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.

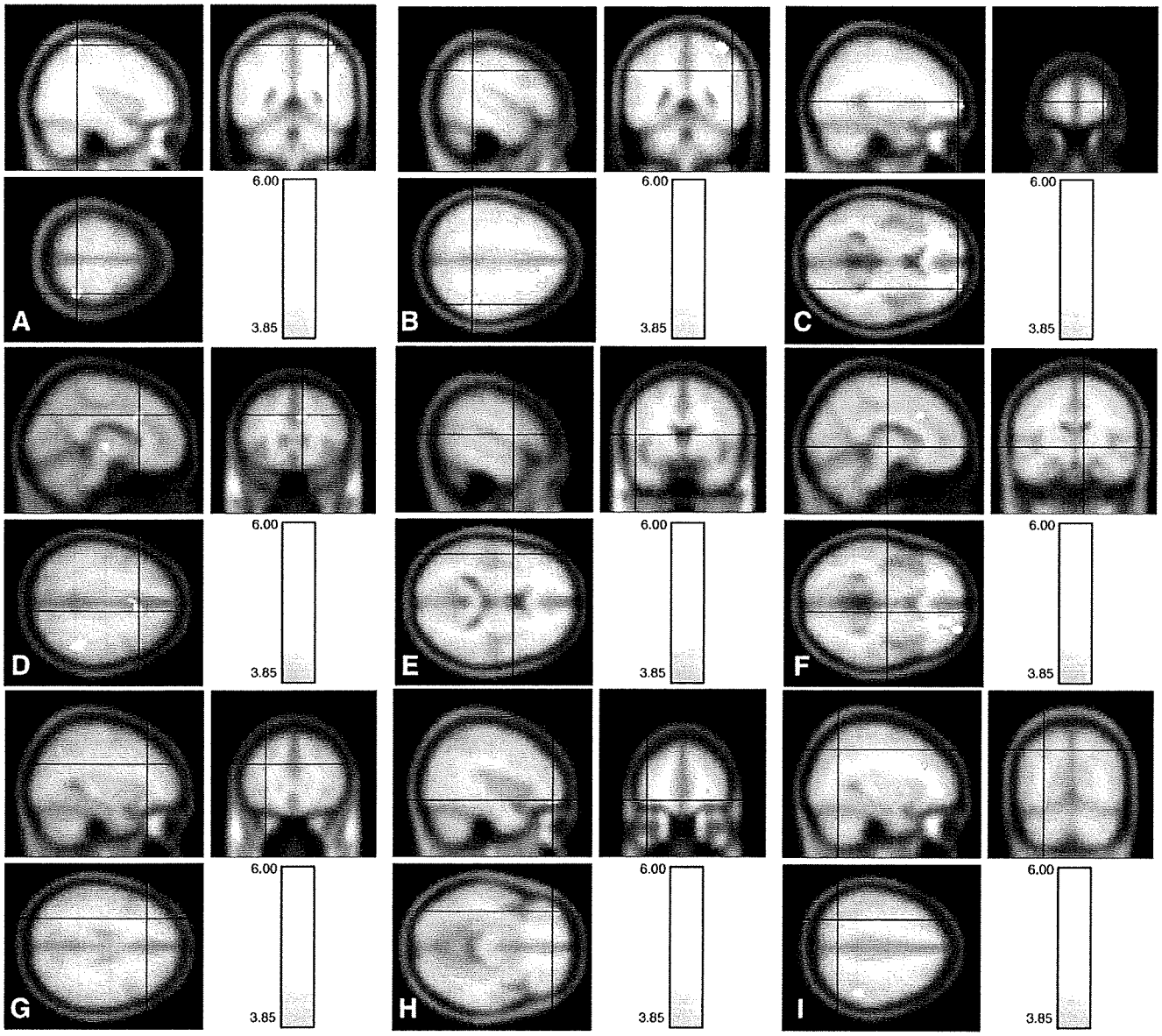

Fig. 2. Statistical parametric maps (*Z* maps) of intensity in normalized images. Comparison of rCBF before and after SCS by positioning the affected sides on the left shows that rCBF is increased after SCS in the contralateral inferior parietal lobules ($Z = 5.48$, 4.96) (A, B), contralateral dorsolateral 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).

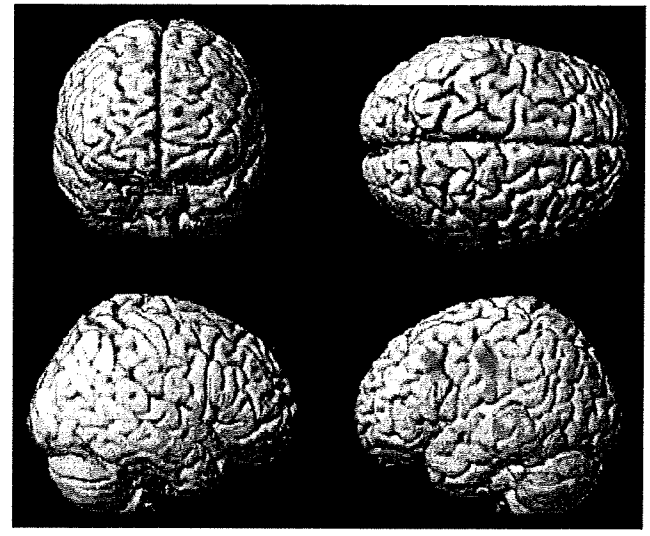

Fig. 3. Areas of significantly increased rCBF correlated to the VAS reduction rate after SCS, rendered in the normalized images, indicate ipsilateral to affected side of dorsolateral prefrontal cortex (BA9), ipsilateral lateral precentral cortex (BA6), and bilateral medial prefrontal (BA8) (threshold,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

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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Review Article

rTMS for Suppressing Neuropathic Pain: A Meta-Analysis

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Abstract: This pooled individual data (PID)-based meta-analysis collectively assessed the analgesic effect of repetitive transcranial magnetic stimulation (rTMS) on various neuropathic pain states based on their neuroanatomical hierarchy. Available randomized controlled trials (RCTs) were screened. PID was coded for age, gender, pain neuroanatomical origins, pain duration, and treatment parameters analyses. Coded pain neuroanatomical origins consist of peripheral nerve (PN); nerve root (NR); spinal cord (SC); trigeminal nerve or ganglion (TGN); and post-stroke supraspinal related pain (PSP). Raw data of 149 patients were extracted from 5 (1 parallel, 4 cross-over) selected (from 235 articles) RCTs. A significant ($P < .001$) overall analgesic effect (mean percent difference in pain visual analog scale (VAS) score reduction with 95% confidence interval) was detected with greater reduction in VAS with rTMS in comparison to sham. Including the parallel study (Khedr et al), the TGN subgroup was found to have the greatest analgesic effect (28.8%), followed by PSP (16.7%), SC (14.7%), NR (10.0%), and PN (1.5%). The results were similar when we excluded the parallel study with the greatest analgesic effect observed in TGN (33.0%), followed by SC (14.7%), PSP (10.5%), NR (10.0%), and PN (1.5%). In addition, multiple (vs single, $P = .003$) sessions and lower (>1 and ≤10 Hz) treatment frequency range (vs >10 Hz) appears to generate better analgesic outcome. In short, rTMS appears to be more effective in suppressing centrally than peripherally originated neuropathic pain states.
Perspective: *This is the first PID-based meta-analysis to assess the differential analgesic effect of rTMS on neuropathic pain based on the neuroanatomical origins of the pain pathophysiology and treatment parameters. The derived information serves as a useful resource in regards to treatment parameters and patient population selection for future rTMS-pain studies.*

Key words: *Transcranial magnetic stimulation, TMS, rTMS, neuropathic pain, neuromodulation, meta-analysis.*

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Neuropathic pain is broadly defined as chronic pain resulting from injury or dysfunction of the nervous system. The underlying pathophysiology is usually associated with plastic changes both functionally and structurally in the nervous system, and depending on the areas of the nervous system being affected, different neuropathic pain states may respond differently to pain interventions.[1,6] Transcranial magnetic stimulation (TMS) offers a noninvasive and nonpainful means of central neuromodulation for both studying and treating neuropathic pain states.[7] The technology uses electromagnetic principles to produce small and localized electrical currents in the cortex. With technological advancement in capacitors that allow rapid electrical charge and discharge, repetitive transcranial magnetic stimulation (rTMS) has been made available as a treatment option for a variety of psychiatric and neurological diseases including various chronic neuropathic pain states.[8-13] Several recent articles have provided a preliminary qualitative and quantitative overview of rTMS in treating various chronic pain states.[13,14] However, definitive and quantitative information is still lacking in the current literature in regard to the relative rTMS efficacy in treating various neuropathic pain conditions, based on their neuroanatomical origins. Similarly, the current literature lacks information regarding combinations of treatment parameters that are likely to provide favorable clinical outcome. Given that the locations of neuronal injury or lesions may significantly affect the underlying pathophysiology that leads to neuropathic pain states and the subsequent response to rTMS, assessing the analgesic effect based on neuroanatomical origins of pain may shed light on the underlying analgesic mechanisms of rTMS. Therefore it will be important to assess whether:

(1) rTMS is effective in suppressing all or only certain types of neuropathic pain conditions;
(2) the neuroanatomical origins of pain pathophysiology and their relative cranio-caudal (top-down) neuroanatomical locations may affect the outcome;
(3) the different combinations of treatment parameters may affect the analgesic benefit.

