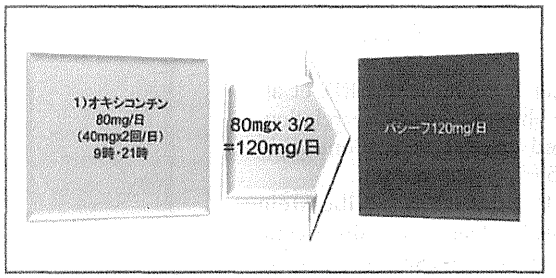


図8　オキシコドンからモルヒネ製剤へ
パシーフは，速放：徐放＝2：8なので，実質モルヒネ徐放分は96 mg/日となり，やや少なめに変更することになるので安心である

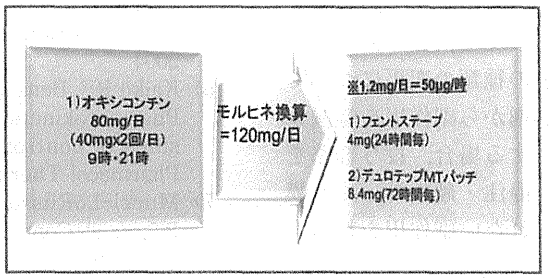


図9　オキシコドンからフェンタニル貼付剤へ

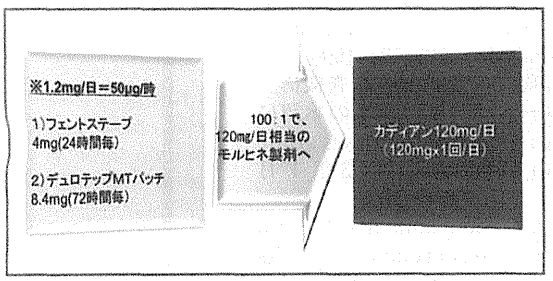


図10　経皮吸収型フェンタニル貼付剤からモルヒネ製剤へ
変更前のオピオイドの効果発現時間と貼付剤の剥離後の効果減衰時間を考慮しながら変更を行う．痛みが出現した場合，内服可能であればレスキューで対応し，内服できない場合はモルヒネ注射薬で対応する（Eq：上記なら5 mg/回）

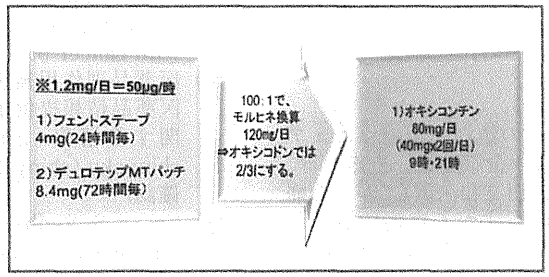


図11　モルヒネ製剤から経皮吸収型フェンタニル貼付剤へ
変更前のオピオイドの効果発現時間と貼付剤の剥離後の効果減衰時間を考慮しながら変更を行う．痛みが出現した場合，内服可能であればオキノームで対応し，内服できない場合はモルヒネ注射薬で対応する（Eq：上記なら5 mg/回）

せずに痛みが出現し始めてから，または12時間後に内服を開始するようにしている．前述のように，フェンタニル貼付剤は貼付後の血中濃度の上昇がゆっくりであること，剥がした後の血中濃度の下降もゆっくりであることを考慮に入れて変更しなくてはならない．

### 5）経皮吸収型フェンタニル貼付剤⇒オキシコドン徐放剤（図11）

フェンタニル貼付剤からオキシコドンに変更する理由で多いのは，疼痛管理不十分，発熱，皮膚疾患などである．

上記モルヒネへの変更と同様に行う．上記のモルヒネ量の2/3の量のオキシコンチンへと変更する．

## ま と め

これからも多くの新オピオイド製剤が出現してくることになるが，各薬剤の特性を知って，変更する時の等鎮痛用量はあくまで参考にするというスタンスでコントロールすることが肝要である．図中にもあるように，変更後の痛みのアセスメントと投与量調節を怠らないようにすることが何よりも重要である．

また，オピオイド変更時には，製剤の効果発

現までの時間，半減期などを知った上で行うと，有害事象があっても慌てなくて済むであろう．

本稿では，オピオイドの種類の変更について説明したが，モルヒネ製剤から副作用を軽減する目的でローテーションする場合，投与経路を変える（経口→皮下注・静注・硬膜外・くも膜下など）ことも，耐えられない副作用を軽減する一つの方法である[13]．

最後に，オピオイド・ローテーションは必要ないのにすることではない．安易なオピオイド・ローテーションは，その後，病状が変化していった時の選択肢を削ってしまうので，慎むべきであると考える．

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# 脊髄くも膜下腔カテーテル・ポート留置後に遅発性髄液漏，皮下水腫を生じた1症例

症例報告
Clinical Report

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**要　旨**
大腸がんの転移性腫瘍の仙骨部浸潤による右臀部痛を有する43歳，男性患者に対し，脊髄くも膜下腔カテーテルおよび皮下埋め込み型アクセスポート植え込み術を行った．施術2週間後に著明な髄液漏，皮下水腫を認め，小切開髄液漏根治術，硬膜外自己血パッチ療法を必要としたが，がん性疼痛コントロールは良好で，低髄液圧症候群の症状を認めることなく退院した．
（ペインクリニック31：1215-1219，2010）

キーワード：がん性疼痛，持続脊髄くも膜下鎮痛法，髄液漏

## はじめに

がん性疼痛は，WHO（世界保健機関）のガイドラインに従って痛みの強さに応じた鎮痛薬を投与することにより，ほとんどの患者で痛みを改善することができる．しかし，鎮痛薬の量を増やしても痛みが改善しない，嘔気や眠気など副作用のために鎮痛薬の量を増やせないといった患者が1～3割存在する．このような難治性の痛みに対し，脊髄鎮痛法が試みられている．その中で，脊髄くも膜下腔にカテーテルを留置し皮下埋め込み型アクセスポートを設置する持続脊髄くも膜下鎮痛法は，鎮痛薬の投与量が少なくて済むためにオピオイドの副作用が軽減され，かつ経済的であり，薬液ポンプ交換が週に1回程度と在宅での使用も可能である[1,2]．

今回，脊髄くも膜下腔カテーテルおよび皮下埋め込み型アクセスポート植え込み術を行った患者で，遅発性に髄液漏，皮下水腫を合併した症例を経験したので報告する．

## Ⅰ．症　例

43歳，男性．身長170 cm，体重50 kg．

**主　訴**：右臀部痛．

**既往歴**：特記すべき事項なし．

**現病歴**：3年前，大腸がんに対しハルトマン手術が施行された．その5カ月後，局所再発したため放射線治療が行われた．さらに2カ月後よりFOLFOX＋ベジスズマブ，FOLFIRI＋ベジスズマブ，セツキシマブによる化学療法を行ったが，腹壁・骨盤部の転移性腫瘍は縮小せず，3カ月前から在宅ホスピス治療へと移行した．仙骨部浸潤による右臀部痛に対し，ジクロフェナクナトリウム（ボルタレンSR®）37.5 mg×2回/日，オキシコドン（オキシコンチン®錠）200 mg×2回/日，疼痛時屯用オキシコドン（オキノーム散0.5%）1回50 mg，フェンタニル貼付剤（デュロテップMTパッチ®）12.6 mg×2枚，8.4 mg×1枚，ガバペンチン（ガバペン®）

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〈Clinical Report〉
**A case of delayed CSF leakage and hygroma after intrathecal catheterization**
Madoka Shirasawa, et al
Department of Anesthesiology and Pain Service, Cancer Institute Hospital of JFCR

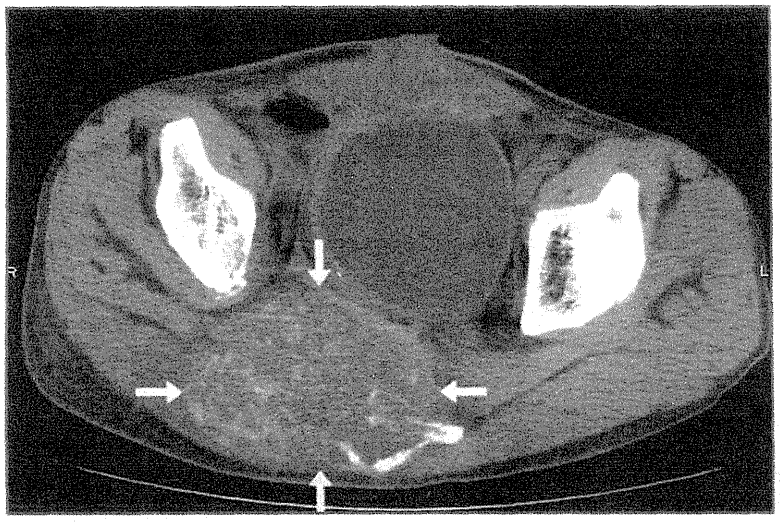

**図1　骨盤部CT**
仙尾移行部を中心とする転移性腫瘍（矢印）があり，仙骨は構造破壊をきたしている

400 mg×2回/日が投与されていた．オピオイドは経口モルヒネ換算で1,080 mgに達していたが，疼痛コントロールは不十分であり，また薬剤費の経済的負担が大きくなっていたため，2カ月前に在宅医療を依頼された往診医より，疼痛治療法の整理とコントロールを目的に当院麻酔科外来に紹介された．CT上，仙尾移行部を中心とする転移性腫瘍があり，仙骨中央から右側，坐骨，恥骨下枝に溶骨性変化を認めた（**図1**）．

2010年X月，脊髄くも膜下腔に1日経口モルヒネ換算量と等価の塩酸モルヒネ3 mg，0.5%等比重ブピバカイン0.2 mlに生理食塩水1.5 mlを加えた2 mlを投与してテストブロックを行い，良好な鎮痛が得られたため，その翌週に脊髄くも膜下腔カテーテルおよび皮下埋め込み型アクセスポート植え込み術を施行した．施術は過去に報告した手順[3,4]で，硬膜外アクセス用ポートを用い，透視下に17Gの硬膜外針で穿刺を行った．第1～2腰椎間より尾側にカテーテルを進め，第5腰椎下縁にカテーテル先端を留置し，塩酸モルヒネ0.5 mg/ml，等比重ブピバカイン0.08%溶液を0.5 ml/hrで持続投与を開始した（モルヒネ1日量：6 mg）．Pain scoreは2/10と疼痛コントロール良好となり，以前よりあった下肢の軽度のしびれの増強は認めたが，その他に合併症はなかった．感染予防として，セファゾリンナトリウム1 gを術前と1PODに投与した．全身投与のオピオイドは，オキシコドン（オキシコンチン® 錠）40 mg×3回/日，疼痛時屯用オキシコドン（オキノーム散0.5%）1回20 mgまで減量して退院となった．

