Reported predictive factors of MCS efficacy in post-stroke pain patients include the absence of severe motor weakness (Katayama et al., 1998), some types of pain, such as trigeminal neuropathic pain (Rasche et al., 2006), and good pain relief with rTMS of M1 (Andre-Obadia et al., 2006; Saitoh et al., 2006). In the present study, pain relief was not associated with patient characteristics (age, sex, presence or absence of cerebral lesion, treated painful region). The latest pain reduction in patients with longer pain duration history ($\geqslant$5 years) was statistically larger than that in the others (<5 years), however, this relationship might be confounded by other variables that were not tested in this study.

The effects of MCS differ according to the lesion causing intractable pain. Post-stroke pain and trigeminal neuropathic pain are both improved significantly by MCS. However, in several reports, trigeminal neuropathic pain appears to respond more favorably than post-stroke pain (Rasche et al., 2006; Saitoh and Yoshimine, 2007). We recently reported that subthreshold high-frequency rTMS of M1 was more effective in patients with spinal cord or peripheral lesions than in those with cerebral lesions (Saitoh et al., 2007). In the present study, MCS was also suggested to be more effective in patients with non-cerebral lesions than in those with cerebral lesions, although the difference was not significant.

The detailed mechanisms underlying the effect of MCS remain to be elucidated. Several positron emission tomography activation studies suggested that MCS might activate the thalamus, anterior cingulate, orbitofrontal cortex and upper brainstem which related the affective-emotional component of chronic pain and the descending inhibition of pain (Garcia-Larrea et al., 1999; Kishima et al., 2007). Katayama et al. (1998) speculated that the pain control afforded by MCS requires neuronal circuits maintained by the presence of intact corticospinal neurons originating from M1. These findings suggested several brain regions and pathways might somewhat play a role in pain relief provided by MCS. Our findings that MCS appeared to be more effective in patients without cerebral lesion were consistent with this concept.

Based on the success of MCS, rTMS is now being applied to intractable neuropathic pain. It was reported that high-frequency rTMS (5 Hz or 10 Hz) of M1 resulted in significant but transient relief of intractable neuropathic pain (Migita et al., 1995; Lefaucheur et al., 2001, 2004; Hirayama et al., 2006; Saitoh et al., 2007). It has been suggested that results with rTMS may predict the effectiveness of MCS in the treatment of neuropathic pain. In a few recent studies, a correlation between the efficacy of rTMS and that of MCS was reported (Migita et al., 1995; Lefaucheur et al., 2004; Andre-Obadia et al., 2006; Saitoh et al., 2006). In the present study, the rate of pain reduction in response to rTMS was significantly correlated with that of MCS over the short term. Although it needs a further study, our results suggested that preoperative rTMS would be helpful in selection of MCS candidates.

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Mechanistic analysis of motor cortex stimulation for phantom limb pain

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Abstract

Phantom limb pain and other deafferentation pain are characterized by changes in cortical processing and organization (cortical reorganization), poor response to conventional treatments. Whereas several studies reported a close relationship between imagery movements of the amputated or paralyzed limb and the intractable pain, the alterations in the motor cortex related to the imagery movements has not yet been explored in detail. Here, we studied the electrocorticogram (ECoG) of sensorimotor cortex in deafferentation pain to reveal the relationship between some imagery movement tasks and the dynamical pattern of ECoG during the tasks. A clear correlation between the ECoG and imagery movements was observed in a patient who well responded to motor cortex stimulation (MCS). On the other hand, there was little correlation between them in a patient who did not respond to MCS. For the former patient, the optimal stimulation site for MCS located around the primary motor cortex, where the pattern of ECoG well differentiated among types of imagery movements. We will discuss the relation between imagery movements and the effects of MCS.

Key words: Cortical reorganization; Phantom limb pain; Deafferentation pain; Imagery movements, Motor cortex stimulation

幻肢痛に対する大脳皮質刺激療法のメカニズム解析

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はじめに

外傷などの神経損傷で四肢からの神経連絡が絶たれた後に，損傷した神経に関連した部位が激しく痛む求心路遮断性疼痛は多くの場合に難治性であり治療に苦慮する[12]．近年，動物実験やヒトでの観察から，求心路遮断後に体性感覚野や運動野で著明な大脳皮質再構築（cortical reorganization: CR）が生じることが明らかになり，求心路遮断性疼痛患者における疼痛とCRの程度との間に相関関係が報告されている[4,5,8,13,16]．また，求心路遮断性疼痛である幻肢痛患者に鏡を用いたリハビリテーション（鏡療法）などを行い，患者が切断肢（幻肢）の運動のイメージを取り戻すことで幻肢痛が改善されることから，運動想起の変化と幻肢痛，CRとの関係が検討されている[6,15]．難治性求心路遮断性疼痛の発生機序解明と治療には体性感覚野や運動野でのダイナミックな変化に注目する必要がある．

我々は難治性求心路遮断性疼痛に対して，感覚運動野上に硬膜下電極を留置し，大脳皮質を電気刺激（motor cortex stimulation: MCS）することで疼痛が軽減することを報告してきた[14]．しかし，MCSによる求心路遮断性疼痛軽減のメカニズムは明らかでなく，個人個人におけるMCSの効果を的確に予測することは難しい．今回，我々は求心路遮断性疼痛に対してMCSが著効した症例と無効であった症例について，運動想起を行った際の皮質脳波活動を比較検討した．MCS著効症例では，想起する運動種類毎に皮質脳波活動が特異的な活動パターンを示すのに対し，無効症例では想起する運動種類毎の特異的なパターンが認められなかった．運動想起時の皮質脳波活動パターンとMCSとの関係について論じる．

症例と方法

大阪大学脳神経外科でMCSを施行した末梢神経障害による難治性求心路遮断性疼痛患者12例中，特にMCSが有効であった症例と無効であった症例各1例を解析の対象とした．症例1は31歳男性，バイク事故による左腕神経叢引き抜き損傷の患者である．事故直後より左上肢にVisual analog scale（VAS: 視覚的アナログ尺度）6～8程度の痛みが出現し難治であった．発症より5年後に当科でMCSを施行し，VASは1～3まで低下しMCSが著効した．症例は患側上肢の神経移行術を受けていたが，運動の想起も行うことができた．症例2は46歳男性，転落事故による左上腕切断の幻肢痛患者である．VAS 8程度の幻肢痛が事故直後より発生し難治であったため，発症4年後に当科でMCSを施行したが，疼痛改善を認めなかった．症例は幻肢の指先を軽度屈曲させる程度の運動しか想起できなかった．

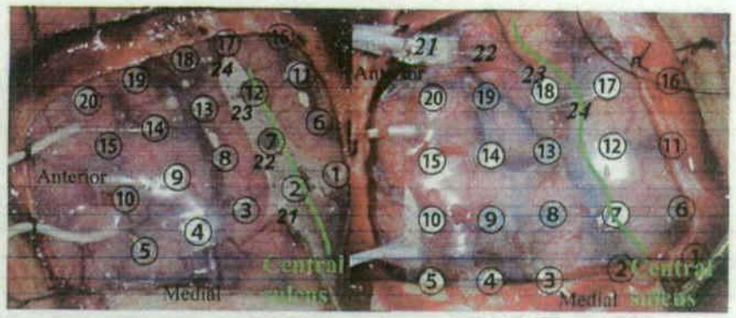

Fig.1 Location of implanted subdural electrodes.
Two pictures of brain surface and subdural electrodes were taken at the surgery of patient 1 (left) and 2 (right). For each patient, grid and strip arrays of planar surface platinum electrodes were temporarily placed over the sensorimotor cortices. Green curves indicate the location of the central sulcus. A four-strip electrode array was inserted on the anterior wall of the central sulcus after dissecting the sulcus. A twenty-pole grid electrode array (4 × 5 electrodes) was placed over the central sulcus to cover the sensorimotor area.