With these questions in mind and in hopes of better characterizing the effect of rTMS in treating different neuropathic pain states, we conducted a pooled individual data (PID) meta-analysis to specifically address these crucial issues related to the use of rTMS in chronic pain management.

Our main objectives are as follows:

(1) To quantitatively assess the overall analgesic effect of rTMS at the motor cortex for neuropathic pain states;
(2) to assess the overall and the differential analgesic effect of rTMS among individual neuropathic pain states in regard to their corresponding neuroanatomical origins of pain and their relative cranio-caudal (top-down) neuroanatomical order;
(3) to assess the effect of treatment parameters such as pulses, frequency, and number of treatment sessions on the outcome.

Methods

Guidelines for meta-analysis were followed whenever applicable.[15]

Search Strategy

An extensive literature search was conducted in August 2007 in the following databases: PubMed, Psycinfo, Cinahl, Cochrane, and EMBASE, using the following key words: pain, transcranial magnetic stimulation (TMS), repetitive transcranial magnetic stimulation (rTMS), transcortical electrical stimulation. Studies identified as randomized controlled trials (RTC) in either cross-over or parallel designs were individually screened for analysis, based on the following inclusion and exclusion criteria.

Inclusion criteria:

(1) Human study
(2) Neuropathic pain related
(3) Pain diagnoses of the subjects can be attributed to a neuroanatomical origin
(4) Primary motor cortex (M1) as the treatment site
(5) rTMS was used as treatment intervention
(6) Pain visual analog scale (VAS) score as 1 of the primary outcome measurements

Exclusion Criteria:

(1) Studies published in non-English literature
(2) Studies published in non–peer review journals
(3) Studies used treatment paradigm outside the published safety guidelines[16]

Trial Quality Assessment

Authors of articles that met the above criteria were contacted for providing individual subject level data for the meta-analysis. The articles were further reviewed by 2 independent reviewers (a neurologist with an extensive TMS experience and a pain specialist) for study inclusion.

Data Extraction

The raw data provided by the authors of the final chosen studies were pooled for the meta-analysis. The outcome data collected after the last treatment of the studies were used for the analysis. Percentage changed for the treatment effect was calculated by the following equation:

% of pain VAS score change
= (Post-treatment Pain VAS score − Pretreatment Pain Vas Score)/(Pretreatment Pain VAS Score)

The PID was coded for further analysis as follows:

(1) Age;
(2) Gender;

(3) Pain diagnoses based on their neuroanatomical origins in the cranio-caudal (top-down) order: post-stroke supraspinal related pain (PSP); trigeminal nerve or ganglion (TGN); spinal cord (SC); nerve root (NR); and peripheral nerve (PN);
(4) Treatment frequency: high range (>10 and ≤20 Hz) vs low range (>1 and ≤10hz);
(5) Number of pulses given per treatment session: high (>1000) vs low (≤1000); and
(6) Total number of sessions: single (S) vs multiple (M)

Since none of the included studies have systematically reported medication utilization with all the information in regard to the duration, dosage, and class of medications used by subjects at either the baseline or the postintervention level, it was deemed unfeasible to include pain medications in the current analysis.

Statistical Method

In studies with the cross-over design, the same subject was treated with both sham (placebo) and real rTMS. To account for this within-subject correlation, the generalized estimating equations (GEE) were used to estimate the parameters of the model[17]:

$$Y_{ij} = \alpha_1 1\{study_i = 1\} + + \alpha_5 1\{study_i = 5\} + \beta 1\{trt_j = TMS\} + \epsilon_{ij}$$

where Y_{ij} denotes the percent decrease in pain for subject i under treatment (trt_j) with values sham (placebo) or TMS, $study_i$ is a 5-level factor covariate, ϵ_{ij} are errors (correlated within subject), and 1 is the indicator function. The model includes the study indicators, $study_i$, to account for potential study effects. Next, the effect of subject level covariates (gender and diagnosis) and their interaction with treatment was estimated by adding parameters to the above model and fitting again using GEE. We also assessed the effect of study level covariates: number of pulses given per treatment, frequency of rTMS, and number of sessions. Number of pulses and frequency could only be assessed within the rTMS condition because the sham condition had no real number of pulses or frequency directly being delivered to the subjects. These 2 variables turned out to be collinear with the study indicators. Therefore, 2-sample *t* tests (high versus low) were performed. Finally, because the sham condition could be described as having a particular number of sessions, we reasonably modeled the interaction between treatment and sessions and fitted such a model using GEE. All analyses were conducted using R version 2.6.1 (R Development Core Team 2007, http://www.R-project.org). The GEE analysis was conducted using the GEE package [Ported to R by Thomas Lumley (versions 3.13, 4.4) and Brian Ripley (version 4.13), 2007].

Results

Search Result

A total of 235 articles were identified in the initial data base search. Of those articles, 35 were identified as randomized controlled trials (Table1A).

Table 1A. Initial Search Summary

PUBMED	140	21
PSYCHOI	49	1
CINAHL	29	1
COCHRANE	8	8
EMBASE	9	4
Total	235	35

These 35 articles were subsequently individually screened based on the additional inclusion and exclusion criteria listed in the previous section, and 7 articles were selected by 2 independent reviewers.[18-25] The excluded 28 articles and the reasons for exclusion are listed in Table 1B.[27,30-38,40-43] Three of the 7 selected published articles came from the same group of authors.[18-20] However, due to computer data loss, this author was able to provide data from 1 of the articles. This resulted in the final 5 studies to be included in the meta-analysis (Fig 1, search flow sheet).

Overall, raw data of 149 subjects (75 women and 74 men) were extracted from the 5 articles. Summary statistics of demographics and outcomes for the individual studies were demonstrated as follows: (1) Tables 2 and 3 summarize patient gender distribution and neuroanatomically related pain etiology, respectively; (2) Table 4 summarizes the treatment parameters of each of the 5 studies; and (3) Table 5 lists the sham conditions of the studies.

Treatment Effect

Because the study by Khedr et al[22] used a parallel design that was distinct from the other cross-over studies, we conducted initial analyses both with and without this particular study. Overall, we detected a significant treatment effect (Fig 2) with greater reduction in pain VAS associated with rTMS in comparison to sham (mean reduction = 16.7%, $P < .001$ with Khedr et al; 13.7%, $P < 0.001$ without Khedr et al). In the 2 studies that qualified for the analysis but the authors were unable to provide us with the raw data due to computer data loss, 1 of 2 studies consists of 18 subjects with pain related to supraspinal (12 subjects) and nerve root (6 subjects) etiologies. The summarized result of this study indicated a significant post-rTMS pain VAS scores reduction with a single session of 10 Hz rTMS ($P = 0.001$) in comparison to sham and 0.5 Hz rTMS.[18] In the other study with a cross-over design, the authors reported a significant reduction of pain VAS in 14 subjects (7 with PSP and 7 with TGN) with a single session of 10 Hz rTMS M1 treatment in comparison to sham.[20] The single-session treatment effect lasted up to 1 week. Given that these 2 studies consisted of a relatively small number of subjects (less than 18% of the potential PID) and their summary results were similar to the observed overall treatment effect, we estimated the statistical impact of those nonincluded data on the overall analysis was minimal. In the analyzed data, no significant age or gender effect on analgesia between rTMS and sham in the current meta-analysis was found. In addition, duration of pain data was only available from