在宅での脊髄くも膜下鎮痛を行うために，ディスポーザブル型インフューザー，95 ml充填で0.5 ml/hr（BAXTER 7 days type：0.5 ml/hr）のものを使用して薬物の持続投与を行った．

退院後は，週1回外来通院して薬液ポンプの交換，薬液の充填を行った．2回目のポンプ交換前日に，家族より「ポート用針の穿刺部から液体の漏出があり，服がびしょびしょになる」との報告があった．外来で診たところ，髄液漏が疑われたため，緊急入院して背部のTouhy針を刺入した部位を切開してカテーテル周囲の筋膜縫縮を行った．しかしながら，翌日には同部の皮下水腫と膨瘤がみられたため，翌日に硬膜外腔自己血パッチ療法を行った．2日間のベッド上安静，背部の圧迫の後，頭痛，ふらつきなどがないことを確認後，安静解除・圧迫解除とした．穿刺部の皮下水腫の消失には通常1～

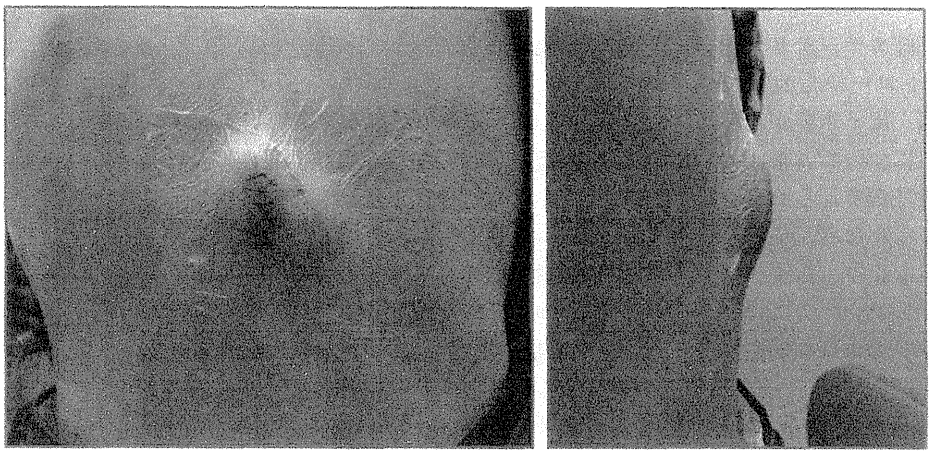

**図2　Touhy 針穿刺部**
縦 7 cm × 横 6 cm 大の皮下水腫を認める

2 週間を要するため，2 回目の入院期間中に皮下水腫の消失を確認することはできなかったが，膨隆が増大傾向にないこと（**図2**），皮下ポート植え込み部に水腫がみられないこと，患者自身が退院して在宅での療養を希望したことから，低髄液圧症候群の症状が認められないことを確認して退院となった．退院時の脊髄くも膜下腔への薬液組成は，塩酸モルヒネ 0.5 mg/ml，等比重ブピバカイン 0.04% 溶液で，0.5 ml/hr の速度で持続注入していた．なお，髄液漏に伴う薬液の漏出による疼痛の増悪が懸念されたが，総じて経過中のがん性疼痛コントロールは良好であった．

退院後，在宅往診医での疼痛治療を継続した後，近隣の病院の緩和ケア病棟に入棟した．

## Ⅱ．考　察

欧米では，WHO 除痛ラダーの第四段階目として脊髄くも膜下鎮痛法が行われており，米国では，がん性疼痛管理におけるインターベンション治療として，くも膜下注入用埋め込み型ポンプ（implantable drug delivery system：IDDM）が主流となっている[5]．

脊髄くも膜下鎮痛法に伴う合併症としては，髄液漏と低脊髄圧性頭痛，髄膜炎，神経損傷，出血，血腫，カテーテルの位置移動，断裂，閉塞，先端の肉芽形成，感染などがあり，特に頻度が高いものとして髄液漏が挙げられる．

腰椎穿刺後頭痛（post dural puncture headache：PDPH）の発生頻度は，穿刺針のサイズに比例し，Quincke 針では 24～27G の使用で 5～12%，20 ～ 22G で 20 ～ 40%，16 ～ 19G で 約 70% と報告されている[6]．脊髄くも膜下麻酔では，PDPH のリスクを減らすために径の細い針や pencil point 針を選択することにより，発生頻度は 2～10% 程度に抑えることができると報告されている[7]．一方，カテーテルを挿入する場合には，閉塞を回避するために太いカテーテル（通常 22G 以下）が用いられ，太いガイド針（通常 17G 以下）が必要となる．IDDM では，16G の Touhy 針を用いるため，カテーテル周囲からの髄液漏出が起きやすく，施術後の髄液漏出は 20% 程度にみられ，重症な場合には背部やポンプポケット部の皮下に髄液が貯留して水腫がみられる場合がある[8]．

髄液漏に起因する症状は 48 時間以内に起こることが多く，腰椎穿刺後の安静は，多くの教科書で頭痛予防のために推奨されており，数時間から 24 時間の安静時間が様々な国でとられているが，短時間安静と長時間安静の間で PDPH の発生率で有意差は示されていない[9]．また，水分補給を増やすことが予防策にならないことも示されており[6]，PDPH を完全に防ぐ

ことは難しい．

本症例では，脊髄くも膜下腔カテーテル留置後には頭痛もなく疼痛コントロールも良好であったが，２週間後に髄液漏，皮下水腫がみられた．遅発性に出現した理由については推測の域を出ないが，二通りの可能性が考えられる．一つは髄液漏が少しずつ起こったために皮下水腫となるまでに時間がかかったこと，もう一つは，痛みが改善してADLが上がったことに伴う体動によって，カテーテルの硬膜貫通部の穴が大きくなったことである．

重症PDPHの治療法である硬膜外自己血パッチ療法は，有効率90～99%と効果的であるが，合併症として腰痛，下肢痛，発熱，感染，硬膜外血腫による神経障害，硬膜外腔癒着などがある[10]．本症例でも硬膜外自己血パッチ療法後は背部の膨瘤は止まり，皮下ポート部の水腫や髄液の漏出はみられなかったことから，有効であったと思われる．

PDPHを予防するためには，硬膜を貫通するカテーテルの穴をなるべく細くする必要がある．over-the-needle typeの持続脊髄くも膜下麻酔用カテーテル（Spinocath, B. Braun社製）は，スパイナル針の外径がカテーテルの内径よりも小さく，カテーテル周囲からの髄液漏出が少なくなるようにデザインされており，持続脊髄くも膜下麻酔においてPDPHの発生率は1.6%[11]，microcatheter-through-the-needleと比較して，カテーテルの挿入，髄液の吸引や薬液の注入が容易で，閉塞やねじれが少ない[12]と報告されている．2000年以降，国内においてもSpinocathを用いた予定手術患者への持続脊髄くも膜下麻酔において，PDPHの発症が少ないことからその有効性を示す学会発表や，脊椎手術後の妊婦の帝王切開時，心疾患合併妊婦の分娩時にSpinocathを使用し，PDPHなしまたは抜去後の軽度のPDPHで管理した１症例報告があり[13,14]，今後は長期留置への応用を含めた検討が期待される．

## まとめ

脊髄くも膜下モルヒネ鎮痛法は，比較的安全で長期的に安定して強力な鎮痛効果が期待できるため，主にオピオイド抵抗性の難治性がん性疼痛患者に対して行われており，今後は非がん性疼痛患者への拡大も予想される[15]．しかし，合併症の一つである髄液漏は，発生した場合に患者のQOLに影響を及ぼすため，髄液漏を最小限に抑えることのできる新しいデバイスの開発などPDPH発生の予防への取り組みが今後も重要な課題となるであろう．

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# Using the intact hand for objective assessment of phantom hand-perception

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ABSTRACT

After amputation, most patients experience a phenomenon known as a phantom limb (PL). A variety of PL experiences appear to be associated with neural plasticity within the CNS. However, due to the subjective nature of PL experiences, there was no definitive way to reliably assess PL experiences other than using patients' direct reports. Here, we were able to obtain patients' indirect responses to PL experiences, for a more objective evaluation. First, we conducted a study with normals and 17 non-PL patients experiencing pathological pain in one hand. We took digital photographs of their affected and unaffected hands, altered the sizes of the images digitally, and then asked each subject to choose the image that most closely matched the actual size of their own hands (from a series of images presented on a video screen). Subjective size perceptions of the hands were homologous, regardless of the pathological condition of one hand ($p < 0.0001$, Spearman $R^2 = 0.82$). Next, we used the same method for total 19 patients with a phantom hand. The intact hand-size perception was linearly correlated with phantom hand-size perception (weighted linear regression analysis: $p < 0.0001$, $R^2 = 0.75$, adjusted $R^2 = 0.73$, $F$-value = 50.1, degree of freedom = 18). Thus, without requiring a subjective description about PL, the patients' evaluation of the intact hand-size precisely but indirectly indicated whether the PL was perceived to be telescoped (shrunken), normal or enlarged. This more objective evaluation of PL phenomena could become a key tool for disentangling the neural mechanisms involved.