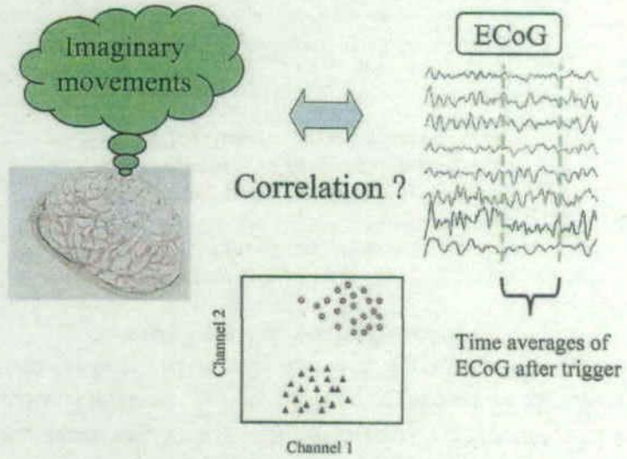

Fig.2 Schema of experiment.
Patients were instructed to image three types of upper limb movements: flexion of thumb, grasping of hand and flexion of elbow. The ECoG was recorded simultaneously with the image. A part of the ECoG was averaged by a time window of 100 ms. The values of averaged ECoG were plotted to clarify the difference of patterns of ECoG among the each movements. If there is a clear correlation between the imaginary movements and the pattern of ECoG, the plotted values will be divided into three groups.

両症例に対して直径3 mm，電極間隔1 cmのプラチナ製電極（Unique Medical Co., Tokyo, Japan）を硬膜下へ一時的に留置しMCSの最適刺激領域を検索した[14]．電極は中心溝内の運動野側に4極，脳表の感覚運動野を覆うように20極を留置した（**Fig.1**）．中心溝はMagnetic resonance image（MRI）による脳表再構成画像を用いて解剖学的に同定し，また術中正中神経刺激による体性感覚誘発電位（somatosensory evoked potential: SEP）を用いて電気生理学的にも同定した．

電極留置術後約10日目に，患者に運動想起

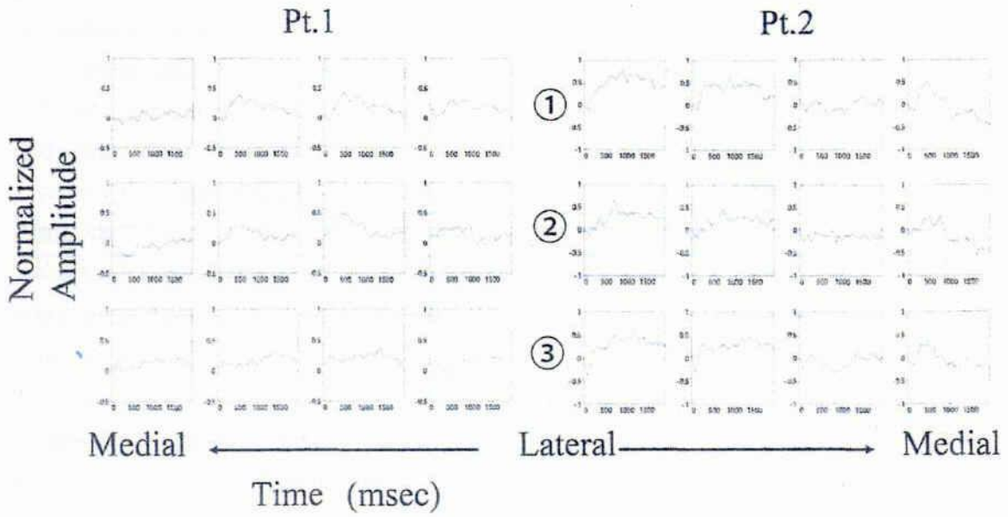

Fig.3 An example of averaged ECoG.
The ECoG of four-strip electrode on the anterior wall of the central sulcus was averaged for each type of imaginary movements. Each raw corresponds to the type of imaginary movements: ① flexion of thumb, ② grasping of hand, ③ flexion of elbow. Each column corresponds to the each electrode on the anterior wall of the central sulcus. Graphs show the normalized amplitude of averaged ECoG after the trigger.

課題を施行した．シールドルームにて患者を安静・座位とし，留置した硬膜下電極を 64 チャンネルデジタル脳波計（EEG2000, Nihon Koden, Japan）に接続した．患者に 5 秒間隔の視覚信号を与え，それをトリガーとして患側上肢の運動を 1 回ずつ想像させた．想起する運動は，① 拇指屈曲，② 握手，③ 肘屈曲の 3 種類とし，各種 20 ～ 100 回の運動想起を行った．脳波はフィルターをかけず抽出率（sampling rate）1000 Hz で計測した．トリガー前 500 msec の平均値と分散にて正規化し，トリガー後 1000 msec の脳波を計測した．

記録された脳波の振幅が最も大きい特徴的な時間区間を選び，その区間で各電極での時間平均値を計算した．全 24 電極毎の時間平均値から，3 種類の運動想起を分類するのに最適な電極を選択した（**Fig.2**）．つまり各電極の時間平均値を，選択した電極についてプロットすると，各プロットが想起した運動種類毎にできるだけ分かれて分布するように最適な電極を選択した．この際，スパース推定を用いた判別プログラムを用いた[7,17]．これにより，得られた皮質脳波のパターンが，想起した運動種類毎にどの程度異なるかを検討した．また，選択された電極と MCS による疼痛減弱効果を比較した．MCS の効果は施行前と施行直後での VAS の変化率【〔（施行前 VAS – 施行後 VAS）／施行前 VAS〕×100】にて評価した．

結　果

症例 1, 2 について，中心溝内運動野側へ留置された 4 極の硬膜下電極から記録された皮質脳波を運動想起課題毎に加算平均した．症例 1, 2 共に，トリガー後 400 ～ 500 msec にピークを持つゆっくりとした電位変化を認めた（**Fig.3**）．

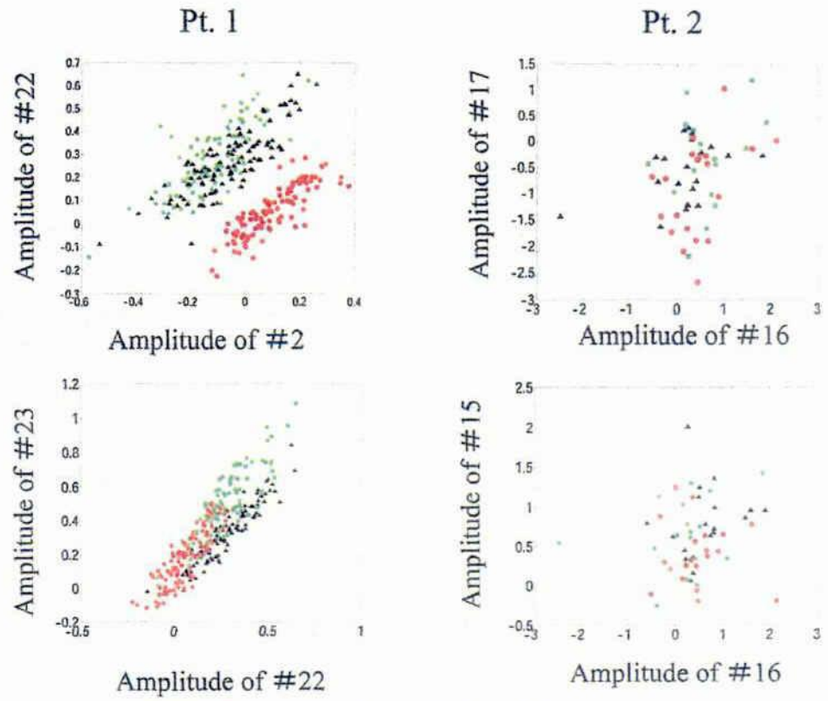

Fig.4 Distribution of time averaged ECoG.
The time averages of ECoG during 400 – 500 ms after the trigger were plotted. For patient 1, the electrodes 2, 22 and 23 were selected (left). The graphs show the distribution of the time averaged ECoG of electrodes 2 and 22 (upper left) and electrodes 22 and 23 (lower left). Green squares, black triangle and red circle correspond to the flexion of thumb, grasping of hand and flexion of elbow for each. As shown in the graphs, the plots of three types of imaginary movements were divided into three groups. For patient 2, the electrodes 15, 16 and 17 were selected (right). The graphs show the distribution of the averages of electrodes 16 and 17 (upper right) and electrodes 16 and 15 (lower right). As shown in the graphs, the plots of three types of imaginary movements were not divided into different groups.