Table 1B. Excluded Studies

	Data Base	Authors (Year)	Abbreviated Publication Name	Subject Population	Main Reasons of Exclusion
1	PubMed	Avery et al (2007)[26]	J Nerv Ment Dis	Chronic pain patients of depression (n = 68)	Left DLPFC as the simulation site and no clear description of neuroanatomical origin of pain
2	PubMed	Borckardt et al (2006)[27]	Anesthesiology	Postop patients (n = 20)	Left prefrontal cortex stimulation. Nonchronic neuropathic pain patients and no clear description of neuroanatomical origin of pain
3	PubMed EMBASE	Brighina et al (2004)[28]	J Neurol Sci	Migraine patients (n = 11)	Left DLPFC stimulation and no clear description of neuroanatomical origin of pain
4	PubMed EMBASE	Clarke et al (2006)[29]	J Headache Pain	Migraine patients (n = 42)	rTMS given over headache area and no clear description neuroanatomical origin of pain
5	Cochrane	Dougall et al (2006)	Cochrane Database of Systematic Reviews	Schizophrenic patients	Non–pain-related review article
6	PubMed Psychoinfo	Fregni et al (2005)[30]	Annuals of Neurology	Patients with visceral pain (n = 5)	No clear description neuroanatomical origin of pain
7	PubMed	Fregni et al (2006)[31]	Pain	Patients with traumatic spinal cord injury (n = 17)	Transcranial direct current stimulation of the motor cortex was used for the study; a non-rTMS study
8	Cochrane Cinahl	Furlan et al (2002)	Cochrane Database of Systematic Reviews	Nonspecific low back pain	Non–rTMS-related review article
9	PubMed	Graff-Guerrero et al (2005)[32]	Brain Res Cogn Brain Res	Healthy subjects	Nonchronic pain study with DLPFC rTMS stimulation
10	Cochrane	Hoare BJ et al (2007)	Cochrane Database of Systematic Reviews	Children with cerebral palsy	Non–pain-related review article
11	PubMed	Inghilleri et al (2004)[33]	Exp Brain Res	Neuropathic pain patients on anticonvulsants (n = 23)	Only change in motor evoked potentials were assessed in the study
12	EMBASE	Iribacher et al (2006)	Nervernarzt	Patients with central (n = 13) and phantom limb (n = 14) pain	Non-English publication
13	PubMed	Kofler et al (1998)[34]	Neurosci Lett	Healthy subjects (n = 5)	Nonchronic pain study
14	PubMed	Lee et al (2005)[35]	Neurosci Lett	Patients with schizophrenia (n = 39)	Non–pain-related studies with rTMS at temporoparietal areas
15	Cochrane	Martin et al (2001)	Cochrane Database of Systematic Reviews	Patients with depression	Non–pain-related review article
16	Cochrane	Martin et al (2003)	Cochrane Database of Systematic Reviews	Patients with obsessive-compulsive disorder	Non–pain-related review article
17	Cochrane	Martinsson L et al (2007)	Cochrane Database of Systematic Reviews	Post-stroke patients	Non–pain-related review article
18	PubMed	Mosimann et al. (2000)[36]	Psychiatry Res.	Healthy subjects (n = 25)	Nonchronic pain subjects
19	PubMed	Padberg et al (2002)[37]	Neuropsycho-pharmacology	Patients with depression (n = 31)	Not a neuropathic pain rTMS study
20	PubMed	Pleger (2004)[23]	Neurosci Lett	Patients with complex regional pain syndrome (n = 10)	No clear description of neuroanatomical origin of pain
21	PubMed	Pope et al (1994)[38]	Spine	Patient with low back pain	A transcutaneous muscular stimulation (TMS) study
22	PubMed	Passard et al (2007)[39]	Brain	Patients with fibromyalgia (n = 30)	No clear description of neuroanatomical origin of pain
23	PubMed	Rosenberg et al (1985)[40]	Ann Emerg Med	Patient with urinary tract infection (n = 52)	An antibiotic study with trimethoprim-sulfamethoxazole (TMS). Non–pain-related study
24	PubMed	Schwenkreis et al (2003)[41]	Neurology	Patients with CRPS (n = 25) and healthy subjects (n = 20) as controls	Main assessment was intracortical motor cortex stimulations

Table 1B. Continued

	Data Base	Authors (Year)	Abbreviated Publication Name	Subject Population	Main Reasons of Exclusion
25	PubMed	Smania et al (2005)[42]	J Neurol	Patients with myofascial pain (n = 56)	A non-rTMS study
26	PubMed EMBASE	Svensson et al (2003)[43]	Eur J Pain	Healthy subjects with experimental pain	Non-neuropathic pain states
27	Cochrane	Tharyan et al (2005)	Cochrane Database of Systematic Reviews	Patients with schizophrenia	Non–pain-related review article
28	Cochrane	Van der Wurff et al (2003)	Cochrane Database of Systematic Reviews	Depressed elderly	Non–pain-related review article

3 studies (Andre-Obadia et al, Hirayama et al, and Khedr et al). The interaction of pain duration and treatment was not significant. None of these studies reported any major side effect such as seizures or any significant neurological deficits related to the rTMS interventions. The pretreatment VAS scores were only available from 3 studies (Hirayama et al, Lefaucheur et al, Khedr et al). The interaction of pretreatment VAS scores and treatment was not significant either including or excluding the Khedr et al study.

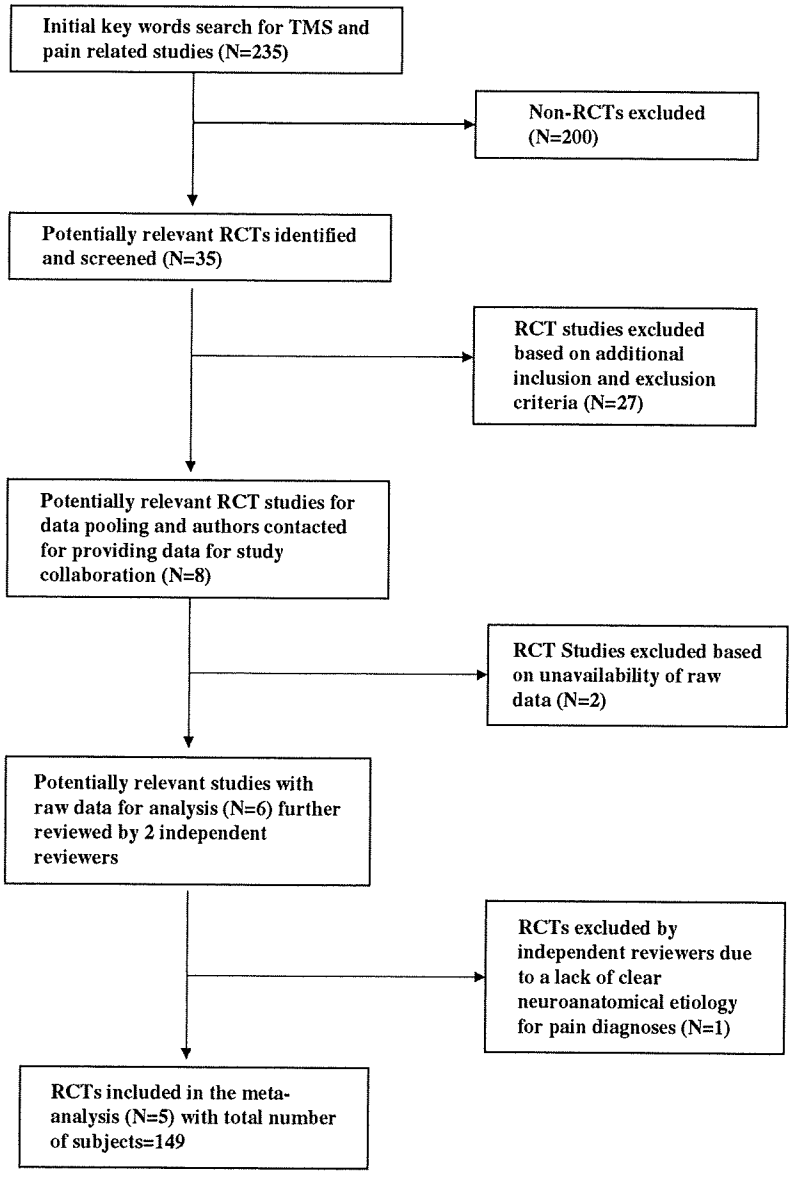

Figure 1. Search flow sheet. RCT, randomized controlled trials; TMS, transcranial magnetic stimulation.

Table 2. Summary of Studies and Gender Distribution

Gender	Female		Total
Khedr et al (2005)[22]	26	53.1%	49
Rollnik et al (2002)[24]	6	50.0%	12
Lefaucheur et al (2004)[19]	32	53.3%	60
Andre-Obadia et al (2006)[25]	4	33.3%	12
Hirayama et al (2006)[21]	7	43.8%	16
Total	75	50.3%	149

Neuroanatomical Origins of Pain and Treatment Effect

The effect of diagnosis (Fig 3) by treatment interaction was marginally significant (Wald test $P = .053$). We found the TGN subgroup (Fig 3) to have the greatest treatment effect (28.8% mean difference in VAS reduction), followed by PSP (16.7%), SC (14.7%), NR (10.0%), and PN (1.5%). In addition, the results were similar when we excluded the Khedr study, with the greatest treatment effect observed in TGN (33.0%), followed by SC (14.7%), PSP (10.5%), NR (10.0%), and PN (1.5%).