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## 1. Introduction

After amputation of a limb, most patients experience a phenomenon known as phantom limb (PL). The missing limb is often perceived to be intact, resembling a normal limb, or telescoped and shrunken so that the proximal portion of the limb is perceived to be missing or shortened, with the more distal portion floating near the stump. Occasionally, PL patients perceive that the missing limb is swollen or enlarged compared with the intact limb, and a majority of PL patients suffer from perceived pain in the missing limb. A new therapy called mirror visual feedback, in which the patient views the amputated limb "moving" (through a mirror reflection of the intact limb), has been shown to both alleviate the PL pain and cause qualitative changes in various sensations and aspects of the PL experience (Sumitani et al., 2008; Chan et al., 2007; Hunter et al., 2003; Ramachandran and Roger-Ramachandran, 1996). A variety of PL experiences appear to be associated with neural plasticity within the CNS (Flor et al., 2006). In particular, cerebral reorganization in the primary somatosensory cortex (S1) accurately correlates with PL experiences. For example, phantom hand movement of a completely telescoped PL creates activity in the S1 cortical region that normally manifests the shoulder somatotopy, indicating enlargement of the hand region in S1. Phantom hand movement of a partially telescoped PL creates activity in the S1 region of the arm under normal circumstances, and that of a non-telescoped PL activates the hand region (Flor et al., 2006). Thus, the perceived size of the PL appears to be regulated according to the size of the hand region in S1.

Following physiological deafferentation (by local anesthesia) of a body part, the somatotopic region responding to the body part in S1 shrinks promptly (Rossini et al., 1994). Anecdotal evidence of feeling enlargement of affected body parts following dental anesthesia and psychological findings (Gandevia and Phegan, 1999) clearly indicate that physiologically deafferentated body parts are perceived to be expanded. Feeling the enlargement of a physiologically deafferentated body part appears to correlate with somatotopic shrinkage of the region responding to the body part in S1. Furthermore, complex regional pain syndrome (CRPS) patients report that they feel their affected hand more largely than the actual

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hand (Moseley, 2005), and the somatotopic region of the affected hand shrinks (Pleger et al., 2004; Maihofner et al., 2003). Thus, concerning the relationship between hand-size perception and somatotopic reorganization of the hand region in S1, physiological deafferentation and CRPS seem to contradict PL data.

Hand size plays a crucial role in handling instruments (Seo and Armstrong, 2008), suggesting that hand size representation in the CNS would be important for understanding manual dexterity (Wiesendanger and Serrien, 2001). However, we do not yet fully understand how hand size is represented in the CNS. The purpose of the present series of experiments is twofold: first, to ascertain hand-size perception in varied patients with neuropathic pain conditions and to extract any regulatory rules of perceiving hand size, and second, to seek any characteristics that could indicate a more objective evaluation of size perception in cases of PL because all studies to date have relied on patients' direct reports about their PL perceptions due to the subjective nature of PL experiences.

## 2. Materials and methods

### 2.1. Experiment 1

#### 2.1.1. Participants

Subjects were 10 normals (mean age 46.6 ± 10.5; all statistics reported as mean ± SD; all-right handed) and 17 patients with pathological pain in one hand [affected hand: left 11, right 6; mean age 57.6 ± 13.6; an 11-point numerical rating scale (NRS) of pain intensity 5.8 ± 1.4; disease duration 23.6 ± 21.3 week]. All of the patients were diagnosed with CRPS type 1, in accordance with the IASP diagnostic criteria (Merskey and Bogduk, 1994). Table 1 provides demographic and clinical information on the patients. All participants had normal or corrected-to-normal eyesight and each gave their informed consent to participate in the study. None of them showed any clinically apparent cerebral dysfunction.

#### 2.1.2. Procedure

Digital images of the palm and back of the intact hand were taken using a flatbed-scanner. This was done instead of taking images of the affected limb because some patients reported severe allodynia in the affected hand. We left–right reversed these images, yielding identically sized hand images for each subject that appeared to be the front and back of the left and right hands (four perspectives per subject). Each of the four images was digitally scaled in two dimensions to a range of sizes (70–130% of actual size), in 1% increments. We presented the range of image sizes for one hand-perspective in ascending order (70–130%) and then descending order (130–70%), or vice-versa, on a video-monitor positioned at eye-level. The subject was comfortably seated in front of the monitor 50 cm away, placing their hands palm-down on the monitor stand at waist-level, and the hands were covered up by a black opaque cloth. Following the experimenter's description about the laterality (left or right) and posture (front or back) of the hand image presented on the monitor, the subjects were asked to choose the image (verbally) that most closely matched the size of their own hand. Each of the four hand-perspective images were presented separately. Four study-blocks of each hand-perspective image were conducted in a random order. We averaged the two judgments for each of the four hand-perspectives. Then, to obtain one measure for each hand per subject, we averaged the front and back perceptions for the left and right hand separately, and thus measured subjective hand-size perceptions.

#### 2.1.3. Data analysis

A Kruskal–Wallis test was performed to test whether there was any difference among left and right hand-size perceptions of normals and the affected and intact hand-size perceptions of the patients. We used the Spearman's rank correlation analysis to assess the relationships between left and right hand-size perceptions, between age and the hand-size perceptions, between pain intensity and the hand-size perceptions, and between disease durations and the hand-size perceptions. We also took objective data on the appearance of the affected hand (i.e., edematous, normal, and atrophic). After termination of the procedures, we asked all patients to verbally report whether they perceived the affected hand as expanded, shrunken, or within the normal range of size. Procedures were approved by the institutional ethics committee and complied with the Declaration of Helsinki.

### 2.2. Results

There was no difference among respective hand-size perceptions of normals and patients ($p = 0.90$). Normals perceived the left hand to be as large as the right hand (left 98.1 ± 1.9%; right 98.1 ± 1.7%; Spearman's rank correlation analysis: $p < 0.02$, $R^2 = 0.64$). The patients perceived their intact hand to be the same size as the affected hand (intact 97.5 ± 6.0%, affected 96.8 ± 7.1%; Spearman's rank correlation analysis: $p < 0.0001$, $R^2 = 0.82$) (Fig. 1). The patients showed a larger dispersion of hand-size perceptions than normals, and the data for many of the patients fell at the extremes of the normal range (Fig. 1). We found no significant correlation between age and hand-size perceptions (affected hand: $p = 0.27$; intact hand: $p = 0.60$), between pain intensity and hand-size perceptions (affected hand: $p = 0.60$; intact hand: $p = 0.74$) or between disease duration and hand-size perceptions (affected hand: $p = 0.40$; intact hand: $p = 0.22$).

The patients with enlarged hand-image perspectives reported verbally that they felt their affected hand expanded; those with

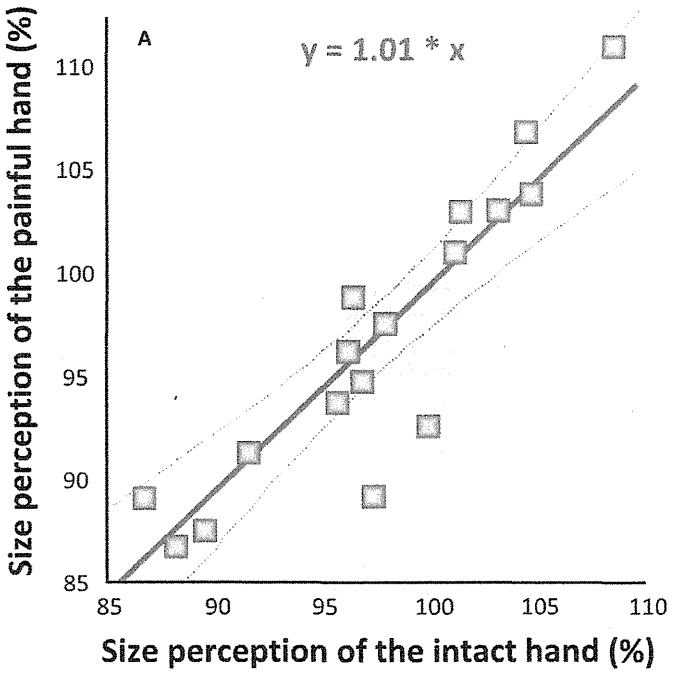


**Fig. 1.** Scatter plots showing the relationship in individual patients between size perceptions of the intact and pathologically painful hands. Green areas represent the normal range of hand-size perception (10–90 percentiles: 95.7–100.1%) obtained from normal subjects ($n = 10$). Each square represents performance of individual patients with pathological pain in one hand. Spearman correlation analysis reveals that bilateral hands are represented in a homologous manner ($p < 0.0001$, $R^2 = 0.82$), suggesting that a distorted size perception of the affected hand "spreads" to one's perception of the intact hand size. Dotted lines indicate 95% confidence limit for the regression line.

**Table 1**
Demographic features and results of patients with CRPS.

| Patient | Age (year) | Sex | Affected side | Duration (week) | NRS | Appearance of the affected hand | Subjective feeling of the affected hand size | Size judgment of the intact hand | Size judgment of the affected hand |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 72 | Male | Left | 9 | 6 | Atrophic | Shrinking | 97.25 | 89.25 |
| 2 | 74 | Male | Left | 6 | 5 | Edematous | Shrinking | 95.5 | 93.75 |
| 3 | 38 | Male | Left | 34 | 8 | Normal | Enlarged | 103 | 103 |
| 4 | 54 | Female | Left | 25 | 4 | Normal | Enlarged | 104.25 | 106.75 |
| 5 | 68 | Female | Left | 8 | 6 | Edematous | Enlarged | 101 | 101 |
| 6 | 68 | Female | Left | 10 | 8 | Edematous | Shrinking | 88.25 | 86.75 |
| 7 | 70 | Female | Left | 43 | 7 | Atrophic | Normal | 97.75 | 97.5 |
| 8 | 37 | Male | Left | 35 | 3 | Normal | Normal | 96.25 | 98.75 |
| 9 | 53 | Male | Left | 28 | 5 | Normal | Normal | 96 | 96.25 |
| 10 | 64 | Female | Left | 6 | 7 | Normal | Enlarged | 104.5 | 103.75 |
| 11 | 66 | Female | Left | 8 | 5 | Atrophic | Shrinking | 99.75 | 92.5 |
| 12 | 62 | Male | Right | 20 | 7 | Edematous | Shrinking | 96.75 | 94.75 |
| 13 | 29 | Female | Right | 88 | 6 | Atrophic | Shrinking | 89.5 | 87.5 |
| 14 | 47 | Female | Right | 14 | 5 | Normal | Enlarged | 101.25 | 103 |
| 15 | 69 | Female | Right | 9 | 7 | Edematous | Shrinking | 86.75 | 89 |
| 16 | 48 | Female | Right | 12 | 6 | Atrophic | Enlarged | 108.25 | 111 |
| 17 | 60 | Female | Right | 46 | 4 | Normal | Shrinking | 91.5 | 91.25 |
| Mean ± SD | 57.6 ± 13.6 | | | 23.6 ± 21.3 | 5.8 ± 1.4 | | | 97.5 ± 6.0 | 96.8 ± 7.1 |

