysfunction appears only in the ipsilateral injured side and persists from 5 days to 4 weeks [64, 75]. Mechanical allodynia and thermal hyperalgesia are bilaterally observed in above-level and below-level cases [61, 76–81].

*5.3. Photochemical Model.* Over the past two decades, the photochemical model of spinal cord injury, developed by Watson et al. [82], has proven to be one of the most reliable and reproducible graded experimental rat models of spinal cord injury [83–94] and has been widely used to study neurotrauma in mice [88]. The biggest advantage of

Table 3: Animal spinal cord injury models and symptoms.

| Impact to spinal cord | Laterality and devices | Injury area | | | Sensory abnormality | | | Duration | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cervical | Thoracic | Lumbar | At-level | Below-level | Above-level | Allodynia | Maximal motor dysfunction |
| Transection | Bilateral | | ○ | ○ | ○ | ○ | × | Several weeks or more | Less than 4 weeks |
| | Unilateral | | | | | | | 1–5 weeks or more | Ipsilateral to injury: 4 weeks |
| Compression | Contusion | | ○ | | ○ | ○ | ○ | Weeks to months | 1-2 weeks |
| | Hemi-contusion | ○ | | | | | | | 3 weeks |
| | Clip | | ○ | | ○ | ○: severe injury impossible | | 4 weeks | 4 weeks severe injury |
| | Displacement | | | | | | | 4–6 weeks | 2 weeks |
| | Canal stenosis | | | ○ | | ○ or × | | 8 days or hypoalgesia | |
| Photochemically | | | | | | | | 10–20 days | Various |
| Excitotoxic | | | ○ | | ○ | ○ | ○? | 5 weeks or more | |
| Spinothalamic tract lesions | | | | | | | | Several weeks | Less than 1week |

Many spinal cord injury models exist for pain research. Pain behavior should not be measured in injured animals during maximal motor dysfunction.

this method is that the resulting injury does not induce mechanical trauma to the cord, because there is no need for laminectomy. Instead, an intravascular photochemical reaction occurs through the use of a dye that is activated by an argon ion laser to produce single oxygen molecules at the endothelial surface of spinal cord vessels. This results in an intense platelet response, as well as subsequent vessel occlusion and parenchymal tissue infarction [83]; the pathology is of a purely ischemic origin. Motor deficits are related to irradiation duration, as well as mechanical allodynia (cold, not thermal), which lasts for several days [91]. Following application of the von Frey filament to the trunk, behavioral analysis is performed according to vocalization threshold. Antiallodynic effects of analgesics have been determined using this model [84, 85, 90]. However, extent of injury is difficult to control. Therefore, motor deficit scores, such as BBB [95] and CBS [96], have been widely utilized [86, 90].

*5.4. Excitotoxic Models.* Intraspinal or intrathecally injection of some excitotoxins, such as quisqualic acid or other excitatory amino acids (glutamate, N-methylasparate, and kainic acid), produces long-lasting spontaneous pain, mechanical allodynia, and thermal hyperalgesia in rats and mice [97, 98]. Following excitotoxin injections, neuronal loss, cavity formation, astrocytic scaring, and prominent inflammation occur. The advantage of this model is the ability to correlate specific areas of tissue damage with behavioral changes. Moreover, the percentage of animals that exhibit pain-related behaviors following injury is greater than with other models; induced mechanical allodynia was 67% in the contusion injury model [99], in contrast to 44% chronic allodynia following ischemic injury [86]. In excitotoxic animal models, nearly 100% animals develop varying degrees of hypersensitivity to mechanical and thermal stimuli [98].

*5.5. Other Mechanical Spinal Cord Injuries*

*5.5.1. Clip Compression Injury.* Clip compression injury resembles spinal contusion injury at the point of the injury caused by pressure to the spinal cord. Following laminectomy, compression injury is induced with clips calibrated to exert a force of 50 or 35 g. The 50-g clip induces severe injury and the 35-g clip induces moderate injury. Either clip is dorsoventrally closed over the entire cord for 1 min and then subsequently removed [58, 100–102]. A vascular clip is used for this procedure in mice [103]; the spinal cord becomes ischemic and mimics common clinical injuries and outcomes.

*5.5.2. Spinal Cord Displacement.* The spinal cord displacement model attempts to regulate trauma impact by controlling displacement length of the spinal cord. Through the use of this model, a cutoff for normal sensory function has been determined [104]. In human SCI, trauma severity is not proportional to pain severity, because the method of injury varies. The unique features of controlled displacement and monitoring of biomechanical parameters at the time of impact help to reduce outcome variability [105].

*5.5.3. Canal Stenosis.* Lumbar canal stenosis is due to entrapment of the cauda equine and/or lumber nerve roots by hypertrophy of osseous and soft tissue structures

surrounding the lumbar spinal canal. A typical pathology is reduced blood flow to the peripheral nerve, resulting in demyelination or axonal degeneration, depending on the magnitude of ischemic injury. Canal stenosis can also be termed a spinal cord injury model, in which square-shaped pieces of silicon are placed into the epidural space in the rat [106, 107]. However, these procedures also induce mechanical hypoalgesia [107]. Nevertheless, this model could help to clarify pathophysiology of chronic, light pressure to the spinal cord.