Treatment Parameters

Because of the statistical concern of colinearity, we performed the expected analyses for outcome related to treatment parameters by reducing the analytical approach to simple 2-sample *t* tests (low number of pulses vs high and low range frequency versus high) in which we pooled all experimental arms. The effects of the number of pulses (low: ≤1000 vs high) and frequency (low: >1 and ≤ 10 Hz vs high: >10 and <20 Hz) were sensitive to the inclusion of the Khedr et al study. When we excluded Khedr (a high-pulse, high-frequency study), low pulse ($P = .038$), and frequency in the range of ≤10 and >1 Hz ($P < .001$) are more efficacious compared with frequency above 10 Hz. However, including the Khedr et al study, more pulses given per session of treatment appeared to be more effective (2-sample *t* test, $P = .043$) and there was no significant difference between high frequency (>10 and ≤20 Hz) and low frequency (≤10 and >1 Hz). This paradox might be explained by the multiple (n = 5) therapy sessions being used by Khedr et al, whereas the other studies used single therapy session. Comparing the results of Khedr et al with the other studies, we found that the reduction in VAS with TMS compared with sham was 20.4% ($P = .003$) greater with 5 sessions compared with the single session studies. Of note, Rollnik's study used a nonfocal circular coil, whereas all the other 4 studies adopted a figure-of-8 coil. This difference in TMS coil design may attribute to the less robust effect reported in Rollnik's study as compared with the other studies included in the analysis.

Discussion

Statistical Concern

Previous reviews have provided the readers with useful qualitative overviews about the analgesic effect of rTMS and its potential usage in clinical pain management.[14,44-46] However, to the best knowledge of the authors, this is the first PID-based meta-analysis conducted to qualitatively assess the efficacy of rTMS in treating different neuropathic pain states related to their neuroanatomical origins. Although using summary statistics extracted from the literature is a common means to conduct a meta-analysis, PID is by far the preferred method for this type of analysis.[47,48] Stewart et al[47] suggest that PID should be used for meta-analysis whenever possible because this "provides the least biased and most reliable means of addressing questions that have not been satisfactorily resolved by individual clinical trials." Therefore, to address the clinically and mechanistically relevant issues being raised in the current study, a PID-based meta-analysis with the appropriate selection criteria serves as the most effective analytical approach for the task. Given that 1 of our main objectives was to specifically assess whether neuroanatomical origins of pain could affect rTMS analgesic effect, it was necessary for the analysis to strictly exclude studies in which neuroanatomical origins of pain were not clearly indicated. Despite these stringently designed selection criteria, 2 of the available articles that consisted of the highest number of subjects for RCTs in this field were included in the analysis.[19,22] Therefore, the analysis was equipped with the adequate statistical power to address the specific questions being raised, especially when we were able to obtain and combine individual raw data (n = 149) from studies containing the highest number of subjects.

Treatment Efficacy

The result of this PID-based meta-analysis indicates that rTMS can provide significant pain reduction in patients with various neuropathic pain conditions. The analysis also suggests that rTMS treatment may be

Table 3. Summary of Studies and Neuroanatomical Etiologies for Pain

	NR	PN	PSP	SC	TGN	Total
Khedr et al (2005)[22]	None	None	25 (51.0%)	None	24 (49.0%)	49
Rollnik et al (2002)[24]	3 (25.0%)	7 (58.3%)	None	2 (16.7%)	None	12
Lefaucheur et al (2004)[19]	12 (20.0%)	None	24 (40.0%)	12 (20.0%)	12 (20.0%)	60
Andre-Obadia et al (2006)[25]	1 (8.3%)	1 (8.3%)	9 (75.0%)	1 (8.3%)	None	12
Hirayama et al (2006)[21]	1 (6.2%)	1 (6.2%)	8 (50.0%)	3 (18.8%)	3 (18.8%)	16
Total	17 (11.4%)	9 (6.0%)	66 (44.3%)	18 (12.1%)	39 (26.2%)	149

Abbreviations: NR, nerve root; PN, peripheral nerve; PSP, post-stroke supraspinal related pain; TGN, trigeminal nerve or ganglion.

Table 4. Summary of Treatment Parameters

Study	Design	Pulses/Session	Coding for Pulses	Frequency	Coding for Frequency	Sessions	Coding for Sessions
Khedr et al (2005)[22]	Parallel	2000	High	20 Hz	High	5	Multiple
Rollnik et al (2002)[24]	Cross-over	800	Low	20 Hz	High	1	Single
Lefaucheur et al (2004)[19]	Cross-over	1000	Low	10 Hz	Low	1	Single
Andre-Obadia et al (2006)[25]	Cross-over	1600	High	20 Hz	High	1	Single
Hirayama et al (2006)[21]	Cross-over	500	Low	5 Hz	Low	1	Single

particularly effective in alleviating pain in patients with TGN-related pain. Since our estimate of treatment effect for TGN subjects both with and without the Khedr et al study was similar and consistently the highest among all coded pain origins (33.0% and 28.8%, respectively), we discerned that this observation was due to the fact that the Khedr et al study was the only study that used multiple treatment sessions and 61.5% of the TGN data were extracted from this study (49.0% of the subjects in Khedr et al study were TGN). Instead, we postulated that this observed analgesic effect was largely due to the neuroanatomical origins of pain and the underlying analgesic mechanisms of rTMS.

Neuroanatomical Origins of Pain and Treatment Outcome

Although statistically marginally significant, the overall trend of efficacy related to the pain origins as observed in the current analysis suggests that rTMS study may have a differential analgesic effect based on neuroanatomical origins of the neuropathic pain pathophysiology with more effective treatment response observed in neuropathic pain states originating from the "top" (supraspinal, cranial or spinal) than the "bottom" (nerve root or peripheral nerve) locations in the overall cranio-caudal neuroanatomical scheme. This observed differential trend is unlikely simply due to sample size or treatment session differences because overall there were more subjects with PSP (44.3%) than TGN (26.2%) related pain etiologies, and a similar differential effect was observed with or without the Khedr et al study, in which multiple treatment sessions were used. In addition, 1 of the important distinctions among the pain pathophysiology originating from the "top" locations is that subjects with pain related to PSP usually consist of lesions that may directly impact centrally mediated pain modulatory pathways, whereas in TGN-related neuropathic pain conditions, these pathways are usually uninterrupted. Therefore, this observed differential response pattern alludes to the underlying mechanisms of rTMS induced analgesic mechanisms further discussed in the "Potential Analgesic Mechanisms of rTMS" section of the report.

In addition, outside the scope of the current analysis are neuropathic pain states that may involve both peripheral and central nervous systems as in the case of complex regional pain syndrome (CRPS Type I). A single session of rTMS in patients with CRPS Type I has demonstrated significant short-term analgesic benefit with rTMS in comparison to sham.[23] Similarly, due to the absence of clearly defined neuroanatomically correlated etiology, not included in the analyses were also RCTs that have demonstrated the analgesic effect of rTMS for fibromyalgia and migraine headache.[28,29,39] Although some may consider these chronic pain conditions consist of a more centrally than peripherally originated pathophysiology, the exact neuroanatomical correlation and the underlying pain pathophysiology of these conditions have not been well defined in current literature. In addition, 2 of these studies also used stimulation sites other than the motor cortex.[28,29] Therefore, considering the objectives of the current analysis, to include these studies in the current analysis would undoubtedly cloud the interpretation of the analyzed result. With these concerns, these studies were reasonably excluded.

Table 5. Sham Conditions

Study	Sham Conditions
Khedr et al (2005)[22]	Coil elevated from the skull with a nonspecified angle
Rollnik et al (2002)[24]	Coil elevated with a 45° angle from the skull
Lefaucheur et al (2004)[19]	Placebo coil
Andre-Obadia et al (2006)[25]	Sham coil on top of active coil at a 90° angle
Hirayama et al (2006)[21]	Coil elevated with a 45° angle from the skull

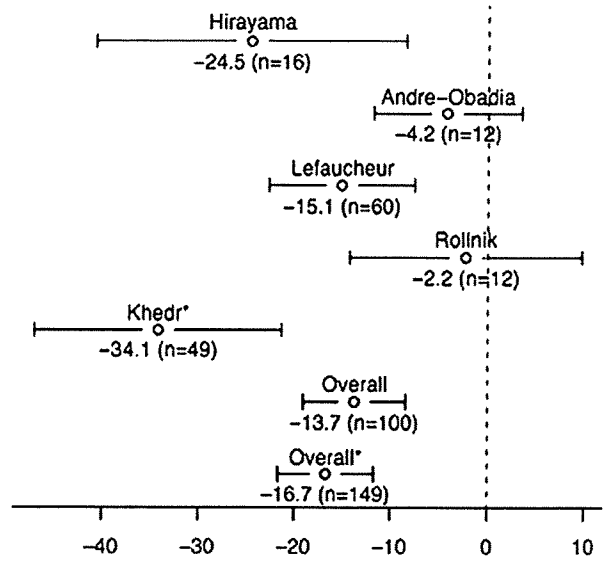

Figure 2. Treatment effect analysis. Mean difference (95% confidence interval) in percent of pain visual analog scale (VAS) score change. *$P < .05$.