**Table 2**
Demographic features and results of patients with phantom hand.

| Patient | Age (year) | Sex | Affected side | Duration (week) | NRS | Number of times of the hand size evolution | Movement representation of the phantom hand | Subjective feeling of the phantom hand size | Size judgment of the intact hand | Size judgment of the phantom hand |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 75 | Female | Left | 4 | 5 | Three times | Absence | Normal | 95 | 99.25 |
| 2 | 22 | Male | Left | 4 | 5 | Twice | Presence | Shrinking | 102.25 | 93.75 |
| 3 | 67 | Male | Left | 2 | 8 | Once | Presence | Shrinking | 95.5 | 93.75 |
| 4 | 48 | Male | Left | 28 | 8 | Twice | Absence | Shrinking | 90.5 | 84.75 |
| 5 | 44 | Male | Left | 56 | 5 | Once | Presence | Enlarged | 103.75 | 105.75 |
| 6 | 47 | Male | Right | 900 | 8 | Three times | Presence | Shrinking | 90.5 | 93.25 |
| 7 | 64 | Male | Right | 3 | 5 | Once | Absence | Normal | 104.75 | 98.75 |
| 8 | 65 | Male | Right | 3 | 5 | Twice | Absence | Shrinking | 89.25 | 89 |
| 9 | 62 | Male | Right | 2 | 6 | Once | Absence | Normal | 99.75 | 99.25 |
| 10 | 70 | Female | Right | 16 | 6 | Three times | Absence | Shrinking | 95.5 | 93.75 |
| Mean ± SD | 56.4 ± 16.0 | | | 101.8 ± 281.0 | 6.1 ± 1.4 | | | | 96.7 ± 5.7 | 95.1 ± 5.9 |

small hand-image perspectives reported feeling the reduced size of the affected hand; and those with normal hand-image perspectives (within 10–90 percentile of normals) clearly reported feeling an ordinal size of the affected hand (Table 1). Thus, the hand-size evaluation by presentation of hand-image perspectives that we used here completely corresponded with the subjectively reported size of the affected hand. Some patients presented with swelling of the affected hand, some showed a normal appearance (but sudomotor abnormality and/or skin color change), and others presented with a severely atrophic appearance. Results of the hand-size evaluation were inconsistent with the actual appearance of the affected hand, suggesting that CRPS patients tend to misperceive size of the affected hand (Table 1).

### 2.3. Experiment 2

Ten patients with a painful phantom hand (affected side: left 5, right 5; disease: post-amputation PL 6, post-brachial plexus injury supernumerary PL 4; mean age: 56.4 ± 16.0; NRS: 6.1 ± 1.4D; disease duration: 101.8 ± 281.0 week) participated in Experiment 2 after giving informed consent (Table 2). Four patients participated in this study once, three patients participated twice and three patients participated three times. We therefore conducted Experiment 2 using a total of 19 patients. The experimental procedure was exactly the same as in Experiment 1, except in evaluating the appearance of the affected hand. The weighted linear regression analysis was performed with the phantom hand-size perception as a dependent variable and the intact hand-size perception was used as an independent variable. We additionally took dichotomous data on the perceived phantom hand movement (i.e., presence or absence) and analyzed the relationship between the movement representation and the hand-size perceptions by Spearman's rank correlation.

### 2.4. Results

The intact hand-size perception linearly matched the subjectively perceived phantom hand size (intact 96.7 ± 5.7%; phantom 95.1 ± 5.9%; the weighted linear regression analysis: $p < 0.0001$, $R^2 = 0.75$, adjusted $R^2 = 0.73$, $F$-value = 50.1, degree of freedom = 18) (Fig. 2). After termination of the procedures, we asked all PL patients to verbally report whether they perceived the phantom hand to be expanded, shrunken, or within the normal range of size. Our hand-size evaluation by presentation of hand-image perspectives completely corresponded with their subjectively perceived size of the phantom hand. Our evaluation therefore could consistently reveal the alteration of the phantom hand-size perception in numerical terms, although some of the patients who made multiple evaluations reported a different size perception of the phantom hand in each evaluation. Furthermore, although some patients showed expanded and shrunken hand-size perception at each of the multiple evaluations, the one-to-one linear correlation between the intact hand size and the phantom hand size was maintained. We found no significant correlation between hand-size perceptions

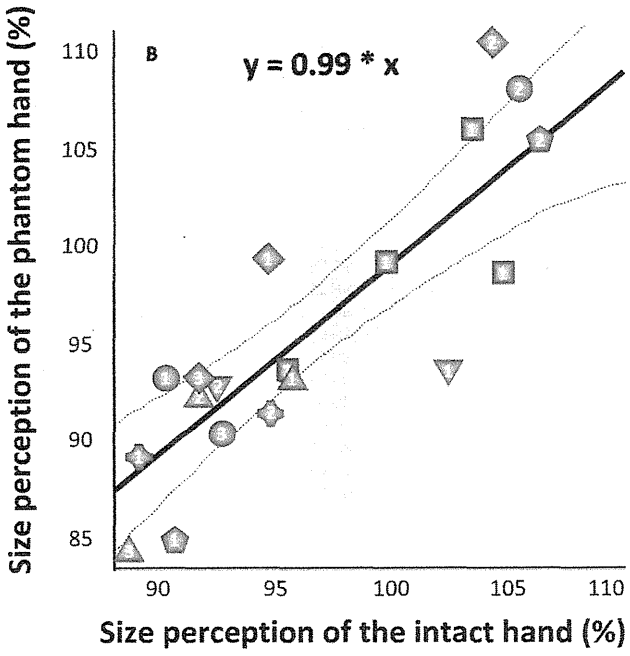


**Fig. 2.** Scatter plots showing the relationship in individual patients between size perceptions of the intact and phantom hands. Each symbol represents performance of individual patients with a phantom hand. Digits in the symbols indicate the number of times in which hand size was evaluated: Four patients participated once (squares); three participated twice (crisscrosses, pentagons and inverted triangles); and three patients participated three times (circles, diamonds and triangles). Weighted linear regression analysis shows that distortion of the intact hand-size perception precisely reflects that of the phantom hand-size perception ($p < 0.0001$, $R^2 = 0.75$, adjusted $R^2$=0.73, $F$-value = 50.1, degree of freedom = 18; otherwise as in Fig. 1).

and age (phantom hand: $p = 0.85$; intact hand: $p = 0.48$), pain intensity (phantom hand: $p = 0.15$; intact hand: $p = 0.13$), disease duration (phantom hand: $p = 0.80$; intact hand: $p = 0.33$) or movement representation (phantom hand: $p = 0.56$; intact hand: $p = 0.59$).

## 3. Discussion

Based on psychophysical findings (Gandevia and Phegan, 1999) and anecdotal evidence of feeling enlargement of affected body parts following dental anesthesia or a painful blow, it has been widely assumed that nociceptive pain or physiological deafferentation (by local anesthesia) expands sensory representation of the body parts. Some results of our pathological pain patients with or without deafferentation (by nerve injury) were in accord with the expanded sensory representation of the affected hand. Additionally, supporting evidence comes from our limited number of CRPS patients ($n = 3$): therapeutic deafferentation (Bier block: 1% lidocaine at 20 ml for the affected limb) acutely induced not only feeling size-enlargement of the affected hand but also that of the intact hand (data not shown). However, the present study showed that sensory representation of the pathological hand did not necessarily expand. Rather, some patients showed a much smaller sensory representation of the hands than normals. A common phenomenon regarding phantom limb is 'telescoping', which is when the affected limb is sensed as foreshortened and shrinking, despite the intense pain. Furthermore, CRPS patients and other neuropathic pain patients sometimes have an involuntary neurological neglect-like behavior, whereby they perceive their affected limb as not being part of their body and it feels foreign to them (known as "cognitive neglect") (Frettloh et al., 2006; Galer and Jensen, 1999). This neglect-like behavior might be associated with reduced size perception of the affected hand, which has been observed in hemispatial neglect patients (Robertson, 1999). Our results may be in accord with such reduced-size sensory representation of the affected body parts.

In Experiment 1, we found that left and right hand sensory representations are homologous in both normals and patients with a pathological hand (i.e., CRPS). And then, in Experiment 2, we validated the homology even if the pathological hand is incorporeal, by using patients with etiologies (i.e., phantom limb pain) that are distinct from CRPS. By conducting this two-stage experiment, we ascertained that the homology of the left and right hand sensory representations can be a universal response. Further, the homology of the left and right hand sensory representations is coherently maintained when the representation of one hand alters at any given time. These results suggest that the distorted sensory representation of an intact hand implicitly reflects that of the pathological hand. That is, without requiring a subjective description about PL, the patients' evaluation of the intact hand-size precisely but indirectly indicated whether the PL was perceived to be telescoped (shrunken), normal or enlarged. Thus, we can access the sensory representation of a phantom hand independent of the patients' subjective description of it, for a more objective evaluation of PL phenomena. What is the determinant of such homologous sensory representations of the two hands? There is a substantial cluster of neurons in the primary and secondary somatosensory cortex with symmetrically bilateral receptive fields representing the hands (Iwamura, 1998; Iwamura et al., 1994). Somatosensory information from bilateral hands would be convergent to one sensory representation in the hierarchical somatosensory processing, and possibly our finding that a pair of hands is perceived homologically indicates a behavioral outcome of the convergent sensory representation of bilateral hands. Practically, humans can transfer sensory information from one hand to the other, thereby coordinating appropriate motor actions without necessarily having direct sensory information for the second hand (e.g., after lifting an object with one hand, humans can often generate the precise grip force that would be needed to lift the same object with the other hand) (Gordon et al., 1994). Convergent sensory representation of bilateral hands might serve such inter-limb sensory transfer. Additionally, local anesthesia at the intact limb contralateral to the painful limb displayed a clear analgesic effect (Gross, 1984). This mysterious treatment might relate to convergent sensory representation, proposed here. In conclusion, convergent sensory representation of bilateral hands would offer a profound breakthrough in elucidating how the brain interacts with the body, and with bilateral hands in particular. More objective evaluation of PL experiences could help disentangle the neural mechanisms involved.