これは運動に関連した課題を行う際に感覚運動野で認められる slow cortical potential（SCP）であると考えられる[2]．運動想起課題に伴い運動関連電位が記録され，そのピークはトリガー後 400 ～ 500 ms であった．

MCS が著効した症例 1 において電極 2, 22, 23（中心溝付近の電極）のトリガー後 400 ～ 500 msec での皮質脳波の時間平均値をプロットした（**Fig.4**）．3 種類の運動想起時の皮質脳波の時間平均値は各施行に対応して非常に明確に分離された．**Fig.1** 左上に示されるように，電極 2 と 22 の時間平均値の分布は，拇指屈曲もしくは握手を想起した際と肘屈曲を想起した際とで明らかに異なっていた．また，更に電極 22 と 23 についての分布も合わせて検討すると，3 種類の運動想起が皮質脳波だけから，ほぼ完全に予測できるほど分離した分布が得られた．つまり，MCS が著効した症例 1 では想起した運動種類毎に皮質脳波に特徴的なパターンがあり，皮質脳波が運動想起に関する明確な情報を持つことが明らかになった．一方，MCS が無効であった症例 2 では電極 15, 16, 17 を選

+	-	VAS reduction (%)
22	21	55
3	1	50
24	21	46
2	1	33
21	22	25
3	8	25
13	11	14
24	23	0
24	22	0
8	6	0

Fig.5 Effects of MCS.
Electrical stimulation was applied between several sets of electrodes of patient 1. For each sets of electrodes, the VAS reductions by MCS were represented by colored arrows on the picture. The arrow was drawn from positive to negative of stimulation. As shown in the figure, the stimulation around the selected electrodes (2, 22 and 23) revealed significant VAS reduction of 40 – 50%.

択したが，3種類の運動想起時の皮質脳波を分離することはできなかった．これは，全ての電極の組み合わせにつき行われたが，明らかな分離を得られなかった．つまり，MCSが無効であった患者では，留置した硬膜下電極にて，運動想起パターンに特異的な皮質脳波活動を捉えることができなかった．

MCSが著効した症例1について選択された電極とMCSの効果について検討した．**Fig.5**に示すように，選択された電極は中心溝内運動野側の内側とその直上にある．この周囲を刺激するとVASにて50%程度の低下を認め，他の領域と比較して高い疼痛減弱効果を認めた．ただし，同じ電極の組み合わせでも刺激の方向によって疼痛減弱効果は異なり，電極の場所のみから疼痛減弱効果を予測することは難しかった．

考　察

MCSが著効した患者と無効であった患者について，患側上肢の運動想起課題を行った際の皮質脳波パターンを比較した．皮質脳波は運動想起課題に伴ってSCPを示した．SCPが最大振幅を示す時間区間（トリガー後400～500 ms）において各電極からの皮質脳波の時間平均値を求め，運動想起課題毎に特徴的な分布を示す電極を選んで描画した．MCSが著効した患者では皮質脳波の時間平均値の分布が運動想起課題毎で明らかに異なり，皮質脳波のパターンが想起する運動に強く相関していることが示された．一方，MCSが無効であった患者では皮質脳波の時間平均値の分布に特徴的なパターンを認めなかった．またMCSが著効した患者では，想起する運動毎に特徴的な皮質脳波パターンを示す電極周囲で，MCSによる疼痛減弱効果が高かった．

求心路遮断性疼痛患者が運動を想起する際，一次運動野周辺で運動毎に特徴的な皮質脳波活動を認めた．求心路遮断性疼痛患者の運動野はCRにより正常とは異なる構造となっていると考えられるが，運動想起との関係は明らかではない[3,9,10,11]．幻肢患者に幻肢の運動を想起させると切断肢断端部の筋活動が生じることが知られている[12]．この際，幻肢の運動を想起できる患者では，切断部の筋電図が想起する運動毎に異なるパターンの活動を示す．一方，幻肢の運動を想起できない患者では断端の筋電図は想起する運動によらず常に同じパターンを示す．本研究でも，幻肢の運動を想起する能力と複数の運動想起を異なるパターンで表現する能力（切断部の筋反応もしくは一次運動野の皮質脳波活動）との間には関連が示唆された．今後症例を重ねることで，幻肢の運動想起という主観的現象を皮質脳波の活動パターンによって客観的に評価できるようになることが期待される．

幻肢の運動想起能力を回復させることで痛みが軽減する現象が多く知られているが，運動想起と疼痛との関係は明らかでない[1,6,10]．本研究では想起する運動に対して特異的に皮質脳波活動が変化する患者ではMCSの効果が高いことが示唆された．また，運動想起とCRによる皮質脳波活動パターンの変化を検討するために，ECoG計測が有用であることが示された．これらの知見から，運動想起と求心路遮断性疼痛との関係を明らかにするだけでなく，MCSの効果を運動想起能力から推測し，逆に運動想起能力を高めることでMCSの効果を高めることが期待される．

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Spinal cord stimulation therapy for localized central pain

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Abstract

We studied the pathophysiology of localized central pain and the surgical result of spinal cord stimulation. There were 10 cases; 7 males and 3 females from 24 to 77 years old. Pain was caused by peripheral nerve injury in one case, spinal cord injury in two cases and cerebrovascular disease (CVD) (thalamic pain) in 7 cases. All cases were treated by epidural spinal cord stimulation and followed from 0.8 to 8.8 years. Sufficient pain relief was achieved in one case of peripheral nerve and spinal cord injury and in 4 cases of CVD. Moderate pain control was achieved in 2 cases of CVD. In one each case of spinal cord injury and of CVD, pain control was ineffective. In cases with thalamic pain, we studied the correlation between the surgical result of spinal cord stimulation and the clinical features, MRI, fluoro–deoxyglucose (FDG)–PET, and somatosensory evoked potentials (SEP) findings before operation. MRI revealed a small to moderate sized lesion on the thalamus or putamen in each case. PET also showed decreased accumulation of FDG on the affected thalamus. In all cases without one fair responder to spinal cord stimulation, we could recognize definite SEP originating in the sensory cortex ipsilateral side to the CVD lesion during contralateral median or posterior tibial nerve stimulation. In the good responders, we could recognize SEP originating in the sensory cortex of the lesion side with less delayed latency or decreased amplitude than in the moderate responders. In this group, test stimulation with low voltage on the spinal cord evoked a sensory effect (paresthesia) over the painful part of the body.

Spinal cord stimulation proved to be an effective treatment for localized central pain. In cases with localized central pain after CVD, we could expect to ameliorate the intractable pain in those cases in which SEP or spinal cord test stimulation revealed that the thalamo–cortical system was preserved.

Key words: Central pain; Localized pain; Thalamic pain; Spinal cord stimulation; SEP

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中枢性疼痛局所痛の病態と脊髄刺激療法の効果

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Diffusion tensor fiber tracking in patients with central post-stroke pain; correlation with efficacy of repetitive transcranial magnetic stimulation

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Abstract

Central post-stroke pain (CPSP) is one of the most common types of intractable pain. We reported that repetitive transcranial magnetic stimulation (rTMS) of primary motor cortex relieves pain for patients who were refractory to medical treatment. But the mechanism is unclear. In the present study, we investigated relations between the characteristics of CPSP and the results of fiber tracking, which is the only noninvasive method of evaluating the anatomical connectivity of white matter pathways. Fiber tracking of the corticospinal tract (CST) and thalamocortical tract (TCT) was investigated in 17 patients with CPSP. The stroke lesion was located in a supratentorial region in all cases (corona radiata, one case; thalamus, seven cases; putamen, nine cases). Relations between the delineation ratio (defined as the ratio of the cross section of the affected side to that of the unaffected side) of the CST and of the TCT, manual muscle test score, pain score, region of pain, and efficacy of rTMS were evaluated. Fiber tracking was successful in 13 patients with the stroke lesion involving the TCT. The rTMS-effective group had higher delineation ratio of the CST ($p = 0.02$) and the TCT ($p = 0.005$) than the rTMS-ineffective group. Previous studies suggested that an intact CST allows pain control but did not discuss the TCT. Our results suggest that the TCT also plays a role in pain reduction by rTMS of the primary motor cortex and that the efficacy of rTMS for patients with CPSP is predictable by fiber tracking.

Keywords: Central pain; Fiber tracking; Repetitive magnetic stimulation; Corticospinal tract; Thalamocortical tract

1. Introduction

Central post-stroke pain (CPSP), characterized by constant or intermittent pain occurring after ischemic or hemorrhagic stroke and associated with sensory abnormalities, is one of the most common types of intractable pain. Typical associated abnormalities are decreased perception (hypoesthesia) and unusually high sensitivity (hyperesthesia), often accompanied by allodynia and hyperalgesia [4]. These features indicate lesions of the spinothalamocortical pathways relaying in the thalamic ventral posterolateral nucleus, whereas tactile and vibratory sensations are usually considered unrelated to CPSP [4].