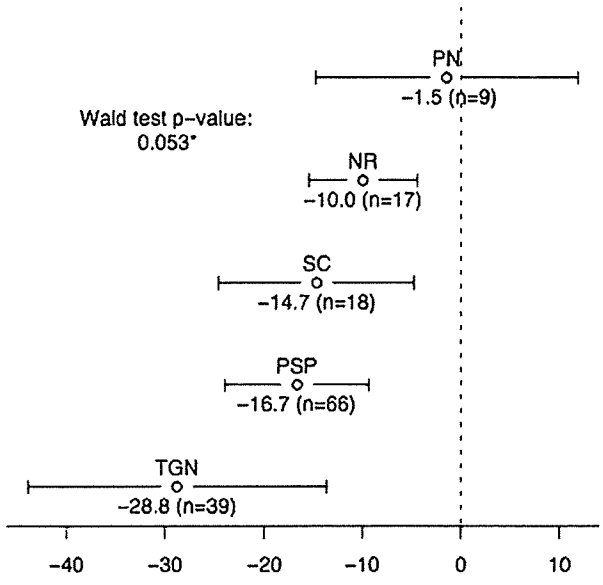

Figure 3. Diagnosis and treatment effect. Mean difference (95% confidence interval) in percent of pain visual analog scale (VAS) score change.*P value is from Wald test for the interaction effect of diagnosis and treatment on the percent decrease in VAS score. This P value increases to 0.140 when we exclude the Khedr study. NR, nerve root; PN, peripheral nerve; PSP, post-stroke supraspinal related pain; TGN, trigeminal nerve or ganglion.

Site of Treatment

To minimize confounding factors such as stimulation location difference in the analysis and considering most RCTs in pain with rTMS were conducted with motor cortex stimulation, we selectively included studies with motor cortex (M1) stimulation in the analysis. Of the excluded chronic pain RCTs, which used rTMS stimulation at locations other than the motor cortex, other selection criteria such as "no clear description of neuroanatomical origin of pain" also attributed to their exclusion (Table 1B).[26,28,29] Therefore it would not be feasible to include those studies in the site-related treatment effect analysis. Of note, the favorable analgesic effect of M1 in comparison to other cortical areas (premotor, primary somatosensory, and supplemental motor association cortex), except the prefrontal cortical areas, was nicely demonstrated by Hirayama et al[21] in a previous study. However, considering the small number of RCTS that used prefrontal cortical rTMS for pain and other aforementioned confounding factors, to further compare the analgesic effect of motor verses specific prefrontal cortical rTMS stimulations would be beyond the scope of the current analytical power.

Treatment Parameters

Previous studies with measurement of motor-evoked potentials have demonstrated that the effect of TMS in cortical excitability was frequency and intensity dependent. Traditionally, stimulation below or equal to 1 Hz is considered low frequency rTMS, which has been shown to decrease cortical excitability, whereas high frequency (>1 Hz) rTMS can increase cortical excitability.[49,50] There is evidence to suggest that treatment frequency above 1 Hz provides better analgesic effect than low frequency (≤1 Hz) for pain.[51] In the current analysis, all the studies (except 1 group from André-Obadia) used high stimulation frequency in the range of 5 to 20 Hz. When we assessed the treatment effect within the high frequency stimulation at either above (higher range) or below (lower range) 10 Hz with a single treatment session, we established that the treatment effect at the lower range were more effective in comparison to higher range frequency stimulation. However, adding the Khedr et al study with multiple sessions at 20 Hz, we found that stimulation given at the higher range to have a better analgesic effect as compared with the lower range frequency stimulation. This paradoxical observation suggests that the number of treatment sessions rendered may have a more profound impact on the overall analgesic effect than the treatment frequency itself. However, considering other variables involved in the analysis, further controlled studies are required to assess how these specific treatment parameters may differ in analgesic efficacy in specific neuropathic pain conditions.

Furthermore, as noticed in the result difference between Rollnik's study and other included studies, TMS coils such as the figure-of-8 coil that can deliver more focal stimulation may generate a more favorable clinical outcome in comparison to coils that deliver less focal stimulation. The importance of the coil design in regard to stimulation precision and the corresponding clinical outcome may be largely due to the fact that M1 consists of a clear somatopical boundary as demonstrated in previous studies with either noninvasive or invasive M1 stimulation.[7,52] Therefore, information derived from the current analysis can serve as a useful reference in considering coil selection and the choice of frequency, pulse, and number of session rendered per treatment protocol.

Potential Analgesic Mechanisms of rTMS

It is now well known that chronic pain states are associated with plastic changes in the nervous system and that the development of neuropathic pain states may involve functional changes in supraspinal components involved in pain perception.[53-75] Therefore, 1 of the hypothesized mechanisms for the observed analgesic effect of rTMS is that the noninvasive stimulation can induce plastic changes in the brain, which in turn corrects or modulates plastic changes associated with chronic pain. Initial evidence suggests that TMS affect central neurotransmitters activity in other neurological diseases.[76-78] However, how these TMS-related neurochemical changes may functionally affect supraspinal pain processing is largely unknown. Studies from direct motor cortex stimulation (MCS) suggest that motor cortex stimulation may result in direct inhibition of regions of brain involved in emotional response of pain and/or induce mechanisms that will trigger descending inhibitory pathway to act at the dorsal horn level. The former consists of brain region such as the anterior cingulate cortex (ACC), and the later consists of brain areas such as the brainstem periaqueductal grey matter (PAG).[79-85]

Other studies also indicate the possible role of endogenous opioid secretions triggered by long-term MCS.[86,87] Although whether similar analgesic mechanisms may occur with rTMS or not has yet to be defined, the observed neuroanatomically based differential order of clinical efficacy in the current analysis is in line with these hypothesized analgesic mechanisms of rTMS. The current analysis also suggests the importance of the proximity of pain origin to the central nervous system and the overall intactness of the pain modulatory pathways in affecting the potential analgesic effect of rTMS.

Study Limitations

Potential limitation of the analysis is unequal and unbalanced number of subjects per diagnosis with respect to the parameters of the treatment (eg, number of treatment sessions). In particular, this imbalance made it impossible to control for diagnosis while assessing the effect of the number of treatment session.

In short, this is the first PID-based meta-analysis that quantitatively and collectively demonstrates the overall treatment effect of rTMS in various neuropathic pain conditions. This analysis further suggests the effect of rTMS on neuropathic pain may consist of a differential "top-down" pattern based on the neuroanatomical origins of the neuropathic pain pathophysiology and the intactness of the intrinsic pain modulatory pathways. On the other hand, treatment parameters may also affect the outcome. A multiple session and/or low range, high frequency rTMS treatment protocol may generate better analgesic effect for neuropathic pain conditions compared to a single session protocol with higher frequency range stimulation. However, the authors cautioned that a definitive conclusion should and could not be solely derived from a single analysis. Further studies are required to thoroughly assess the effect of treatment parameters and/or duration on analgesia in patients with presumably centrally originated neuropathic pain. In addition, long-term cost analysis comparing rTMS with other pain management modalities should be conducted if repetitive/maintenance treatments are to be considered as a routine ongoing pain intervention option.

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Neural decoding using gyral and intrasulcal electrocorticograms

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ABSTRACT

Electrocorticography of the primary motor cortex (M1) is a promising tool for controlling a brain–computer interface (BCI). Electrocorticograms (ECoG) of the human M1 within the central sulcus (intrasulcal ECoG) have been rarely examined. In order to evaluate the usefulness of intrasulcal ECoG for BCI, we examined patients with subdural electrodes placed temporarily inside the central sulcus and over the sensorimotor cortex (gyral ECoG). Five patients were asked to perform or imagine two or three classes of simple upper limb movements. Univariate statistical analysis of the results revealed that the intrasulcal ECoG on M1 showed significant variability across movement classes. A support vector machine was used for classification of single-trial ECoG signals to infer movement class (neural decoding). The movement classes were predicted with 80–90% accuracy (chance level: 33% or 50%). To reveal the relative importance of anatomical areas for neural decoding, the decoding performance was compared between gyral and intrasulcal ECoGs. The intrasulcal ECoG on the motor bank showed higher performance than the equally-sized gyral ECoG or the intrasulcal ECoG on the sensory bank. Analysis using a short time window revealed that movement class could be decoded even before movement onset. These results suggest the usefulness of intrasulcal ECoG on M1 to infer upper limb movements and present a promising application for a practical BCI system.

Introduction

The primary motor cortex (M1) is one of the most important regions for a brain–computer interface (BCI), such as a prosthetic device for paralyzed humans (Wolpaw et al., 2002). Previous studies have demonstrated encouraging results from application of M1 activities for a BCI with various types of signal platforms: electroencephalography (EEG) and/or magnetoencephalography (MEG) (Birbaumer et al., 1999; Blankertz et al., 2007; Georgopoulos et al., 2005; Mellinger et al., 2007; Waldert et al., 2008; Wolpaw and McFarland, 2004), neuronal ensemble activity recorded intracortically (Donoghue, 2002; Georgopoulos et al., 1986; Hochberg et al., 2006; Serruya et al., 2002; Truccolo et al., 2008; Wessberg et al., 2000), local field potentials (Andersen et al., 2004; Mehring et al., 2004, 2003; Rickert et al., 2005) and electrocorticography (Leuthardt et al., 2004; Pistohl et al., 2008; Schalk et al., 2008). Each type of signal has proven to be useful for a BCI. Of these, using the electrocorticogram (ECoG) has several advantages as a candidate for a clinically feasible BCI signal platform. It has higher spatial resolution and better signal-to-noise ratio compared to EEG/MEG, with lower technical difficulty, lower clinical risk, and superior long-term stability compared to intracortical single-neuron recording (Leuthardt et al., 2006).