The present study has one main limitation. Different from Moseley's study using the affected hand image (Moseley, 2005), we did not ascertain whether CRPS patients perceive their affected hand more largely than the actual affected hand image. Since one of our purposes was to find any characteristics indicating a more objective evaluation of phantom hand size, and we could not use an actual image of a phantom hand, we conducted a common evaluation for patients with CRPS and PL. In future investigations about hand-size perception of CRPS patients, strict classification of CRPS-associated symptoms and signs (e.g., swelling, cognitive neglect, and so on) should be prepared and then the hand-size perception should be evaluated. In addition, using CRPS patients without allodynia, the evaluation in which the hand-image perspectives are derived from the actual affected hand, as in the Moseley study, might reveal that the affected hand-size perception really matches the actual size of the affected hand and the intact hand-size perception.

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# Modulation of neuronal activity after spinal cord stimulation for neuropathic pain; $H_2{}^{15}O$ PET study

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ABSTRACT

Spinal cord stimulation (SCS) is an effective therapy for chronic neuropathic pain. However, the detailed mechanisms underlying its effects are not well understood. Positron emission tomography (PET) with $H_2{}^{15}O$ was applied to clarify these mechanisms. Nine patients with intractable neuropathic pain in the lower limbs were included in the study. All patients underwent SCS therapy for intractable pain, which was due to failed back surgery syndrome in three patients, complex regional pain syndrome in two, cerebral hemorrhage in two, spinal infarction in one, and spinal cord injury in one. Regional cerebral blood flow (rCBF) was measured by $H_2{}^{15}O$ PET before and after SCS. The images were analyzed with statistical parametric mapping software (SPM2). SCS reduced pain; visual analog scale values for pain decreased from $76.1 \pm 25.2$ before SCS to $40.6 \pm 4.5$ after SCS (mean $\pm$ SE). Significant rCBF increases were identified after SCS in the thalamus contralateral to the painful limb and in the bilateral parietal association area. The anterior cingulate cortex (ACC) and prefrontal areas were also activated after SCS. These results suggest that SCS modulates supraspinal neuronal activities. The contralateral thalamus and parietal association area would regulate the pain threshold. The ACC and prefrontal areas would control the emotional aspects of intractable pain, resulting in the reduction of neuropathic pain after SCS.

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## Introduction

Neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system (Loeser and Treede, 2008). It is generally more severe and more likely to be drug-resistant and persistent than nociceptive pain (Finnerup et al., 2005; Dworkin et al., 2003). Thus, chronic pain is often under-diagnosed and under-treated (Taylor, 2006), and it impairs quality of life. The causes of neuropathic pain vary and include such conditions as failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), central post-stroke pain, phantom limb pain, peripheral and central nerve system injury, and post-spinal cord injury pain (Dworkin et al., 2003). Chronic neuropathic pain is most common in the back and legs.

Shealy et al. (1967) were the first to report that electrical stimulation of the dorsal spinal cord relieves cancer pain. Spinal cord stimulation (SCS) has since been applied not only to numerous cases of intractable pain but also to other conditions such as angina pectoris (AP), ischemic pain, and persistent vegetative state (Morita et al., 2007; Börjesson et al., 2008; Pedrini and Magnoni, 2007). Taylor (2006) reported that SCS not only reduces the pain but also improves quality of life in patients with FBSS or CRPS. He also reported that SCS is a cost-saving therapy. Kumar et al. (2007) reported that SCS provides better pain relief than conventional medical management alone in FBSS patients, and this was supported by a multicenter trial (Manca et al., 2008). Furthermore, the European Federation of Neurological Society guidelines support the effect of SCS in patients with FBSS or CRPS (Cruccu et al., 2007). For the central pain (spinal cord or brain lesions), SCS was reported to have some effect for pain relief. Katayama et al. (2001) reported that 7% of post-stroke pain patients revealed pain reduction with SCS and Kumar et al. (2006) also reported that SCS relieved 79% of the chronic pain due to multiple sclerosis. Thus, SCS is an essential treatment for relief of chronic neuropathic pain.

Oakley and Prager (2002) investigated some of the mechanisms underlying relief of pain by SCS. SCS was shown to stimulate the neurons of the dorsal horn of the spinal cord to release increased amount of acetylcholine and GABA and decreased amounts of aspartate and glutamate in rat models (Meyerson and Linderoth,

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2000; Schechtmann et al., 2008). SCS was also shown to induce neurophysiological change, normalizing neuronal hyperexcitability in the dorsal horn (Yakhnitsa et al., 1999). In addition to these spinal mechanisms, functional alteration at the supraspinal level has been suggested to play an important role in pain reduction. Physiological study revealed cortical modulation during SCS (Polácek et al., 2007; Schlaier et al., 2007). However, the mechanism of pain relief by SCS is not fully understood. Brain activation during SCS has been analyzed by means of $H_2{}^{15}O$ positron emission tomography (PET) in patients with AP (Hautvast et al., 1997) and by means of functional magnetic resonance imaging (fMRI) in patients with FBSS (Kiriakopoulos et al., 1997; Stancák et al., 2008).

The investigators reported that SCS activates the primary and secondary sensorimotor cortex, cingulate cortex, insula, thalamus, and premotor cortex. Pain relief continues for several hours after SCS, so most patients with chronic pain use SCS intermittently, for example, several times per day. The modulation of brain activity after SCS has not been thoroughly examined.

In the present study, we used $H_2{}^{15}O$ PET to investigate the pattern of SCS-related neuronal activation and/or attenuation before and after SCS. $H_2{}^{15}O$ PET visualizes regional cerebral blood flow (rCBF), which reflects focal neuronal activation (Kapur et al., 1994). We also used statistical parametric mapping of normalized brain images to identify functionally specialized brain responses.

## Materials and methods

### *Patients and surgical procedure*

Nine patients (six men and three women) with intractable neuropathic pain in their lower extremities were included in this study (Table 1). Patients ranged in age from 28 to 65 years. The intractable neuropathic pain was due to FBSS in three patients, CRPS in two, cerebral hemorrhage in two, spinal cord infarction in one, and spinal cord injury in one. Pain was left-sided in five patients, right-sided in two patients, and bilateral in two patients. One of two patients with bilateral pain (patient 3) had more severe pain in right leg and the other (patient 8) had more severe pain in left leg. Their purposes of SCS were to reduce the pain in the more painful leg. Medical therapy had not been satisfactory, and the nine patients suffered from the intractable pain for 31 to 147 months before SCS was tried. Five of the nine patients showed slight to moderate motor weakness, and all had slight to severe sensory disturbance in the affected legs (Table 1). A visual analog scale (VAS), ranging from 0 to 100, and the short form of the McGill Pain Questionnaire (SF-MPQ) were used to evaluate the degree of pain.

The standard surgical procedure was used to place the SCS lead. In brief, under local anesthesia, a quadripolar electrode lead (Pisces Quad, 3487A; Medtronic, Inc., Minneapolis, MN, USA) was inserted percutaneously into the epidural space of the lumbar or thoracic spine by fluoroscopic guidance. The electrode was finally positioned after electrical sensation was detected in the region of pain upon stimulation. After confirmation of pain reduction in response to stimulation for 5–10 days, the electrode was connected to a subcutaneously implanted stimulator (Itrel III; Medtronic, Inc.).

Habitual bipolar stimulation was used for pain relief, and stimulation parameters varied between patients. General stimulation parameters were as follows: voltage, max 10 V; frequency, 10–85 Hz; pulse width, 210 to 450 μs; and duration of stimulation, 30 min. The patients controlled the stimulation at will and used SCS for at least 6 months before the PET study.

### *PET scanning procedure and activation task*

The PET study was performed 6 to 12 months after implantation of the stimulation electrode. A Headtome-V PET scanner (Shimadzu, Kyoto, Japan) was used to scan in the three-dimensional acquisition mode with a shield to protect against scattered rays. Patients went without spinal cord stimulation for more than 12 h before the PET study. The patients lay with eyes closed in a silent and dim room. A 15-min transmission scan was acquired first with $^{68}Ge$ sources to correct for γ-ray attenuation. Relative CBF was measured based on the distribution of radioactivity after a slow bolus i.v. injection of $H_2{}^{15}O$ (7 mCi/scan, each lasting 90 s). Six PET scans corresponding to six $H_2{}^{15}O$ injections were obtained before SCS, SCS was performed for 30 min under the habitual condition, and six PET scans were obtained after pain reduction was confirmed. The PET protocol was the same as the motor cortex stimulation (MCS) protocol described previously (Kishima et al., 2007).

### *Data analysis*

Attenuation-corrected data were reconstructed into an image (voxel sizes, 2×2×3.125 mm; field of view, 256×256×196 mm) with a resulting resolution of 4×4×5 mm at FWHM (full width at half maximum). The images were analyzed with statistical parametric mapping (SPM) software (SPM2; Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1991). PET images were anatomically normalized to fit with ICBM coordinates of the Montreal Neurological Institute. Images from each patient were realigned to the first volume of PET images and normalized to the template (Friston et al., 1995a) to account for variation in gyral anatomy and inter-individual variability in the structure–function relation and to improve the signal-to-noise ratio. This procedure was used for image realignment, anatomic normalization, smoothing (12 mm at FWHM), and statistical analysis (Kiebel et al., 1997). Data were normalized to global blood flow (average = 50). State-dependent differences in global blood flow were subjected to ANCOVA.