Deafferentation pain, including CPSP, is sometimes difficult to control, and many cases of such pain are refractory to medical treatment. According to recent reports, repetitive transcranial magnetic stimulation (rTMS) successfully relieves pain. A majority of the reports show that pain relief is associated with rTMS of the primary motor cortex [1,6,14,23].

Diffusion tensor imaging (DTI) is a magnetic resonance (MR) imaging technique that allows measurement

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of the restricted diffusion of water in tissue. The architecture of axons in parallel bundles facilitates the diffusion of water molecules along the length of the fibers [27]. It is possible to calculate a tensor for each voxel that describes the three-dimensional shape of diffusion and to display the results on such images as fractional anisotropy (FA) images, three-dimensional anisotropy contrast images, and apparent diffusion coefficient maps [28,30].

Fiber tracking is a relatively new method that applies DTI in vivo to reveal white matter pathways in three-dimensional images, and it is often used to evaluate the spatial relation between a lesion and a white matter pathway [8,18] and the quantity of tracked fibers [31]. Broad bundles such as the corticospinal tract (CST) and the thalamocortical tract (TCT) can be delineated clearly [20] and reproducibly [40], but it is difficult to delineate the fibers separately through each thalamic nuclei related to thermal, tactile, vibratory, and deep sensation [41] and in accordance with the distribution of motor function [40].

The mechanism underlying the efficacy of rTMS of the primary motor cortex in pain relief is still under discussion. While motor cortex stimulation (MCS), electrical stimulation of the brain surface with grid electrodes, has been reported to relieve pain, it provides unsatisfactory pain relief for patients with severe paresis [17]. Although the mechanism of pain relief through rTMS is not necessarily the same, participation of the CST in the pain relief is suspected. Participation of the TCT in pain relief is also suspected because impairment of the TCT causes CPSP. However, there have been few studies making use of fiber tracking to investigate the relations between these tracts and CPSP [34]. In this study, we evaluated the relations between fiber tracking and CPSP, emphasizing not the detailed symptoms, which cannot be represented by fiber tracking, but the efficacy of rTMS which is suspected to relate to the fibers, the CST and the TCT, delineated reproducibly by fiber tracking.

2. Materials and methods

2.1. Patients

We are conducting a clinical trial on efficacy of rTMS for the patients with deafferentation pain originating from stroke, spinal cord injury, root avulsion, or peripheral nerve injury. The present study involved 17 consecutive patients with CPSP who participated in that clinical trial (eight men and nine women; median age, 66 years; range, 44–73 years). Patients were recruited from the outpatient clinic for neurosurgery at the Osaka University Hospital between April 2004 and September 2007. Inclusion criteria were as follows: (1) the presence of central pain secondary to a supratentorial stroke lesion confirmed by clinical and neuroradiological data; (2) a causal relation between the lesion and the pain as indicated by clinical characteristics, notably regional pain distribution; (3) pain lasting more than 6 months; (4) pain not attributable to causes other than central causes (e.g., peripheral inflammation, diabetes); and (5) pain resistant to medication of various kinds (non-steroidal anti-inflammatory drugs, anti-anxiety drugs, anti-epileptic drugs, and antidepressants), and to physical and complementary medicine treatments. Exclusion criteria were as follows: (1) contradictions for rTMS (history of epilepsy, cardiac pacemaker, brain stimulation system, or unruptured aneurysm); (2) two or more stroke lesions; or (3) any other non-stroke lesion of the brain. Patient characteristics are listed in Table 1. Stroke originated from a thalamic lesion in seven cases, putaminal lesion in nine cases, and corona radiate lesion in one case. The mean pain duration was 5.1 years (range, 1.0–8.8 years). Written informed consent was obtained from all patients in accordance with the approval from the ethics committee of Osaka University Hospital.

2.2. rTMS

All patients underwent rTMS, and post-treatment pain relief was assessed. Magnetic stimulation was applied through a figure-eight coil (MC B-70, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark), which provides for focal cortical stimulation. The coil was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnostics A/S). The resting motor threshold of the affected muscles was determined by stimulation of the corresponding motor cortex, the position of which was confirmed by the use of the Brainsight Frameless Navigation System (Rouge Research Inc., Montreal, Quebec, Canada). We determined the resting motor threshold from EMGs of the affected area. Muscle twitches in painful areas were elicited when the motor cortex was stimulated carefully according to the cortical somatotopy. For the patients in whom muscle twitches in the painful areas were difficult to elicit owing to severe damage of the motor pathways, rTMS was applied at an intensity of 100 A/μs. A potential equivalent to 90% intensity of the resting motor threshold was used for treatment. Ten trains of 10-s 5-Hz TMS pulses, with 50-s intervals between trains, were applied to the motor cortex.

2.3. Neurological evaluations

Clinical characteristics of sensation over the painful areas were examined in all cases before rTMS with special emphasis on the level of pain. Somatosensory deficit was assessed by means of standard clinical methods: testing for tactile hypoesthesia with blunted needles.

Table 1
Patient characteristics and results of fiber tracking.

Patient	Age (years)	Sex	Lesion location	Symptom topography	MMT		Painful area	VAS before rTMS	Duration (years)	ΔNRS (%)	DRFT	
					Upper extremity	Lower extremity					CST (%)	TCT (%)
1	48	M	Putamen	L	5	5	F, U, T, L	9.0	1.0	67.0	75.0	100.0
2	73	F	Putamen	R	4	2	F, U, T, L	10.0	5.4	60.0	N/A	N/A
3	44	F	Putamen	R	5	5	L	9.0	7.1	57.0	78.6	75.0
4	59	F	Putamen	R	4	4	L	8.0	4.2	47.1	88.2	71.4
5	57	M	Thalamus	L	5	4	F, U, T, L	8.0	7.6	35.1	78.6	60.0
6	59	M	Corona radiata	R	5	5	F, U, T, L	6.0	6.0	33.3	N/A	N/A
7	71	F	Thalamus	R	5	5	U, T	5.0	8.8	30.0	N/A	N/A
8	66	F	Putamen	R	4	5	F, U, T, L	10.0	7.9	30.0	71.4	77.8
9	67	F	Putamen	L	3	4	U, T, L	10.0	4.2	23.1	13.3	35.3
10	60	F	Putamen	R	4	3	F, U, T, L	7.0	2.1	20.0	0.0	0.0
11	56	M	Thalamus	R	4	4	T, L	7.0	1.1	12.0	73.9	36.4
12	66	M	Thalamus	R	4	4	U, T, L	9.0	3.6	11.1	N/A	N/A
13	60	F	Putamen	R	4	4	L	10.0	3.1	0.0	72.7	44.4
14	68	M	Thalamus	R	4	4	U, L	4.0	6.3	0.0	N/A	0.0
15	73	M	Putamen	R	4	4	F, U, T, L	7.0	3.3	0.0	72.7	0.0
16	73	F	Thalamus	L	4	4	F, U, T, L	10.0	7.0	0.0	52.9	0.0
17	72	M	Thalamus	R	3	4	U, T, L	9.0	7.6	−10.0	64.3	30.0

M, male; F, female; R, right; L, left; MMT, manual muscle test (0: no movement and 5: normal); F, face; U, upper extremities; T, trunk; L, lower extremities; ΔVAS, reduction rate of VAS score after repetitive transcranial magnetic stimulation of the primary motor cortex to that before stimulation; DRFT, delineation ratio of fiber tracking: CST, corticospinal tract; TCT, thalamocortical tract; N/A, not available.

Thermal hypoesthesia was identified with the use of hot (42 °C) and cold (10 °C) tubes. The presence of abnormally provoked pain was tested systematically before rTMS. Allodynia was defined as pain arising in response to innoxious stimuli (i.e. stimuli that never caused pain in normal control subjects) [26]. Whenever possible, mechanical allodynia was tested by means of touch (static) or light rubbing of the skin (dynamic). Hyperalgesia was defined as abnormally enhanced pain sensations in response to noxious stimuli [26] and was tested by means of pinprick [38].

To assess motor weakness on the hemiplegic side, the manual muscle test (MMT) system was applied to the following: elbow flexion and extension, shoulder extension, knee flexion and extension, hip flexion. MMT score ranks function on a scale of 0, indicating that no contractile activity can be felt in a gravity-free position, to 5, if the patient can hold the position against maximum resistance and through the complete range of motion.