Despite its advantages, ECoG of the human M1 has been evaluated only using electrodes on the surface of the gyrus (gyral ECoG), due principally to the limited access to subjects. Notably, ECoGs within the central sulcus (intrasulcal ECoG) have not been studied, though much of the human M1 is located within the central sulcus (Rademacher et al., 2001; Takahashi et al., 2002; White et al., 1997). To record the intrasulcal ECoG, the sulcus must be dissected and the electrodes inserted there. This invasive procedure has discouraged the use of intrasulcal ECoG on the human M1 (sulcal M1).

In order to evaluate the usefulness of sulcal M1, we examined patients who had subdural electrodes placed temporarily inside the central sulcus and over the sensorimotor cortex for the treatment of intractable pain (Hosomi et al., 2008; Saitoh and Yoshimine, 2007).

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Table 1
Clinical profiles and movement types

Patient	Age/ sex	Cause of pain	Gyral electrodes		Sulcal electrodes M1/S1	Classes of movements
			Number	Location		
1	69/M	Lt. TH	18/20	Lt. sensorimotor	+/+	Execution of T/H/E
2	54/F	Lt. TH	20/20	Lt. sensorimotor	+/+	Execution of H/E
3	71/M	Lt. TH	20/20	Lt. sensorimotor	+/−	Execution of H/E
4	33/M	Lt. BPA	20/20	Rt. sensorimotor	+/−	Imagery of T/H/E
5	49/M	Lt. BPA	20/20	Rt. sensorimotor	+/+	Imagery of T/H/E

Abbreviations: M, male; F, female; Rt., right; Lt., left; TH, Thalamic hemorrhage; BPA, Brachial plexus avulsion; T, Thumb flexion; H, Hand grasping; E, Elbow flexion.

The ECoG was recorded while the patients executed or imagined two or three classes of simple upper limb movements once per several seconds. Single-trial ECoG for each movement was analyzed to compare the gyral and intrasulcal ECoG. We performed a univariate statistical analysis and a support vector machine classification (Kamitani and Tong, 2005) of the single-trial ECoG to reveal the relative importance of the gyral and intrasulcal ECoG for predicting upper limb movements. We also studied the time course of classification accuracy using short time windows. The results demonstrated that the sulcal M1 provides the most informative signal to predict executed and imagined movements compared with other electrodes placed on the sensorimotor cortex.

Subjects and methods

Subjects and electrode implantation

The five subjects in this study were patients suffering from chronic intractable neuropathic pain (ICD-10: R52.1). Their pain was refractory, though they were appropriately treated by anesthesiologists for at least 6 months with non-steroidal anti-inflammatory drugs (NSAIDs), anti-anxiety drugs, anti-epileptic drugs, and anti-depressants as required. The clinical profiles of the patients are summarized in Table 1. They underwent temporary placement of subdural electrodes to determine the optimal sites for motor cortex stimulation (MCS), a treatment to reduce intractable pain by electrical stimulation of the sensorimotor cortex (Saitoh et al., 1999; Saitoh and Yoshimine, 2007; Tsubokawa et al., 1991). The decision to administer this treatment was made based on the following factors: the effectiveness of repeated transcranial magnetic stimulation (rTMS) on M1, their unresponsiveness to other treatments, the deficiency of motor functions, and the patient's wishes. All patients provided written informed consent to participate in this experimental treatment, which was approved by the Ethics Committee of Osaka University Hospital (Hosomi et al., 2008). We also explained the purpose and possible consequences of this study of neural decoding to all subjects, and obtained separate written informed consent (approved by the Ethics Committee of Osaka University Hospital).

Each patient had 22 to 28 planar-surface platinum electrodes (configured in grids or strips) placed over the sensorimotor cortex. The electrodes had a diameter of 3 mm and an inter-electrode distance of 1 cm center-to-center (Fig. 1). Patients 1, 2, and 5 had two 4-strip electrode arrays inserted on the anterior and posterior walls of the central sulcus (anterior electrodes: Resume; Medtronic, Inc., Minneapolis, MN) (posterior electrodes: Unique Medical Co., Tokyo, Japan) (see Figs. 1a, b and Hosomi et al., 2008), while patients 3 and 4 had only one 4-strip electrode array implanted on the anterior wall of the central sulcus (Table 1, Fig. 1c). A 20- or 14-grid electrode (4×5 or 2×7 array; Unique Medical Co.) was placed over the sensorimotor cortex. Patient 5 had a 14-grid electrode placed over the precentral gyrus (Fig. 1c). Electrode placements were based solely on the patients' clinical requirements, without any consideration for utility in this study.

The anatomical location of the implanted electrodes was confirmed by standard neurosurgical techniques (both anatomically and electrophysiologically). Under general anesthesia, a fronto-parietal craniotomy (area: 5 cm×6 cm) was performed over the sensorimotor cortex. The location of the central sulcus was targeted using

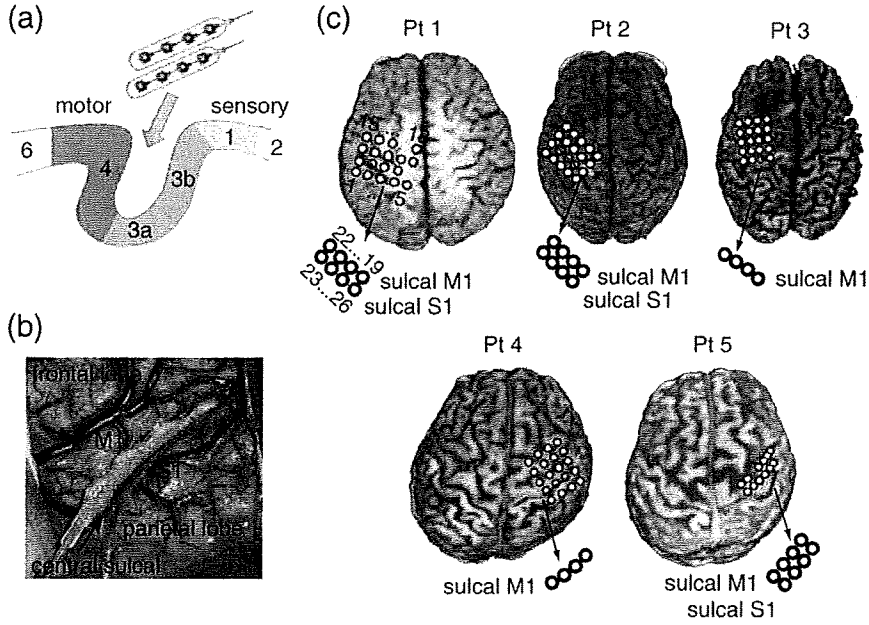

Fig. 1. Location of implanted subdural electrodes. (a) Schematic diagram of intrasulcal ECoG. The sagittal section of the central sulcus is illustrated, with Brodmann area shown. The anterior wall of the central sulcus corresponds to Brodmann area 4 (M1). The central sulcus was dissected to place two electrodes on the anterior and posterior wall. (b) A macroscopic view of the brain surface and implanted intrasulcal electrodes. Two intrasulcal electrodes were inserted on M1 and the somatosensory (S1) cortex within the central sulcus. (c) Structural magnetic resonance imaging of each patient with a superimposed figure showing the position of 20- or 14-channel grid electrodes (white circle) and two 4-channel strip electrodes (red line) within the central sulcus. Two intrasulcal electrodes facing the opposite side of the sulcus were shown as a single line. A green line indicates the location of the central sulcus. For patient 1, the number of the electrode was printed on the figure. For patients 1 and 5, two gyral electrodes were excluded from the analysis due to severe noise contamination.

preoperative magnetic resonance imaging and confirmed by intraoperative somatosensory evoked potentials. Cortical stimulation for motor evoked potentials was performed for patient 5 only; the results showed that the location of the primary motor cortex was accurately estimated by our standard techniques (data not shown). The central sulcus was then dissected with microsurgical manipulation to expose the anterior and posterior walls. The electrode arrays were implanted to record intrasulcal ECoG on M1 (sulcal M1) and S1 (sulcal S1).

Movement tasks

Experiments were performed approximately 1 week after electrode placement. Patients were seated upright in hospital beds. Patients 1, 2, and 3 were instructed to perform movements of the arm contralateral to the implanted electrodes. They performed three classes of upper limb movement (execution of thumb flexion, hand grasping, and elbow flexion) successively 20 to 40 times at a self-paced rate of approximately once per 3 to 8 s for about 5 min. However, patients 2 and 3 performed only two classes of movement (hand grasping and elbow flexion) due to their thumb paresis (Table 1). Electromyogram (EMG) recordings of the contralateral flexor pollicis muscle, the flexor digitorum superficialis muscle, and the biceps brachii muscle were collected at the same time.