All nine patients were included in the same statistical analyses, with voxel-to-voxel comparison. Statistical parametric maps (SPM) were generated with an ANOVA model with the General Linear Model formulation of SPM2 (Friston et al., 1995b). We analyzed the main effect of SCS by comparing images obtained after SCS with those

**Table 1**
General characteristics of patients with deafferentation pain.

| Patient | Age (years), sex | Etiology of pain | Pain laterality | Motor (0–5) | Sensory (0–10) | Duration of pain (months) | Pre-SCS VAS | Post-SCS VAS |
|---|---|---|---|---|---|---|---|---|
| 1 | 44, M | Spinal infarction | Rt | 4 | 4 | 36 | 80 | 40 |
| 2 | 60, F | Putaminal hemorrhage | Lt | 4 | 10 | 99 | 100 | 55 |
| 3 | 65, F | FBSS | Bi (Rt > Lt) | 5 | 10 | 147 | 90 | 30 |
| 4 | 45, M | CPRS | Lt | 2 | 2 | 65 | 60 | 20 |
| 5 | 41, M | FBSS | Rt | 3 | 5 | 54 | 85 | 25 |
| 6 | 28, F | CRPS | Lt | 2 | 2 | 31 | 70 | 60 |
| 7 | 59, M | Putaminal hemorrhage | Lt | 5 | 1 | 59 | 55 | 50 |
| 8 | 50, M | Spinal injury | Bi (Rt < Lt) | 5 | 6 | 42 | 60 | 40 |
| 9 | 38, M | FBSS | Lt | 5 | 10 | 57 | 85 | 45 |

FBSS, failed back surgery syndrome; CRPS, complex regional pain syndrome; Rt, right; Lt: left; Bi, bilateral; Motor, MMT score (0, complete paresis; 5, normal); Sensory, sensory scores (0, anesthesia; 10, normal); Pre-SCS VAS, VAS of pre-SCS; Post-SCS VAS, VAS of post-SCS.

**Table 2**
Increased rCBF after SCS.

| Area | Cluster | | Talairach coordinates (x, y, z mm) | Voxel equiv. Z |
|---|---|---|---|---|
| | p (corrected) | Size (voxels) | | |
| (A) Rt thalamus | 0.006 | 197 | 11.9, −15.6, 0.0 | 4.64 |
| (B) Rt orbitofrontal (BA11) | 0.040 | 161 | 43.6, 51.8, −12.7 | 4.70 |
| (C) Lt Inf. parietal (BA7) | 0.009 | 178 | −33.7, −61.8, 45.5 | 4.39 |
| (D) Rt Sup. parietal (BA7) | 0.014 | 158 | 37.6, −45.9, 53.9 | 4.57 |
| (E) Lt anterior cingulate (BA24) | 0.001 | 301 | −7.98, 38.1, 23.4 | 4.64 |
| (F) Lt dorsolateral prefrontal (BA10) | 0.050 | 100 | −33.7, 36.0, 18.4 | 4.27 |

Rt, right; Lt, left; Inf, inferior; Sup, superior.

obtained before SCS, with the statistical threshold set at $p<0.02$ (corrected for multiple comparisons) in False Discovery Rate (FDW) for peak height, corrected for spatial extent (>8 voxels per cluster), and the cluster size was set at 100 contiguous voxels.

This method was used to generate SPM ($t$) of rCBF changes associated with each comparison. For between-group comparisons, the SPM ($t$) maps were transformed into SPM ($z$), and the levels of significance of areas of activation were assessed according to the peak height of foci estimation based on the theory of random Gaussian fields.

Three patients had been treated to reduce the right lower limb pain (patients 1, 3, and 5). MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html) was used to invert the images obtained from these patients from the right to the left so that statistical analysis would be consistent with that of other patients. The images were then realigned, normalized, and analyzed as previously described. Furthermore, to detect the correlation of the rCBF change and SCS efficacy, these images were performed covariance analysis with the VAS reduction rate after SCS ((pre-VAS – post-VAS) / pre-VAS).

Significance was accepted if a cluster showed a cluster corrected threshold of $p<0.05$. Anatomical locations were indicated according to the atlas of Talairach and Tournoux (1988).

This study adhered to the guidelines of the Declaration of Helsinki on the use of human subjects in research, and the patients provided written informed consent. This study was approved by the ethics committee of Osaka University Hospital.

## Results

### *Pain reduction after SCS*

After SCS, all nine patients showed various degrees of pain reduction according to VAS data (76.1 ± 25.2 to 40.6 ± 4.5) (Table 1). The pain reduction began during SCS and continued for at least 120 min after SCS. The degree of pain reduction remained stable for 60 min during the post-SCS PET scanning phase. In general, results of the SF-MPQ were for the most part compatible with VAS scores.

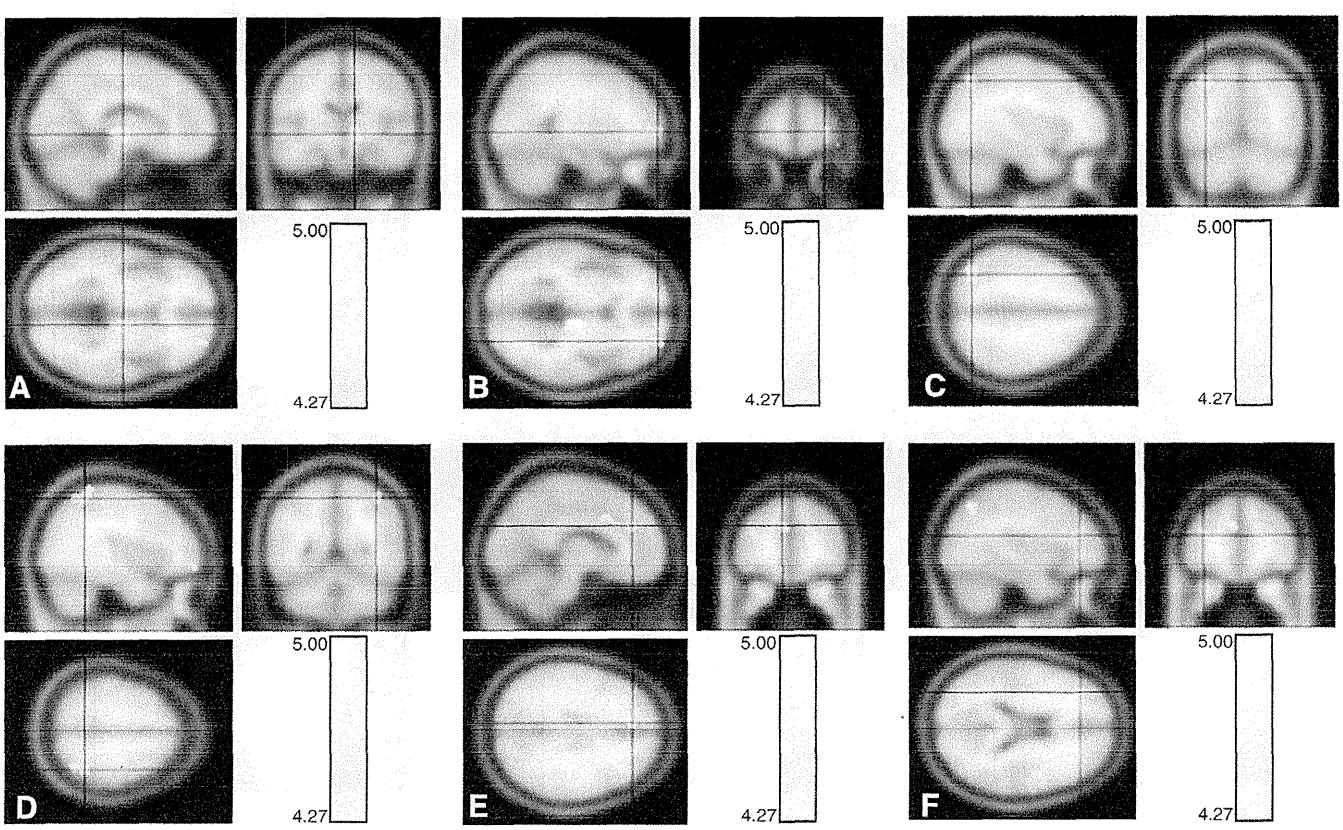


**Fig. 1.** Statistical parametric maps ($Z$ maps) of intensity in normalized images. Comparison of rCBF before and after SCS shows that rCBF is increased after SCS in the right thalamus (A), right orbitofrontal cortex (BA11) (B), left inferior parietal lobule (C), right superior parietal lobule (D), left anterior cingulate cortex (E), and left dorsolateral prefrontal cortex (F). Colored bar indicates $Z$ value (threshold, $p<0.05$). Panels A–F correspond to Table 2.

**Table 3**
Increased rCBF after SCS in reference to the affected side.

| Area | Cluster | | Talairach coordinates (x, y, z mm) | Voxel equiv. Z |
|---|---|---|---|---|
| | p (corrected) | Size (voxels) | | |
| (A) C. Inf. parietal (BA40) | 0.002 | 207 | 30.9, −47.9, 53.5 | 5.48 |
| (B) C. Inf. parietal (BA40) | 0.003 | 432 | 43.2, −46.0, 30.8 | 4.96 |
| (C) C. dorsolateral prefrontal (BA10) | 0.004 | 169 | 25.6, 56.8, 6.2 | 4.78 |
| (D) C. anterior cingulate (BA24) | 0.005 | 183 | 8.0, 18.0, 30.6 | 4.55 |
| (E) I. lateral precentral (BA6) | 0.01 | 109 | −46.6, 0.6, 10.3 | 4.22 |
| (F) C. thalamus | 0.011 | 108 | 8.0, −16.9, −1.14 | 4.17 |
| (G) I. dorsolateral prefrontal (BA9) | 0.013 | 128 | −27.2, 25.8, 25.7 | 4.06 |
| (H) I. orbitofrontal (BA10) | 0.014 | 143 | −34.2, 43.2, −8.6 | 4.02 |
| (I) I. Sup. parietal (BA7) | 0.018 | 127 | −27.2, −67.3, 35.0 | 3.85 |

I, ipsilateral to affected side; C, contralateral to affected side; Bi, bilateral; Inf, inferior; Sup, superior.