It is soon after rTMS that the most pain relief is shown [14]. Before and soon after rTMS, patients evaluated their own level of pain by visual analog scale (VAS), rating from 0 (no pain) to 10 (maximum pain). Stimulation was judged to be effective if the VAS score after stimulation decreased more than 30% from that before stimulation. Subjects were separated into two groups, those in whom rTMS was effective and those in whom rTMS was ineffective.

2.4. DTI

All diffusion tensor images were obtained with a 3.0-T whole-body MR imager (Signa VH/i, GE Medical Systems, Milwaukee, Wisconsin, USA). An acquisition time of approximately 3 min was used. Images were acquired by a single-shot echo-planar imaging technique with TE = 80, TR = 10,000. Diffusion gradient encoding in six directions with $b = 1000$ s/mm^2 and an additional measurement without diffusion gradient ($b = 0$ s/mm^2) were performed. A parallel imaging technique was used to record data with a 256 × 256 spatial resolution for a 260 × 260-mm field of view. A total of 50 sections were obtained, with a section thickness of 3.0 mm and no intersection gap.

2.5. Fiber tracking

The diffusion tensors were calculated, and three-dimensional fiber tracking of the CST and the TCT was performed using Volume-One and dTV software (free software by Masutani, URL: http://www.ut-radiology.umin.jp/people/masutani/dTV.htm). Interpolation along the z-axis was applied to obtain isotropic data (approximately 1.0156 × 1.0156 × 1.0156 mm). The diffusion tensor elements at each voxel were determined

by least-squares fitting and diagonalized to obtain three eigenvalues and three eigenvectors. For fiber tracking, two ROIs, seed and target, were manually placed on the three-dimensional anisotropy contrast image, which shows the diffusion direction in each voxel by color (red for left–right, green for anterior-posterior, and blue for craniocaudal). The seed ROI, from which fiber tracking starts, was placed on the cerebral peduncle (Fig. 1A). The target ROI, at which fiber tracking ends, was placed on the precentral gyrus for the CST and on the postcentral gyrus for the TCT on the basis of anatomical knowledge (Fig. 1B). The thresholds of tracking termination were set at 1.8 for the FA value and 30° for the angle between two contiguous eigenvectors (Fig. 1C).

After tracking the CST or the TCT, the three-dimensional fiber tracking data were converted to grayscale two-dimensional transverse images with the dTV software. Normalization of these images to normal space was performed with SPM2 software (Wellcome Department of Imaging Neuroscience, London, UK). The non-diffusion-weighted (b0) images were normalized to the Montreal Neurological Institute echo-planar imaging template supplied with the SPM2 software. The two-dimensional fiber tracking images were spatially transformed according to the normalized b0 images (Fig. 1D). Normalized images were reformatted into 69 slices with $2 \times 2 \times 2\,mm^3$ voxels. Corresponding slices that included the posterior peduncle of the internal capsule were selected for all patients, and the number of voxels making up the CST and the TCT was counted. The delineation ratio, i.e. the ratio of the cross section of the affected side to the cross section of the unaffected side, was calculated for the CST and the TCT.

2.6. Statistical analysis

Fiber tracking of the CST was successful in 12 patients, and tracking of the TCT was successful in 13 patients; data from these cases were analyzed. Correlation was assessed between the level of paresis and the delineation ratio of the CST and between the level of pain before rTMS and the delineation ratio of the TCT by means of Pearson's correlation coefficient. Difference in the delineation ratio of the fiber tracts between the rTMS-effective group and the rTMS-ineffective group was analyzed by Mann–Whitney U test.

3. Results

3.1. Fiber tracking

Fiber tracking of the CST was successful in 12 patients, and tracking of the TCT was successful in 13 patients. It was impossible to trace the tracts completely from the cerebral peduncle to the precentral gyrus or to the postcentral gyrus in some patients. The FA value was decreased by ischemic changes in the white matter of the corona radiata, resulting in an incomplete trace of the CST in four patients and of the TCT in three patients, and metal artifacts distorted the images, resulting in an incomplete trace of both the CST and TCT in two patients.

3.2. Symptoms before rTMS and fiber tracking

3.2.1. Area of pain

All patients had unilateral pain, which was localized on the right side in 13 patients, and on the left side in four patients. Pain involved the entire half of the body, including the face, in eight patients, an upper and lower extremity in four patients, upper extremity in one patient, and lower extremity in four patients.

Post-stroke lesions shown by b0 images affected the CST and the TCT delineated by fiber tracking. Conventional MR imaging and color-coded DTI show the locations of putaminal and thalamic lesions (Fig. 2). In the case of thalamic lesions, patients with a small lesion tended to have pain in a limited area of the body (Fig. 2A), whereas patients with a large lesion extending to the medial side tended to have pain in the entire half of the body, including the face (Fig. 2B). In the case of putaminal lesions, which damage the TCT from the lateral side, patients with a small lesion limited to the lateral side tended to have pain only in a lower extremity (Fig. 2C), whereas patients with a large lesion that extended to the wall of the lateral ventricle tended to have pain in the entire half of the body, including the face (Fig. 2D).

3.2.2. Intensity of pain

Before rTMS, the VAS score in the most painful area was 10 for five patients, 9 for four patients, 8 for two patients, 7 for three patients, and under 6 for three patients. The VAS score before stimulation did not correlate with the delineation ratio of the TCT (Fig. 3B).

3.2.3. Sensory abnormalities

Hyperesthesia in response to pinprick in the painful area was found in seven patients, and hypoesthesia was found in five patients. The kind of sensory disturbance was not related to the volume of fiber tracking or the location of the stroke lesion.

3.2.4. Paresis

The MMT score was 5 for four patients, 4 for nine patients, 3 for three patients, and 2 for one patient; that is, the paresis tended to be mild. The MMT score correlated with the CST delineation ratio (correlation coefficient 0.69, $p < 0.05$; Fig. 3A), but there was no apparent relation between the lesion location and the region of the paresis.

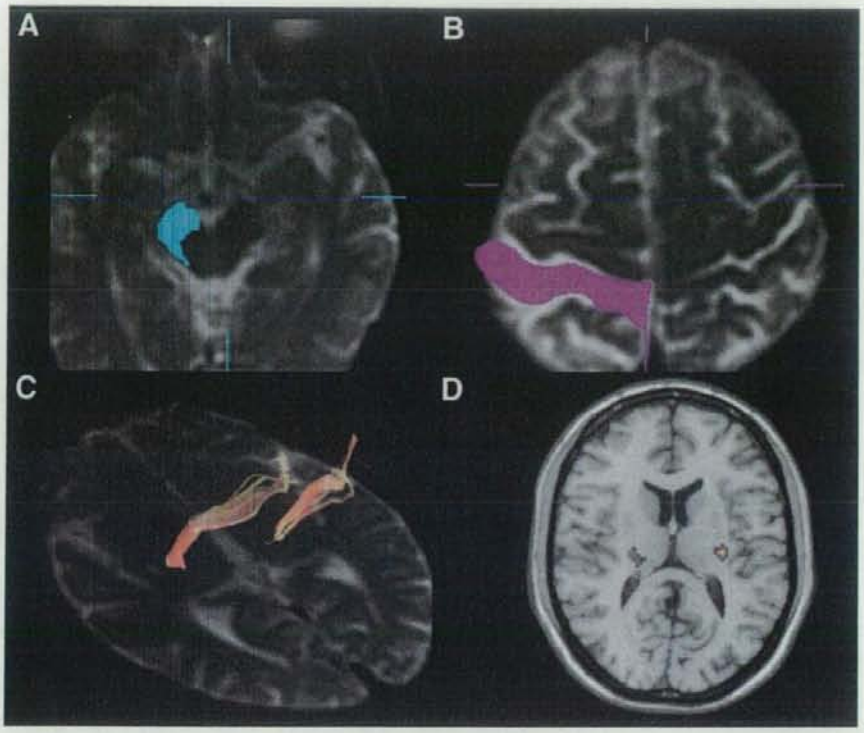

Fig. 1. Diagrams of the fiber tracking procedure. (A) The seed region of interest (ROI) is set at the cerebral peduncle, from which fiber tracking starts. (B) The target ROI is set at the precentral sulcus for the corticospinal tract (CST) and at the postcentral sulcus for the thalamocortical tract (TCT), at which fiber tracking ends. (C) Fiber tracking of the bilateral TCT on a non-diffusion-weight (b0) image. (D) Two-dimensional fiber tracking transformed to normalized space on a T1-weighted image. The number of voxels in this cross section was counted, and the ratio of the number of voxels on the affected side to the number of voxels on the unaffected side was calculated and defined as the delineation ratio.