Patients 4 and 5, who each had monoplegia on their left upper limb due to brachial plexus avulsion, were instructed to attempt to perform or imagine performing three classes of movement (thumb flexion, hand grasping, and elbow flexion). They were instructed not to physically move their limbs, though they each could move only their elbow slightly due to nerve transplantation to their biceps muscle. Their movements were evaluated visually and by EMG. Only slight EMG responses on their biceps muscles were observed, with no visually apparent movement. These patients were instructed to imagine each movement only once immediately after a presentation of a visual cue. The cues were delivered in a presentation window placed in front of the patients once per 4 s. Patients were instructed regarding the movement tasks via cues on the window 40–100 times for each movement.

Data collection and preprocessing

Electrocorticograms were measured using a 64-channel digital EEG system (EEG 2000; Nihon Koden Corporation, Tokyo, Japan) and digitized at a sampling rate of 1000 Hz. All subdural electrodes were referenced to a scalp electrode placed on the nasion. In the case of patients 1 and 5, two electrodes were eliminated from the analysis due to severe noise contamination (Fig. 1c).

For classification of executed or imagined movement, electrical potentials of the ECoG of each electrode and time window during a 1000-ms interval were examined (executed: −500 ms to +500 ms from movement onset; imagined: 0 ms to 1000 ms from cue onset). The signals were normalized by subtracting the mean and dividing by the standard deviation (SD) of the same electrode's potentials during the initial 500-ms interval of each trial (executed: −1500 ms to −1000 ms from the movement onset; imagined: −500 ms to 0 ms from cue onset). The normalized 1000-ms signals correspond to the single-trial ECoG for each movement. The movement onset was determined by the initial rising edge of the EMG waveform.

The normalized amplitudes of each electrode were then re-sampled over an average 100-ms time window, sliding by 50-ms. The averaged normalized amplitude was used as a feature for the classification of movement. We call this feature the 'smoothed movement-related cortical potential' (sMCP) and it corresponds to a slow component of the ECoG signal relating to movement. In previous studies, it was also found to be the most informative signal part of the ECoG, where it was called the local motor potential (Schalk et al., 2007) or the low-frequency component (Pistohl et al., 2008). Both features were successfully used for the decoding of movement trajectories and direction from ECoG (see Discussion). In our preliminary analysis, we tested other features based on the power spectrum of ECoG signals, in an attempt to exploit a wide range of frequency information (mean power in each 5-Hz band ranging from 5- to 100-Hz as a feature). But such features did not outperform the sMCP features. Thus, in this paper, we focus on the results obtained from the sMCP features.

To reveal how classification performance depends on time from movement onset, the short-duration ECoG was examined. For patients 1–3 who performed execution tasks, 4000-ms ECoG signals (−2000 ms to +2000 ms from movement onset) were selected and normalized by the mean and SD of each electrode's ECoG signal over 500-ms intervals (−2000 ms to −1500 ms from the movement onset). The normalized signals from the 4000-ms interval were divided into 200-ms time windows without overlap (a total of 20 time windows). Classification of the movements was performed for each of the 200-ms time domains. The sMCP was used as a feature for classification, and each time domain of each electrode had only three sMCP values. Classification performance of each time domain was compared to evaluate the time dependency.

Univariate analysis

Univariate statistical analysis of each sMCP was performed to reveal which anatomical area and time domain showed statistically significant variability among the movement classes. The *F*-value of the one-way analysis of variance (ANOVA) on each sMCP value was examined across the two or three classes of movement. For each patient, four gyral electrodes were selected in order for the highest averaged *F*-value. The ECoG with the selected four gyral electrodes was called 'gyral (4) — highest F' and compared with the intrasulcal ECoG.

Decoding analysis

We constructed a linear classifier (decoder) to predict movement class on a trial-by-trial basis. The decoder calculated the linearly-weighted sum of the ECoG features plus bias for each class, and the class with the maximum value was chosen as the predicted movement class (Kamitani and Tong, 2005). Individual weights and bias for each class were determined using a linear support vector machine applied to a training data set (Vapnik, 1998). The SVM algorithm was implemented using Matlab 2006b (Mathworks; Natick, MA) (see (Kamitani and Tong, 2005; Vapnik, 1998) for details of the decoding procedure).

In order to test generalization of the decoder, we used 5-fold cross-validation as our performance measure (Bengio and Grandvalet, 2004; Breiman, 1996). We randomly divided the trials into five blocks, using four for training and one for testing. We then used all of the training data to train the classifier and evaluated performance on the test data. This routine was repeated five times, and the averaged percent correct over all runs is presented as a measure of decoder performance. The binomial test was applied to the frequency of correct classification to confirm that the classification performance exceeded the chance level.

We performed the decoding analysis on all or subgroups of electrodes. We compared the following anatomically defined electrode groups: 'all', all the implanted electrodes except the noisy channels; 'gyral', all the gyral electrodes except the noisy channels; 'sulcal M1', the four intrasulcal electrodes on M1; and 'sulcal S1', the four intrasulcal electrodes on S1. In addition, to equalize the number of electrodes with that of the intrasulcal ECoG ('sulcal M1' and 'sulcal S1'), we evaluated the performance of four gyral electrodes by the following ways: 'gyral (4) — mean of all combinations', the mean performance of all combinations of four gyral electrodes; 'gyral (4) — highest F', the performance of the four gyral electrodes that showed the highest *F*-values in the univariate analysis of sMCP (the blue

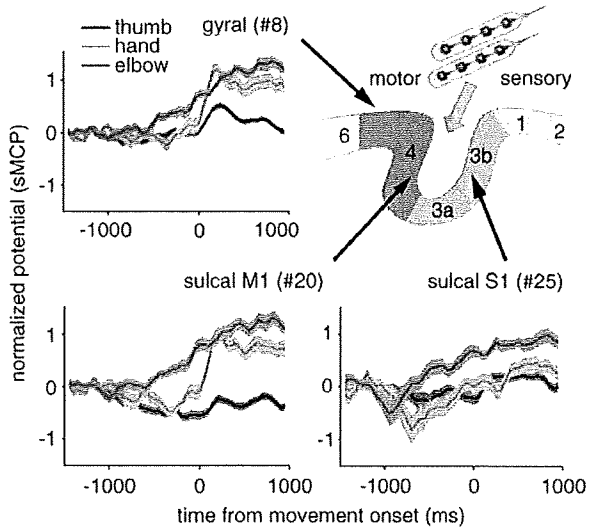

Fig. 2. An example of sMCP values. Each plot shows the time course of the sMCP values in representative electrodes locating adjacent to each other: #8, the gyral ECoG on the precentral gyrus; #20, the intrasulcal ECoG on M1; #25, the intrasulcal ECoG on S1 locating at the opposite side of #20 (patient 1). The curves depict the mean signals (shadow, standard error) averaged in each movement class: black, thumb flexion; green, hand grasping; red, elbow flexion. Time 0 corresponds to the onset of movement.

circles in Fig. 4); and 'gyral (4) – best combination', the performance of the best combination of four gyral electrodes (detailed below).

Since the estimate of classification performance by the cross-validation procedure has variance, the best performance obtained by testing all combinations becomes higher than the true performance: even if movement classes were randomly shuffled across trials such that ECoG signals can never predict the movement class, the 'best' performance among all combinations became significantly higher than the chance level. To obtain an unbiased estimate of performance, we conducted a nested cross-validation procedure. In each of the 5-fold cross-validation steps, the classification performance of all combinations was evaluated by 4-fold cross-validation within the training data (four out of five groups). Then, the electrode combination that produced the highest correct rate was selected, and its generalization performance was evaluated on the independent test data (the remaining one group). This procedure was repeated five times, and the averaged correct rate was used for the performance of 'gyral (4) – best combination'. Note that selected four electrodes could be different in each cross-validation step.

To compare the classification performances between the gyral and intrasulcal ECoG, kappa coefficients (Cohen, 1960) were calculated between the performed movement classes and decoding results. Although 'averaged percent correct' is a simple measure of decoding, we were not able to compare the percent correct between all patients due to the difference in the class size of the movement task (i.e., three classes for patients 1, 4 and 5 versus two classes for patients 2 and 3). To compensate for the differences among patients, the kappa coefficient was introduced, because it does not depend on class size to measure agreement between two groups (Cohen, 1960). The kappa coefficient has been shown applicable in the field of BCI research (Schlogl et al., 2005). We calculated the kappa coefficients between the performed movement classes and the decoding results, then compared the seven electrode groups ('all', 'gyral', 'sulcal M1', 'sulcal S1', 'gyral (4) – mean of all combinations', 'gyral (4) – highest F' and 'gyral (4) – best combination'). A paired t-test was applied to evaluate the statistical differences among 'sulcal M1', 'sulcal S1', 'gyral (4) – mean of all combinations', 'gyral (4) – highest F' and 'gyral (4) – best combination'.