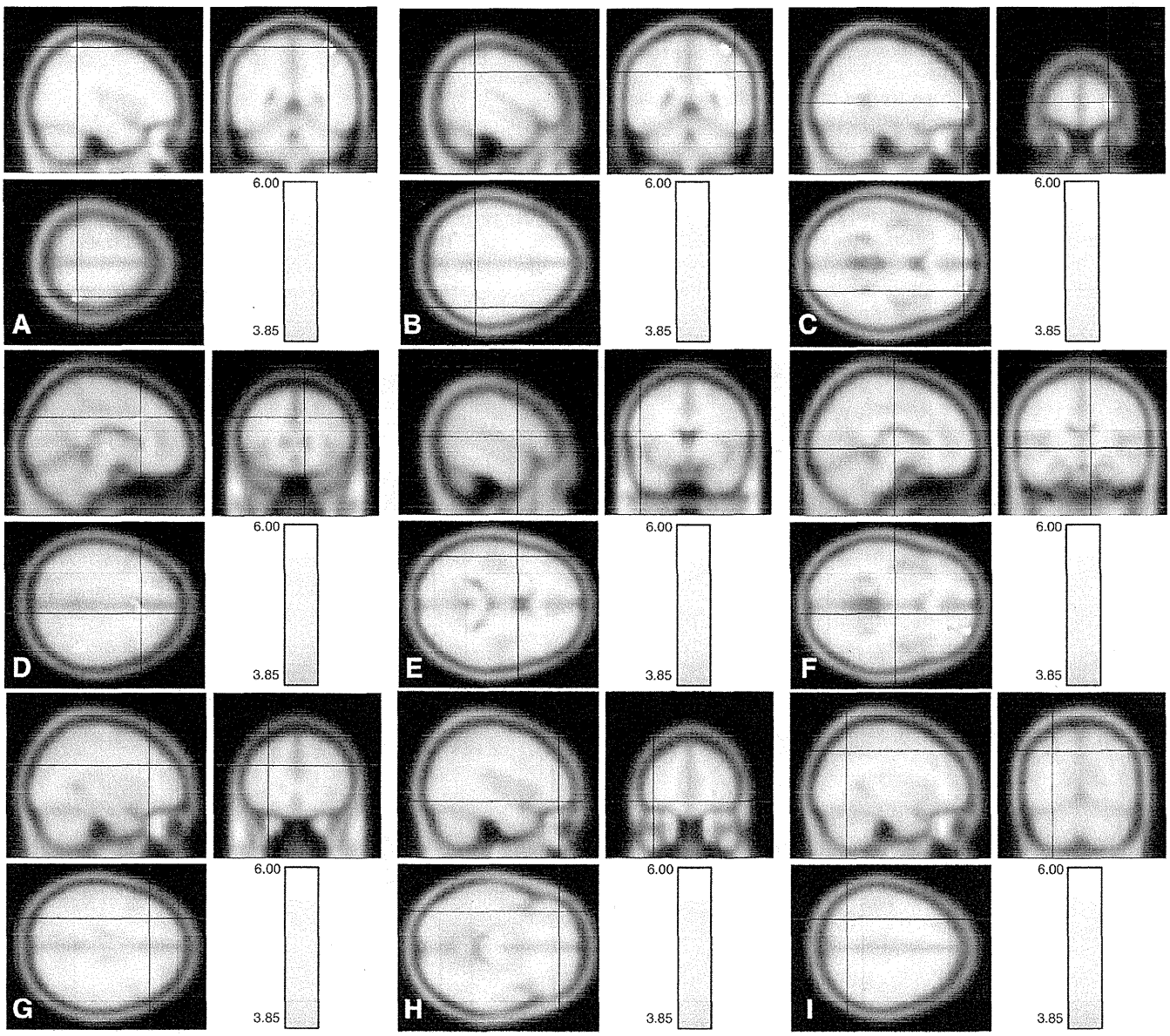


**Fig. 2.** Statistical parametric maps (Z maps) of intensity in normalized images. Comparison of rCBF before and after SCS by positioning the affected sides on the left shows that rCBF is increased after SCS in the contralateral inferior parietal lobules ($Z=5.48$, 4.96) (A, B), contralateral dorsolateral prefrontal cortex (BA10) ($Z=4.78$) (C), contralateral anterior cingulate cortex (BA24) ($Z=4.55$) (D), contralateral orbitofrontal cortex (BA10) ($Z=4.63$) and contralateral medial prefrontal cortex (BA10) ($Z=4.56$), ipsilateral lateral precentral cortex (BA6) ($Z=4.22$) (E), contralateral thalamus ($Z=4.17$) (F), ipsilateral dorsolateral prefrontal (BA9) ($Z=4.06$) (G), ipsilateral orbitofrontal cortex (BA10) ($Z=4.02$) (H), and ipsilateral superior parietal lobule (BA7) ($Z=3.85$) (I). Colored bar indicates Z value. Colored bar indicates Z value (threshold, $p<0.05$). Panels A–I correspond to Table 3.

*Brain activation profiles in response to SCS*

Comparison of rCBF before and after SCS showed significant rCBF increases in the right thalamus ($Z=4.64$), right orbitofrontal cortex (BA11) ($Z=4.70$), left inferior parietal lobule (BA7) ($Z=4.39$), right superior parietal lobule (BA7) ($Z=4.57$), and left anterior cingulate cortex (ACC) (BA24) ($Z=4.64$), and left lateral prefrontal cortex (BA10) ($Z=4.27$) (Table 2, Fig. 1). There was no region where rCBS decreased after SCS.

The result analyzed after three images of patients 1, 3, and 5 were inverted so that the affected side appeared on the left, showed that rCBF was increased in the contralateral (right) inferior parietal lobules ($Z=5.48$, 4.96), contralateral dorsolateral prefrontal cortex (BA10) ($Z=4.78$), contralateral ACC (BA24) ($Z=4.55$), contralateral thalamus ($Z=4.17$), and ipsilateral lateral precentral cortex (BA6) ($Z=4.22$), dorsolateral prefrontal (BA9) ($Z=4.06$), ipsilateral orbitofrontal cortex (BA10) ($Z=4.02$), and ipsilateral superior parietal lobule (BA7) ($Z=3.85$) (Table 3, Fig. 2). There was no region where rCBF decreased after SCS. When these images were performed covariance analysis with VAS reduction rate after SCS, increased rCBF in ipsilateral dorsolateral prefrontal cortex (BA9) ($Z=5.59$), ipsilateral lateral precentral cortex (BA6) ($Z=5.18$), ipsilateral medial prefrontal cortex (BA8) ($Z=4.08$), and contralateral medial prefrontal cortex (BA8) ($Z=4.18$) were positively correlated with pain reduction rate (Table 4, Fig. 3).

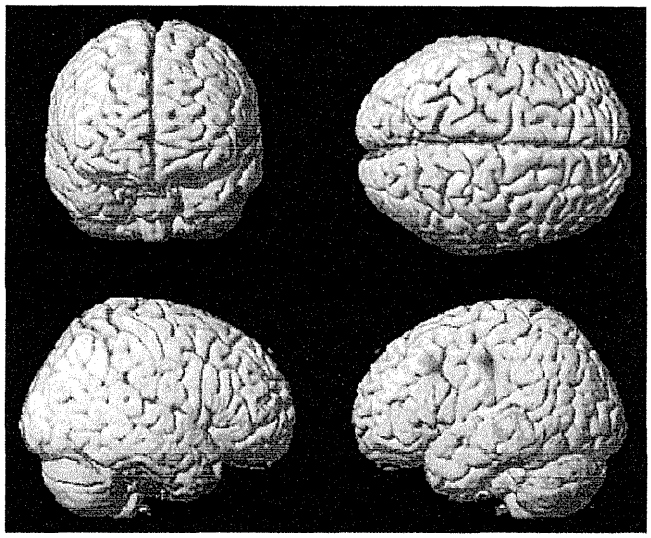

**Fig. 3.** Areas of significantly increased rCBF correlated to the VAS reduction rate after SCS, rendered in the normalized images, indicate ipsilateral to affected side of dorsolateral prefrontal cortex (BA9), ipsilateral lateral precentral cortex (BA6), and bilateral medial prefrontal (BA8) (threshold, $p<0.05$).

## Discussion

This is the first report that rCBF is modified after SCS for chronic neuropathic pain as shown by $H_2{}^{15}O$ PET. rCBF is thought to reflect focal neuronal activation (Kapur et al., 1994). Thus, we concluded that there is a change in neuronal activation after SCS in patients with neuropathic pain. Our study included nine patients who underwent SCS to relieve their neuropathic pain. Although the etiology of chronic pain varied, all nine patients experienced some pain relief with SCS, and all used SCS everyday for more than several months. So we categorized them as SCS responders based on their pain reduction, and we report that the observed rCBF changes may be involved in the pain relieving mechanism of SCS.

We measured neuronal activity with $H_2{}^{15}O$ PET before and after SCS, and all PET images were normalized and then analyzed by SPM (Friston et al. 1991; 1995a,b; Kiebel et al., 1997). Therefore, the results of this study were based on anatomically well-standardized samples. Furthermore, images of three patients having only right-sided pain were reversed to move the affected side to the left and were analyzed with the others. This method statistically enhances the results, especially in pain cognition-related regions.

We found that rCBF increased in the right thalamus and superior parietal lobule (BA7) and left inferior parietal lobule (BA7) after SCS. rCBF was also shown to be increased in the contralateral thalamus and contralateral inferior parietal lobule (BA40), and ipsilateral superior parietal lobule (BA7) when we moved the affected side to the left. BA7 is the secondary somatosensory area (S2), and BA40 is the parietal association area. These areas play important roles for cognition of the somatosensory input.

One interesting finding of this study is that neither the contralateral primary motor cortex (M1) nor S1 corresponding to the affected leg showed rCBF change after SCS. This finding is contrary to previous reports that the contralateral S1 and the contralateral paracentral regions are activated during SCS as shown by electrophysiological methods (Polácek et al., 2007) and fMRI (Stancák et al., 2008). We attribute this difference to the fact that we performed PET scanning before and after SCS rather than during SCS as in the previous studies. During SCS, the patient often feels a stimulating sensation, and this might influence S1. After SCS, this sensation might diminish quickly; consequently, activation of S1 and paracentral regions would normalize. Moreover, the pain relief continues for several hours after SCS. Thus, S2 and the parietal association area are modulated by SCS and would control the threshold of the chronic pain for several hours after SCS.