3.3. Efficacy of rTMS and fiber tracking

The effect of rTMS of the primary motor cortex and its duration varied among the patients. For eight of the 17 patients, the VAS score after rTMS decreased by more than 30% from that before stimulation. They judged the stimulation to be effective. Eight patients indicated less than 30% reduction in the VAS score after stimulation, and only one patient reported that rTMS made the pain worse. These nine patients judged the stimulation to be ineffective.

The symptoms (level of paresis, kind of sensory abnormality, and intensity of pain) before rTMS did not affect efficacy of the stimulation. There was no significant difference in MMT scores between the rTMS-effective group and the rTMS-ineffective group, although the motor weakness tended to be mild in the rTMS-effective group (Fig. 4A). Neither was there a significant difference between groups in VAS scores before rTMS (Fig. 4B).

The rTMS-effective group had higher delineation ratio of the CST ($p = 0.02$) and the TCT ($p = 0.005$) than the rTMS-ineffective group (Fig. 4C and D). In four of the eight patients in the rTMS-ineffective group, fiber tracking of the TCT was completely impossible owing to the post-stroke lesions.

4. Discussion

The present study investigated relations between the characteristics of CPSP and the results of fiber tracking, which is the only noninvasive method of evaluating the anatomical connectivity of white matter pathways. Stroke lesions often affect the CST, the TCT, or both, causing motor weakness or sensory disturbance. Although the mechanisms of both intractable pain generation and pain reduction through rTMS remain unclear, previous studies have suggested that the mechanisms are associated with the CST and the TCT.

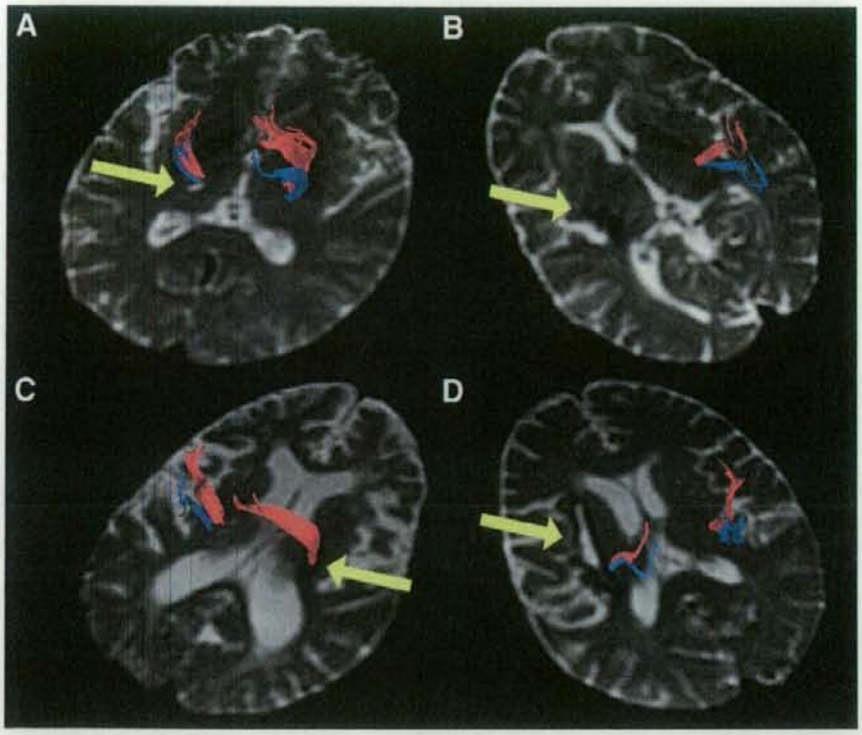

Fig. 2. Fiber tracks of the corticospinal tract (CST, red) and the thalamocortical tract (TCT, blue). b0 images are shown at the level where the CST and the TCT were impaired by post-stroke lesions (A–D). Post-stroke lesions are shown by high-intensity area (A and C) and low-intensity area (B and D) on b0 images (arrow). (A) Patient 11. The TCT is only partially delineated because of the adjacent thalamic lesion. This patient reported trunk and lower extremity pain. (B) Patient 16. The TCT terminates completely at the lesion. This patient reported pain of the entire half of the body, including the face. (C) Patient 13. The TCT is only partially delineated because of the adjacent putaminal lesion limited laterally. This patient reported lower extremity pain. (D) Patient 10. The TCT and the CST terminate completely at the lesion. This patient reported pain of the entire half of the body, including the face.

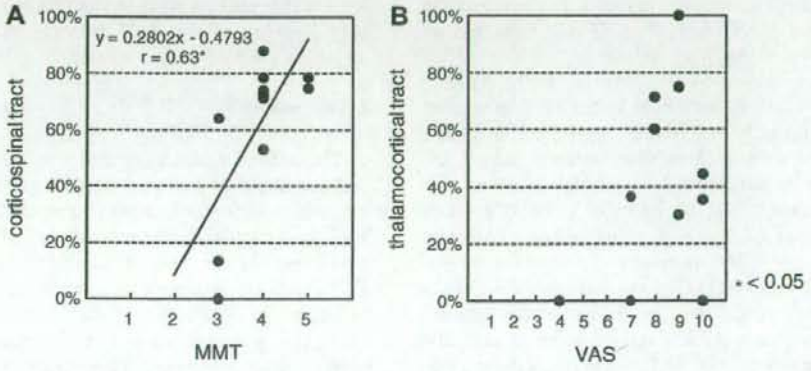

Fig. 3. Correlation between symptoms and the fiber tracking delineation ratio. (A) The manual muscle test score correlates with the delineation rate of the CST ($r = 0.63$, $p < 0.05$). (B) No correlation exists between the TCT delineation ratio and the VAS score.

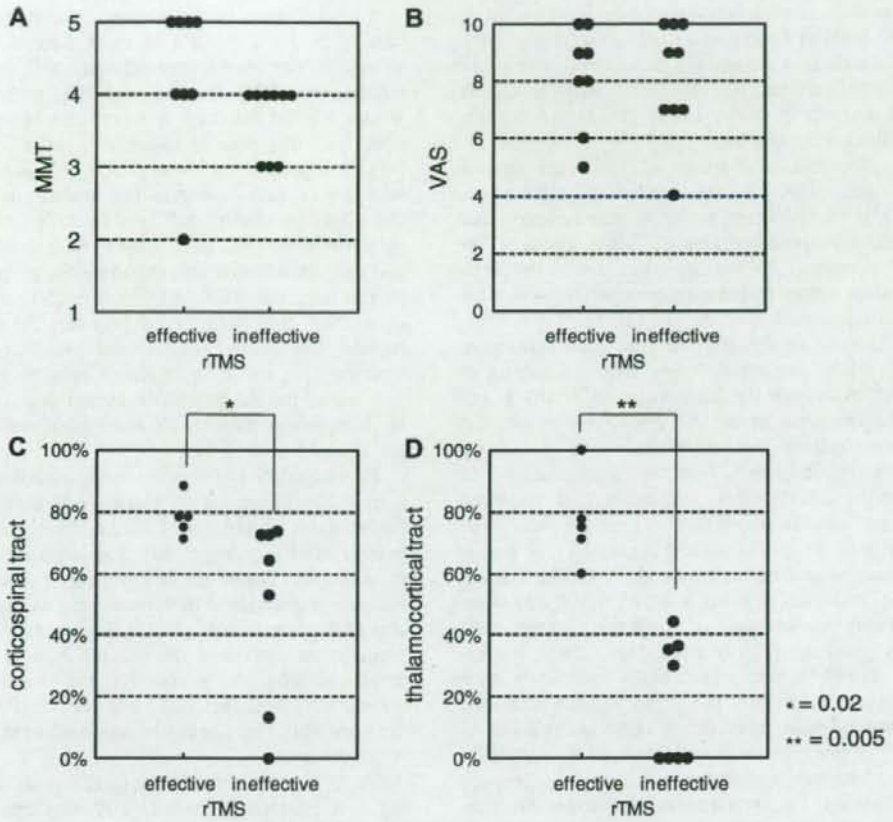

Fig. 4. Efficacy of repetitive transcranial magnetic stimulation (rTMS), pretreatment symptoms, and the fiber tracking delineation ratio. (A) No association exists between the efficacy of rTMS and the MMT score. (B) No association exists between the efficacy of rTMS and the VAS score. (C) Association between the CST delineation ratio and the efficacy of rTMS ($p = 0.02$, Mann–Whitney U test). (D) Association between the TCT delineation ratio and the efficacy of rTMS ($p = 0.005$, Mann–Whitney U test).