*5.5.4. Spinothalamic Tract Lesions.* The spinothalamic tract is the core pain pathway in the spinal cord. This model is designed to lesion only the spinothalamic tract area using a tungsten microelectrode. Although this model injures the unilateral spinothalamic tract, bilateral above- and below-level hyperalgesia, as well as allodynia, is induced and can persist for many weeks. These features resemble allodynia and hyperalgesia experienced by humans suffering from central pain syndromes following spinal cord injury. Therefore, this model could provide useful and novel insights into the underlying biological mechanisms of spinal cord injury [108].

## 6. Pain-Related Behavior As an Evaluation of Symptoms

Pain-related behavior is recorded using various devices applied to the forelimbs, hindlimbs, trunk, and face. If pain behavior appears in the face, it is considered to reflect the reaction to supraspinal mechanisms, because sensory function in the face is regulated by the trigeminal nerve (a cranial nerve). In thoracic spinal cord injury, trunk allodynia reflects at-level neuropathic pain, and allodynia in the hindlimb reflects below-level neuropathic pain. Forelimb allodynia reflects at-level neuropathic pain in cervical injury and above-level neuropathic pain in other injuries.

Abnormal pain behavior is a result of three different stimulations: mechanical, thermal, and cold.

*6.1. Mechanical Allodynia.* Mechanical allodynia can be measured in various ways using the von Frey hair. In one of the methods, the "up-down method" [109], each von Frey hair is applied to the test area for 2-3 s, with a 1-2-minute interval between stimuli. The trial begins with application of the 15-mN von Frey probe to the hindpaws. A positive response is defined as a rapid withdrawal and/or licking of the paw immediately upon application of the stimulus. The von Frey hair can also be used to determine vocalization threshold to graded mechanical allodynia as a means to evaluate at-level neuropathic pain in the trunk [92]. When a positive response to stimulus occurs, the next smaller von Frey hair is applied. If a negative response occurs, the next higher force is applied. Testing continues for five or more stimuli after the first change in response, and the pattern of responses is converted to a 50% von Frey threshold using a previously described technique [109]. If the animal shows no response to the highest von Frey hair (160 mN), a von Frey threshold of 260 mN, corresponding to the next log increment in potential von Frey probes, is assigned to the threshold.

Touch-evoked agitation is another evaluation of mechanical allodynia [110] and can be used to test the animal response to tactile stimulation. The animal skin is briskly stroked with a pencil point in a rostral to caudal direction. The animal response is graded with a score of 0: no response, 1: moderate efforts to avoid the probe, transient vocalization, and 2: vigorous efforts to escape the stimulus, frequent and sustained vocalization in response to the probe.

Pathological reactions between the von Frey probe and pencil point vary due to reactions to the von Frey hair (caused by A-delta-fiber and C-fiber) or the pencil (A-beta fiber).

*6.2. Thermal Hyperalgesia.* Thermal hyperalgesia can be measured by latency of paw withdrawal in response to a radiant heat source [111]. Briefly, animals are placed in Plexiglas boxes on an elevated glass plate heated by a radiant heat source directed by a beam of light to the planter surface of each paw through the glass plate (47°C). The light beam is automatically turned off by a photocell upon limb-lift, allowing for measurement of time between stimulus start and paw withdrawal (paw withdrawal latency). Three to five minutes are allowed between each trial, and three trials are averaged for each limb.

*6.3. Cold Allodynia.* Cold sensitivity to acetone can be quantified by foot withdrawal frequency [112]. A total of 100 $\mu$L acetone is applied to the paw planter surface using a plastic tubule connected to a 1 ml syringe. Acetone is applied 5 times to each paw at an interval of at least 5 minutes. The number of brisk foot withdrawals is recorded.

## 7. Evaluation of Motor Functions in the Spinal Cord Injury Model

Locomotor function is observed and recorded using the Basso, Beattie, and Bresnahan (BBB) Locomotor Rating Scale [95]. Briefly, the BBB is a 22-point ordinal scale ranging from 0 (no discernable hindlimb movement) to 21 (consistent and coordinated gait with parallel paw placement of the hindlimb and consistent trunk stability). Scores from 0 to 7 rank early phase of recovery, with return of isolated movements from three joints (hip, knee, and ankle); scores from 8 to 13 describe the intermediate recovery phase with, return of paw placement, stepping, and forelimb-hindlimb coordination; and scores from 14 to 21 represent late phase of recovery, with return of toe clearance during the step phase, predominant paw position, trunk stability, and tail position. Scores are tabulated and considered to be an indicator of motor recovery.

The Basso Mouse Scale (BMS), a 9-point rating scale, has been specially developed for mouse models [113]. An additional scoring systems, described by Gale et al. [96] and termed the Combined Behavioral Score (CBS) (Table 4), has been used to measure locomotor function.