An important finding is that the contralateral thalamus was shown to be activated in the post-SCS phase after the affected side was adjusted to the left. This finding is contrary to that of a previous report based on fMRI that did not describe thalamic activation during SCS (Stancák et al., 2008). It is also reported that the thalamus contralateral to the painful side shows hypometabolism in cases of central pain (De Salles and Bittar, 1994; Laterre et al., 1998). Hsieh et al. (1995) reported that rCBF in the contralateral thalamus was decreased by the peripheral nerve block with lidocaine in the mononeuropathy patients. We suppose this method might inhibit the sensory input of the peripheral to spinal cord and it might reduce the spino-thalamic information, resulting to the reduction of the contralateral thalamic activity. In our study, however, SCS never blocks the sensory input and it just controls the pain. So the result in this study is different from the previous report of Hsieh et al. Although the detailed role of the contralateral thalamus in the pathology of

**Table 4**
Increased rCBF after SCS covariate with pain reduction rate.

| Area | Cluster | | Talairach coordinates (x, y, z mm) | Voxel equiv. Z |
|---|---|---|---|---|
| | P (corrected) | Size (voxels) | | |
| (A) I. dorsolateral prefrontal (BA9) | 0.001 | 396 | −44.8, 14.1, 32.1 | 5.59 |
| (B) I. lateral precentral (BA6) | 0.002 | 559 | −44.8, −18.8, 34.0 | 5.18 |
| (C) C. Sup. prefrontal (BA8) | 0.008 | 168 | 13.3, 20.0, 53.6 | 4.18 |
| (D) I. Sup. prefrontal (BA8) | 0.01 | 112 | −18.4, 14.1, 49.7 | 4.08 |

I, ipsilateral to affected side; C, contralateral to affected side; Bi, bilateral; Sup, superior.

neuropathic pain remains unclear, it is possible that SCS induces neuronal activity in contralateral thalamus, resulting in pain relief, and that the thalamus alters the pain threshold and sensory cognition after SCS, as previously reported (Garcia-Larrea et al., 1999).

It was shown that the ACC, dorsolateral prefrontal cortex, and orbitofrontal cortex were activated after SCS. The ACC and prefrontal cortex are reported to be involved in the modulation of pain and emotion. The activation of prefrontal cortex and ipsilatearl lateral precentral cortex was correlated with the degree of SCS efficacy (Table 4, Fig. 3). A previous report on MCS showed correlation between pain relief and ACC activation (Kishima et al., 2007; Peyron et al., 2007). Peyron et al. (2007) also reported that the prefrontal region, orbitofrontal region, and ACC act as descending (top–down) inhibitory controls for pain threshold in patients treated with MCS. Ochsner et al. (2004) reported that the prefrontal region and ACC recruit the up- and down-regulation of negative emotion. It has been reported that the activity of the right ventrolateral prefrontal region correlates with reduced negative emotional experience (Wager et al., 2008) and that fear of various types of physical pain predicts activation of the ventrolateral frontal region and anterior and posterior cingulate regions (Ochsner et al., 2006). Furthermore, because the ACC and prefrontal area are components of the brain reward system, it is possible that this system is also activated by SCS. In line with these findings, SCS itself and/or pain relief induced by SCS would control the emotional aspects of pain, resulting in a long lasting effect. The role of ipsilateral precentral area activated after SCS is not clear. The activation of dorsolateral prefrontal regions would reflect the most of the patients' satisfaction.

It was reported that rCBF increases to noxious stimuli are observed in S2, S1, thalamus, ACC, dorsal parietal, and prefrontal area (Peyron et al. 2000). SCS during heat stimuli increased rCBF in S2, S1, and posterior insula (Stancák et al. 2008). Thalamus, ACC, dorsal parietal, S2 and prefrontal regions were activated after SCS with neuropathic pain in this study. In line with those results, we could suppose that both acute pain stimuli and pain reduction by SCS would induce the neuronal activation in the similar regions. After SCS for patients with neuropathic pain, the change of sensory input, pain cognition, attention, and memory network would activate thalamus, parietal areas, ACC, and prefrontal areas.

## Conclusions

For treatment of neuropathic pain, SCS controls pain cognition by modulating the thalamus and parietal association area. SCS also controls the emotional aspects of pain by modulating the prefrontal region and ACC. These findings support the use of SCS for treatment of neuropathic pain.

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JA SYMPOSIUM

# Phantom limb pain in the primary motor cortex: topical review

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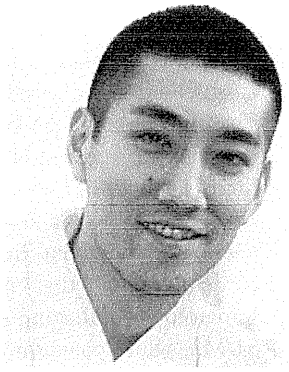

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## Introduction: what is a phantom limb and phantom limb pain?

Following limb amputation, 80% or more of patients perceive the existence of their lost limb, or sensations such as hot–cold or tingling, in the space where their lost limb once existed. The experience of the existence of this lost limb and sensations is known as "phantom limb". Even without limb amputation, phantom limb can develop as a result of motor palsy or sensory deafferentation by cerebral stroke, spinal cord injury, or peripheral nerve injury; in these cases, such a condition is called supernumerary phantom limb. The perception of phantom body parts has also been reported to occur after breast, penis, or eyeball excision. In patients who have had a limb amputated, the incidence rate of phantom limb complicated by pathological pain (phantom limb pain) is 50–80%. According to some reports, a majority of patients continue to suffer from phantom limb pain for several years after onset [1].

In animal experiments, it has been shown that the mechanisms underlying phantom limb pain are induced by various factors, such as neuroma-derived abnormal impulses resulting from peripheral nerve injury, hyperexcitability of neurons on the spinal dorsal horn, and hyperexcitability of neurons in the supraspinal central nervous system. Functional brain imaging studies suggest, however, that functional reorganization of the supraspinal central nervous system plays an important role in the onset of phantom limb pain. Brain regions within the primary somatosensory cortex (S1) correspond to a specific part of the body, constituting a somatotopic map (somatotopy). After amputation of an upper limb, for example, reorganization is observed in S1: the brain region corresponding to the affected upper limb shrinks, and the adjacent area in

S1 corresponding to the mouth/facial surface area expands [2]. Furthermore, a somatotopic map also exists in the primary motor cortex (M1). After amputation of an upper limb in patients with phantom limb pain, both shrinkage of the upper-limb area and expansion of the mouth/facial surface area are observed in M1, and the excitability of neurons in the upper-limb area increases excessively. Because the reorganization of the somatotopic map observed in S1/M1 (the sensorimotor cortex) is observed not only in cases of phantom limb pain but also in cases of pain following spinal cord injury [3] or complex regional pain syndrome [4], it seems to be a common underlying mechanism of neuropathic pain.

## Motor control of phantom limbs: involuntary and voluntary movements of phantom limbs

Patients who have phantom limb pain complain of various kinds of pain. In a study involving 1,250 patients with phantom limb pain who lost a limb during the civil war in Bosnia and Herzegovina [5], approximately 58% of patients complained of pain associated with sensations on the skin surface, such as being cut with a knife, receiving an electrical shock, or feeling a stinging sensation. Approximately 42% of patients complained of pain associated with a sensation of movement (i.e., proprioceptive sensation), such as spasms or cramps in the phantom limb, or feeling that the phantom limb was twisted. Thus, almost half of patients with phantom limb pain perceived unpleasant involuntary movements of their phantom limb. Which neural substrates could underlie movement sensations of phantom limbs? Among phantom-limb patients, there are persons who can voluntarily "move" the phantom limb; that is, they can clearly perceive that the phantom limb is moving voluntarily. Functional brain imaging studies on phantom limb movements show activation of M1/S1 and the supplementary motor area (SMA) similar to that which occurs during voluntary movements of healthy limbs [6]. In the case of involuntary "movements" accompanied by an unpleasant feeling in the phantom limb, in addition to activation of S1/M1 and SMA, activation of the cerebellum, anterior cingulated cortex (ACC), and posterior parietal cortex (PPC) are observed [7]. Both ACC and PPC are known to relate with limb-movement control and the perception of this movement [8]. In one phantom limb study, however, ACC and PPC activations were correlated linearly with the degree of pain and discomfort arising from phantom-limb involuntary movements [9]. The patterns of brain activations (including ACC and PCC activations) accompanying phantom limb movements and healthy limb movements appear to be similar, regardless of whether the phantom limb movements are voluntarily or involuntarily. In terms of the perception of limb movements in the brain, there may be no discrimination between phantom and healthy limbs.

It has recently been revealed that motor commands to the phantom limb are generated from the hand area in M1, which is invaded and submerged by the mouth/facial surface area through M1 reorganization following the limb amputation [10]. It has also been reported that a combination of somatosensory feedback of muscle contractures in the residual limb and motor commands to the phantom limb can produce movement sensations in the phantom limb [11].

Up to this point in this review, we have described movement sensations of phantom limbs. The perception of phantom limb movements, posture (position), and size can fluctuate from moment to moment [12]. The phantom limb is often perceived to be intact, resembling a normal limb, or telescoped and shrunken so that the proximal portion of the limb is perceived to be missing or shortened, with the more distal portion floating near the stump. Occasionally, patients with phantom limbs perceive that the missing limb is swollen or enlarged compared with the intact limb. These phenomena are known as "telescoping". The degree to which telescoping is perceived (how short the phantom limb is felt to be) correlates with the degree of reorganization. As such, phantom hand movements of a completely telescoped phantom limb create activity in the S1/M1 cortical region that normally manifests the shoulder somatotopy, indicating enlargement of the hand region in S1/M1, while phantom hand movements of partially telescoped phantom limbs create activity in the S1/M1 region of the arm under normal circumstances, and those of a non-telescoped phantom limb activate the hand region [2]. Thus, the neural substrates for moving the phantom limb seem to be closely related with those for producing phantom limb sensations.

## Phantom limb pain and the primary motor cortex

Movement sensations of phantom limbs are closely related with activity in M1, but what is the relationship between M1 and pathologic pain occurring in the phantom limb? As described in the Introduction, reorganization in the S1/M1 cortices is one of the underlying mechanisms of phantom limb pain, and the reorganization in M1 is not observed in patients who do not suffer from phantom limb pain following amputation of an upper limb [13]. It has been reported that repeated transcutaneous magnetic stimulation of M1 and electrical motor cortex stimulation (MCS) are effective in cases of neuropathic pain, such as phantom limb pain [14, 15]. Further, in order to produce such analgesic effects, the M1 somatotopic map area related to