All our patients had a lesion impinging on the TCT. The location and size of such lesions affect the fiber tracking delineation ratio. The patients who responded to rTMS of the primary motor cortex had significantly higher CST and TCT delineation ratios than the patients who did not respond to rTMS. The TCT delineation ratio was more significantly different between rTMS-effective group and rTMS-ineffective group than the CST delineation ratio. Our results suggest that the TCT plays an important role in the mechanism of pain relief through rTMS, whereas previous studies suggested that pain control depends on an intact CST, and the relation between the efficacy of rTMS and the TCT was not emphasized.

Cerebral lesions that cause pain involve primarily the nociceptive and temperature pathways [4,5]. Microstimulation of the ventral posterior (VP) thalamus provokes pain and thermal sensations [25,29]. Craig et al. [10] suggested a different region, outside the VP, as a specific relay for pain and temperature, called the posterior portion of the ventral medial nucleus (VMpo). Anatomical and electrophysiological considerations indicate that the VP or the VMpo is the spinothalamic relay for pain and thermal sensations and that the pathway through these nuclei projects to the postcentral gyrus [3,9]. That is, a lesion of the spinothalamocortical tract is a necessary condition for CPSP [34], and in all our patients, lesions to the TCT were confirmed on three-dimensional fiber tracking images. It is proposed that spontaneous pain is linked to hyperexcitability or spontaneous discharge of thalamic or cortical neurons that have lost some of their normal input [39].

In the present study, thermal and tactile abnormalities were not quantitatively measured, and the fibers could not be delineated separately in accordance with the thalamic nuclei by the fiber tracking algorithm we

used. Therefore, comparison between the sensory disturbance and tracked fibers was not adequate. Apparently, it was difficult to evaluate the difference between Aδ fiber mediated cold and pinprick (sharpness) and C fiber mediated warmth in the periphery [13] as far as these tracked fibers were assessed.

MCS, electrical stimulation of the brain surface with grid electrodes, has been reported to relieve pain [1,14,16,24]. In positron emission tomography and functional MR imaging studies, MCS changes the activity not only of the thalamus but also of the anterior cingulate cortex and the anterior insula, which are related to emotional function [11,12]. MCS for treatment of chronic deafferentation pain modulates pain pathways related to emotion and mood, resulting in pain relief. Although the mechanism of rTMS is not necessarily the same as that of MCS, it may be that rTMS also affects the emotional pain pathways. Chronic neuropathic pain, however, is associated with motor cortex disinhibition, suggesting that impaired GABAergic neurotransmission is related to some aspects of pain or to the underlying sensory or motor disturbances caused by an impaired TCT. The analgesic effects produced by MCS could result, at least partly, from restoration of defective intracortical inhibitory processes [22]. In the present study, ineffectiveness of rTMS was significantly associated with poor delineation of the TCT. We suggest that the effectiveness of pain relief is less when delineation of the TCT is poor because modulation of signals in the pain pathway or cortex weakens, or because hyperexcitability or spontaneous discharges in thalamic or cortical neurons enlarge so as to prevent modulation as the degree of TCT impairment increases. In previous studies of MCS, the success rate tended to be lower in cases of CPSP than in cases of pain of spinal cord or peripheral origin [33]. These findings also support the idea that the existence of a lesion of the thalamocortical pathway leads to the inefficacy of rTMS.

Patients with poor delineation of the CST were likely to be unsatisfactory candidates for rTMS. Katayama et al. [17] reported that pain control following MCS tended to be unsatisfactory in patients who displayed moderate or severe motor weakness, and that the pain control afforded by MCS requires intact CST neurons originating from the motor cortex. In the present study, patients with poor delineation of the CST tended not to respond to rTMS, even though our patients did not display severe motor weakness. This result is consistent with the suggestion that intact CST neurons are required for effective pain treatment. Some correlation was also shown between the MMT score and the volume of the CST delineated by fiber tracking, which indicates that poor delineation of the CST reflects the degree of paresis as well as damage to the CST.

Yamada et al. [41] reported somatotopic organization of the TCT using a different fiber tracking algorithm. In our study, conventional MR imaging and color-coded DTI showed patients with putaminal lesions limited laterally to where the lower extremity fiber is in the fiber tracking data of Yamada et al. [41], have pain in the lower extremity, and that patients with lesions that extend to the medial portion, where the upper extremity and face fibers are, have upper extremity and facial pain. This finding shows that pain occurs in accordance with the somatotopic organization of the impaired TCT. As for the CST, although an association has been found between the position of lacunar infarctions and clinical symptoms by fiber tracking [21], we did not find a relation between the location of the lesion and the region of paresis, probably because our patients did not have severe paresis but mainly an impaired TCT.

Reproducibility of fiber tracking in normal subjects is high and asymmetry is not shown, whereas the standard deviation on a quantity of tracked fibers between subjects is relatively large [40]. The absolute volume of tracked fibers could not be compared between patients because of individual differences originating from age, sex, and other factors [35,36]. In our study, the ratio of the cross section of the affected side to that of the unaffected side, the delineation ratio, was calculated for the CST and the TCT, but we could not exclude the possibility that the stroke lesion affected the contralateral fibers.

Our study was limited by several factors. Fiber tracking is a relatively new and still developing method. Methodological issues remain, and results must be interpreted carefully. For example, it is difficult to discern white matter pathways in regions where fibers cross and branch. In such areas, the diffusion anisotropy is low, owing to the partial volume effect. Solutions to these problems can be found by applying such techniques as multiple tensor field regularization [19,37], mutual information image registration procedures [15,32], guided tensor restored anatomical connectivity tractography [7], and probabilistic fiber tracking [2]. In popular streamline tract tracing algorithms, such as the one used in this study, tracking can only progress when there is a high certainty of the fiber direction. This means it is difficult to accurately trace the pathway from a nucleus such as the thalamus, and the streamline represented may be a complex of parts of the various tracts. In addition, because fiber delineation is attenuated by the low FA value of edema, transformation by pressure from the lesion, and artifacts due to hemosiderin depositions, fiber tracking data do not always represent an actual nerve bundle [18]. Therefore, we excluded subjects with two or more stroke lesions, and the effects from the lesion were decreased because more than 6 months had passed from the onset of stroke.

In conclusion, the present study relates the characteristics of CPSP and the efficacy of rTMS to the results of fiber tracking. Previous studies suggested that pain control requires an intact CST, but the relation between the efficacy of rTMS and the TCT was not emphasized. In our study, the efficacy of rTMS was more strongly associated with lesions of the TCT than with lesions of the CST. The efficacy of rTMS for CPSP can be predicted by means of fiber tracking, and severe impairment of thalamic nuclei and the TCT may affect hyperexcitability in the thalamus and cortex or the rTMS pain relief pathway.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

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Ipsilateral Motor-Related Hyperactivity in Patients With Cerebral Occlusive Vascular Disease

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Background and Purpose—Cerebral occlusive vascular disease is an established risk factor for ischemic stroke; however, little is known about its effects on brain function in patients without stroke. To detect possible functional alterations, we used magnetoencephalography and evaluated cerebral cortical activity during hand motor tasks in a group of such patients.

Method—Event-related desynchronization (ERD) during hand-grasping and self-paced finger-tapping tasks was examined in 38 right-hand-dominant patients with occlusive disease of the internal carotid or middle cerebral artery caused by diverse pathologies (atherosclerosis, 28; others, 10) and in 8 control subjects. All patients had no apparent motor impairments. The spatial distribution and the intensity (t value) of ERD in the beta band were analyzed with synthetic aperture magnetometry. According to the laterality index calculated from the ratios of peak t values on ipsilateral vs contralateral (with respect to the hand movement) hemispheres, the distribution of ERD was classified into 3 patterns: contralateral, bilateral, and ipsilateral.

Results—Abnormal ipsilateral dominant distribution of beta ERD was observed significantly more often during contralesional hand grasping in patients with atherosclerotic vascular lesion. It was accompanied by significantly higher t values on the ipsilateral hemisphere, without a decrease in those on the contralateral side. The age, the rating scores of periventricular hyperintensity, and ventricular size were all significantly higher in patients who showed the ipsilateral-dominant pattern.