Following cervical spinal cord injury, recovery of forelimb function can be measured [114] by indicators such as the grooming test and forelimb asymmetry test [115]. Forelimb grooming function has been assessed using a scoring system originally developed to examine recovery in a rat brachial plexus reconstruction model [116]. The forelimb asymmetry, or paw preference test, is sensitive to asymmetries produced by a variety of CNS insults [117]. In addition, forelimb motor function recovery and pain behavior should be coanalyzed, because behavior is a result of motor functions [118].

## 8. Future Direction and Conclusions

*8.1. Spinal Cord Injury As a Musculoskeletal Pain Model.* Spinal cord injury leads to immediate impaired motor and sensory functions, which are also manifested over time. Following an initial period of spinal shock, reflexes become reduced and a disturbing hyperreflexia develops, which is often referred to as spasticity [119].

Spasticity is a disabling complication that affects individuals with spinal cord injury [18, 120]. Approximately 75% of individuals with SCI exhibit spasticity 1 year after injury and half undergo antispasticity treatment [121]. Significant scientific interest has been devoted to spasticity over the past 10–15 years as an example of plastic changes occurring distal to a central lesion.

The primary mechanisms hypothesized to be responsible for spasticity are increased motoneuron excitability [122, 123] and increased synaptic input, as a result of muscle stretch and reduced inhibitory mechanisms (presynaptic [124] and reciprocal inhibitions [125]). The mechanisms underlying decreased inhibition below the lesion remain poorly understood [59].

The most commonly proposed mechanisms to account for decreased inhibition following spinal cord injury include disruptions of facilitatory supraspinal input to inhibitory interneurons [59, 126]. Motoneuron and sensory neurons are often regulated by common mechanisms [127], and common molecular mechanisms could be responsible for below-level neuropathic pain and spasticity [18, 37].

The spinal cord injury model, in particular the spinal transaction model, is considered useful for spasticity research. Because spasticity results in musculoskeletal pain, the spinal cord injury model could be considered a musculoskeletal pain model.

*8.2. Spinal Cord Injury As a Visceral Pain Model.* Visceral pain in spinal cord injury commonly triggers autonomic dysreflexia, a potentially life-threatening hypertensive syndrome due to high thoracic spinal cord injury. Pathology correlates with increased sprouting of primary afferent c-fibers into the spinal cord. During motor dysfunction, visceral pain-related behavior is difficult to analyze. However, based on the above-described mechanisms, a morphological approach to spinal complete transection injury has been utilized [128].

TABLE 4: Combined Behavioral Score (CBS), as reported by Gale et al. [96].

| General description | | Points |
|---|---|---|
| Motor score | | |
| 0 | Normal walking | 0 |
| 1 | Walks with mild deficit | 5 |
| 2 | Hindlimb can support weight | 15 |
| 3 | Frequent movement of hindlimb, no weight support | 25 |
| 4 | Minor movement in hindlimb, no weight bearing | 40 |
| 5 | No movement in hindlimb, no weight bearing | 45 |
| Toe spread | | |
| 0 | Normal, full, toe spread | 0 |
| 1 | Partial spreading of toes | 2.5 |
| 2 | No spreading of toes | 5 |
| Righting | | |
| 0 | Normal righting, counter to direction of roll | 0 |
| 1 | Weakened attempt to right | 5 |
| 2 | Delayed attempt to right | 10 |
| 3 | Delayed attempt to right itself | 15 |
| Extension withdrawal | | |
| 0 | Normal | 0 |
| 1 | Weak and slow reflex to withdraw hindlimb | 2.5 |
| 2 | No withdrawal reflex | 5 |
| Placing | | |
| 0 | Normal placing | 0 |
| 1 | Weak attempt to place foot | 2.5 |
| 2 | No attempt to place foot | 5 |
| Inclined plate | | |
| 0 | 65~70/deg | 0 |
| 1 | 55~60 | 5 |
| 2 | 40~50 | 10 |
| 3 | <40 | 15 |

*8.3. Limitations of Animal Models of Chronic Pain.* Limited success in the pain field during the past few decades has resulted in a plethora of basic scientific data. The use of animal models has increased our knowledge of novel, effective, and safe clinical analgesics. Experimental failures with novel drugs are associated with adverse side effects and the lack of efficacy in humans. In addition, psychosocial aspects of chronic pain due to spinal cord injury have been completely omitted, despite a large body of knowledge emphasizing the importance of these factors in chronic pain. Future studies should extend the scope of inquiry to include the psychosocial aspects of chronic pain and spinal cord injury.

*8.4. Conclusion.* By widening the number of animal models of spinal cord injury, new challenges have emerged. Although experimental methods of spinal cord injury pain lead to various behavioral outcomes, it is clear that some models respond similarly to pharmacological agents. This suggests that common mechanisms could underlie specific symptoms derived from various injury conditions. Etiologies of spinal cord injury pain could vary. However, by focusing on various symptoms of spinal cord injury pain, treatment possibilities for pathologies of spinal cord injury pain could emerge.

Continuous basic and clinical studies focused on different aspects of spinal cord injury pain are needed to better understand the mechanisms involved.

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