Conclusion—Abnormal ipsilateral hyperactivity may indicate the presence of subclinical functional alterations related to atherosclerotic occlusive vascular disease. (***Stroke*. 2008;39:2769-2775.)

Key Words: carotid stenosis ■ functional imaging ■ ischemia ■ neurophysiology

Severe stenosis, or occlusion, of the internal carotid artery (ICA) or middle cerebral artery (MCA) is an established risk factor for stroke and a target for neurosurgical procedures aimed at its prevention.[1,2] Although cerebral blood flow (CBF), metabolism, and morphological changes in this pathology have been evaluated in some detail using modern neuroimaging techniques, little is known if brain function itself is altered under such ischemic conditions, particularly when infarction is absent. It is a common observation that patients with cerebral occlusive vascular disease show no apparent neurological symptoms, even in a state of severe hypoperfusion called "misery perfusion." Nevertheless, some decline in cognition has been detected in asymptomatic as well as symptomatic patients with carotid artery stenosis,[3] which indicates that brain function can be altered even without any history of stroke. Because cognitive function reflects activity of the whole brain, it is not easy to distinguish the contributions from left and right hemispheres in cognitive tests. Hence, development of a more objective and quantitative measure could greatly help in early diagnosis and treatment of functional alteration accompanying ischemic cerebrovascular disease. The objective of this study was to evaluate subclinical alterations in motor-related brain function in patients with cerebral occlusive vascular disease who showed no apparent motor impairments.

Attenuation of the electroencephalographic power in the central brain region during hand movement or sensory stimulation was quantitatively defined as event-related desynchronization (ERD)[4,5] and thought to reflect a correlation between an activated cortical area and an increased level of neuronal excitability.[6] Because of its consistent relation to the movement, ERD in the beta band (βERD) has been considered a physiological phenomenon caused by activation of the sensorimotor cortex.[7] Moreover, it has been shown that βERD represents execution as well as programming or control of the movement.[8] In this study, we have chosen βERD as a parameter of brain

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function and analyzed it using magnetoencephalography (MEG) with synthetic aperture magnetometry (SAM). In particular, we were interested in the behavior of βERD during movement of the hand contralateral to the occlusive vascular lesion (contralesional hand), because such movements could activate the hemisphere of the lesion. The superior spatial resolution of MEG allows identification of the anatomic location of cortical activity with enhanced accuracy.[9] The spatial filtering technique using an adaptive beam-forming method (SAM) is a unique modality for estimating the tomographic distribution of the power or its change within a selected band frequency from MEG data.[10,11] Using SAM, the regions with significant oscillatory change are displayed on individual MR images; recently, that imaging has been clinically applied as functional neuroimaging.[9–13]

Methods

Patients

From April 2005 to June 2007, 62 adult patients with ICA/MCA stenosis, or occlusion, without ischemic stroke during the past 3 months, were admitted to the Department of Neurosurgery of Osaka University Hospital for a surgical procedure or clinical evaluation. Occlusive disease was defined as obstruction >60% according to the criteria of the North American symptomatic carotid endarterectomy trial for cervical ICA[1] and narrowing of >50% on angiography for intracranial ICA or MCA. For the current MEG study, we excluded the following categories of patients: those who showed motor symptoms or who had infarction around the motor-related regions, and those in whom large magnetic artifacts were detected in MEG recordings. After selection, 38 patients were enrolled in this study prospectively. All of them were right-hand-dominant, as determined with the Edinburgh handedness inventory,[14] and presented with no apparent motor symptoms in a routine neurological examination. In 11 patients, MRI revealed previous infarctions located in the frontal lobe (anterior to premotor cortex), occipital lobe, and in the basal ganglia, but no infarction was detected around the sensorimotor or premotor cortices, internal capsule, or corona radiata. Twenty-eight patients had atherosclerotic lesions (cervical ICA stenosis in 16, cervical ICA occlusion in 4, intracranial ICA stenosis in 2, and MCA occlusion/stenosis in 6), and the other 10 had lesions not related to atherosclerosis (intracranial ICA occlusion/stenosis attributable to moyamoya disease in 4, intracranial ICA stenosis attributable to encasement by meningioma in 1, cervical ICA occlusion attributable to Takayasu disease [occlusion from common carotid artery] in 1, occluded ICA for the treatment of tumor, giant aneurysm, and traumatic arterial dissection, respectively, in 3, and an incidental finding in 1).

Control Subjects

Eight right-hand-dominant control subjects (5 men and 3 woman), with a median age of 66 (range 55 to 79), were used as controls.

MEG Study

Motor-related magnetic field was recorded using a helmet-shaped 64-channel SQUID system (NeuroSQUID Model 100; CTF Systems Inc) in a magnetically shielded room. The patients/subjects were seated in a comfortable chair with their eyes open and were asked to stare blankly at a point in front of the chair. The MEG data were acquired with a 625-Hz sampling rate and filtered with a 200-Hz on-line low-pass filter.

After a brief explanation, the patients/subjects were asked to perform 2 kinds of hand motor tests: a hand-grasping task and a self-paced finger-tapping task. Because the latter is relatively more complex and requires greater concentration, the tasks were performed in the following order: (1) right finger tapping; (2) left finger tapping; (3) right hand grasping; and (4) left hand grasping. During performance of these tasks, subjects/patients were monitored continuously on a video camera and checked for the absence of an apparent mirror movement in the other (resting) hand. The ongoing waveform (MEG) results were displayed on a monitor and stored in the workstation memory. Each examination session was begun and terminated by measuring the head position of the patient. Before the acquisition of the actual results, 1 or 2 preliminary trials were performed to ensure that the patient performed the task correctly.

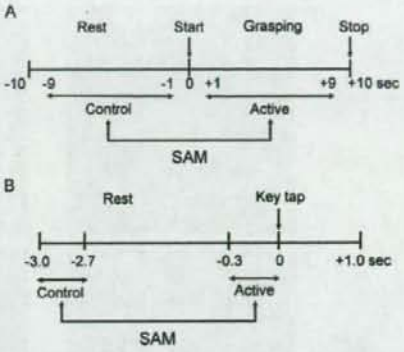

Figure 1. Data collected for a trial of the hand grasping task (A) and self-paced finger-tapping task (B). The powers of beta band between "active" and "control" time windows were statistically compared using SAM.

Task 1, the hand-grasping task (not a tonic sustained grasp), involved grasping with 1 hand weakly at a constant rate while the other hand was resting.[11,12] The working hand was supinated while the resting hand was pronated and placed on an arm rest. The data for each trial were collected relative to the trigger (sound cue or time "0") for 20 seconds and consisted of 2 periods: the "control" state in the time window −10 to 0 seconds, in which the patient remained still, and the "active" state in the time window 0 to +10 seconds, which involved grasp and release movements (Figure 1A). Six such trials, with 5-second intervals between them, were collected as an "examination," first for the right hand. Then, the positions of the hands were changed and an identical examination was performed for the left hand.

Task 2 was a self-paced index-finger-tapping test using a nonmagnetic fiber optical response keypad (LUMItouch; Photon Control Inc), which was placed on either side of the arm rest. The patients were instructed to press the keypad with their index finger, with intervals of ≈5 seconds (but without counting the time) between the taps. The data from 3 seconds before to 1 second after the key input were collected as a trial, and 60 trials were collected for each examination (Figure 1B).

Individual anatomic MR images were acquired using a 1.5-T imaging systems (Magnetom Impact; Siemens). For all measurements, fiducial skin markers were placed on the patient's nasion and at bilateral preauricular points to establish common coordinate systems for MR images and MEG.[9,11–13] This MEG protocol was approved by the ethics committee of the Osaka University Hospital. Informed consent for MEG recording was obtained from all patients and control subjects.

SAM Analysis of Motor-Related Field

Details of SAM algorithm have been described previously.[10,11] In the present study, a volumetric image of root mean squared source activity in the beta band with 5-mm voxel resolution was generated for each "control" and "active" time window: −9 to −1 and 1 to 9 seconds for task 1, and −3.0 to −2.7 and −0.3 to 0 seconds for task 2, relative to the trigger onset, respectively (Figure 1). The statistical imaging was computed subsequently by comparing the powers of the beta band (13 to 30 Hz) in both time windows on a single voxel basis over all trials using the Student *t* test with Jackknife statistics. The *t* value of each voxel was displayed in a color scale on individual MR images using the MRIViewer (CTF Systems Inc).[9] The decrease of