The value of the kappa coefficient is always ≤ 1, with a value of 1 implying perfect agreement between the decoded results and performed movement classes. To estimate the kappa coefficient, the matrix $\boldsymbol{H}_{ij}$ ($i,j=1...M$, where M is the number of movement classes) is defined by the relationship between the 'true' classes and the output of the classifier. Here, we use N as the total number of samples. The value of $N\times\boldsymbol{H}_{ij}$ is the count of j-th output of the classifier when the 'true' class is the i-th class. We can derive the percent correct as $100\times p_0$. Here, p_0 is $\sum_i \boldsymbol{H}_{ii}/N$. The chance expected agreement p_e is defined as $\sum_i(\sum_j \boldsymbol{H}_{ij}\times\sum_j \boldsymbol{H}_{ji})/(N\times N)$. Then the estimate of the kappa coefficient is $(p_0-p_e)/(1-p_e)$.

Results

In order to investigate the usefulness of the intrasulcal ECoG to infer movement class, we compared the signals of gyral and intrasulcal electrodes. Five patients performed or imagined two or three classes of movement. The signals were normalized and smoothed to yield sMCP features for decoding analysis (see Subjects and methods). In the following, we describe the results of univariate statistical analysis applied to the sMCPs of individual electrodes. Decoding performance is then compared between the seven electrode groups. Finally, time dependency of decoding accuracy is examined.

Electrode-based analysis

Fig. 2 illustrates examples of sMCP signals at three anatomical regions, 'gyral', 'sulcal M1' and 'sulcal S1' (patient 1). Each plot shows the time course of the signals in one representative electrode (#8, #20, and #25, shown in Fig. 1c). The sMCPs are compared between three classes of movement: thumb flexion, hand grasping, and elbow flexion. The signals gradually increased from 1 s before movement onset and peaked several hundred milliseconds after onset. The time courses of the sMCP values were different for the three movement classes; in particular, prominent variance was observed for the 'sulcal M1' electrode.

We calculated F-values, which indicate the difference in signal amplitude among movement classes, for each electrode and time window. Fig. 3 illustrates the F-values for patient 1, who performed the motor execution task. Electrodes in 'sulcal M1' show markedly high F-values, while 'gyral' and 'sulcal S1' electrodes show relatively

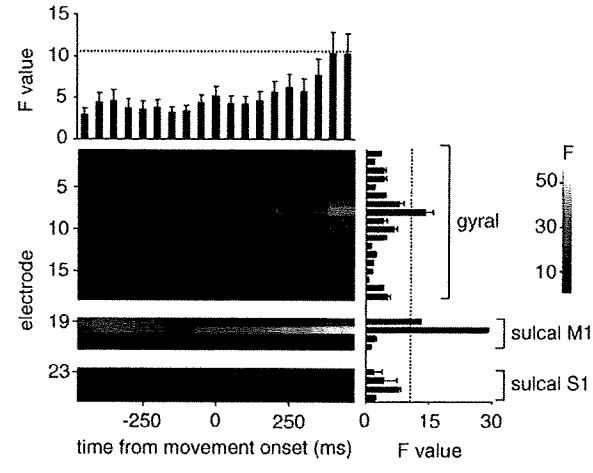

Fig. 3. Univariate statistical analysis on sMCP. Color-coded F-values (of one-way ANOVA) on each sMCP of patient 1 for all electrodes, and time from movement onset. Time is defined as the middle time of each sMCP. The vertical and horizontal bars show the mean of the F-values averaged over each time and each electrode respectively (error bar, standard error). The dotted line shows the F-value at $p=0.05$ (Bonferroni corrected for multiple comparisons).

low values. High *F*-values are broadly distributed within the interval of −500 ms to +500 ms relative to the movement onset. Other patients showed qualitatively similar spatial and temporal patterns of *F*-values.

Fig. 4 summarizes the results of all patients. The electrodes superimposed on the individual structural MRI are colored according to the averaged *F*-values during a 1000-ms interval (patients 1–3: −500 ms to +500 ms from movement onset; patients 4 and 5: 0 ms to 1000 ms from cue onset). Electrodes of 'sulcal M1' and 'gyral' around the central sulcus show relatively high averaged *F*-values. Electrodes with high values tended to be located adjacent to each other. These results indicate that ECoG electrodes on M1, especially on the sulcal M1, provide significantly different signals for different upper limb movements. Thus, sulcal M1 electrodes and adjacent gyral electrodes are expected to be useful for the classification of upper limb movement.

Multi-channel decoding analysis

Next, we performed decoding analysis, which predicted executed or imagined movement on a single-trial basis, using the signals of multiple electrodes. The input features were the signal amplitudes from each electrode and time window during a 1000-ms interval (executed: −500 ms to +500 ms from movement onset; imagined: 0 ms to 1000 ms from cue onset). We compared the classification performance among groups of electrodes defined by their anatomical location: all available electrodes ('all': 20–28 electrodes), all gyral electrodes ('gyral': 12–20 electrodes), intrasulcal electrodes on the motor side ('sulcal M1': 4 electrodes), and those on the sensory side ('sulcal S1': 4 electrodes). To match with the number of intrasulcal electrodes, we performed decoding analysis with all the combinations of four gyral electrodes, and the mean performance was compared with 'sulcal M1' and 'sulcal S1' ('gyral (4) – mean of all combinations').

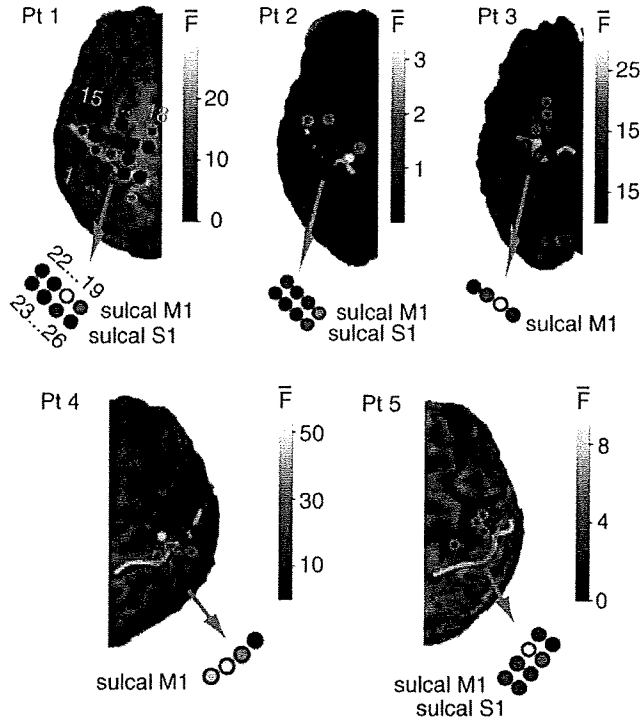

Fig. 4. Variability of sMCP values of each electrode. The *F*-value averaged over each electrode is shown as color on the electrode superimposed on individual structural MRI. The four electrodes of 'gyral (4) – highest F' are indicated with blue circles. These electrodes were selected in order of the highest average *F*-value from each patient's gyral electrodes.

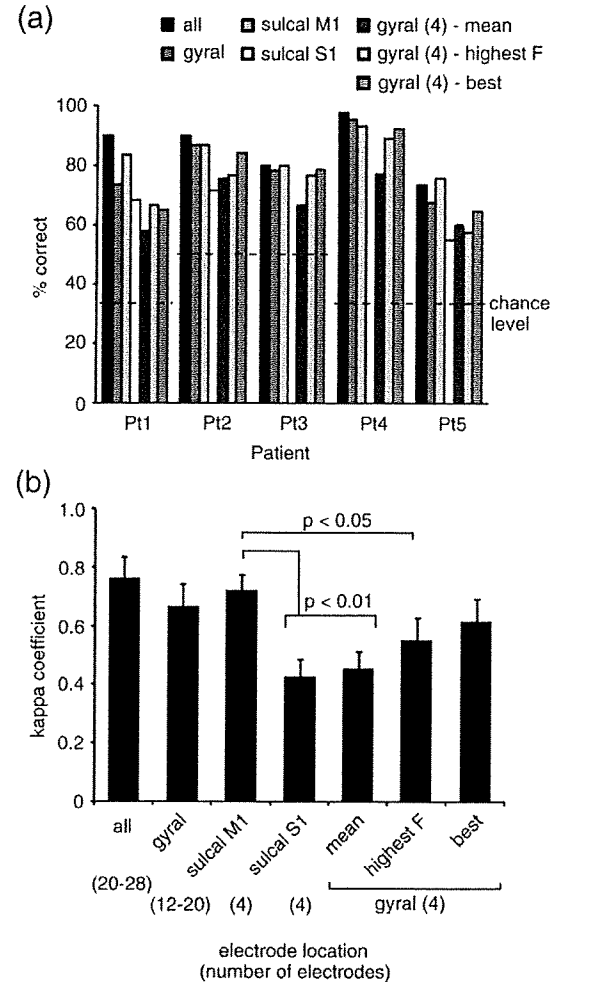

Fig. 5. Comparison of classification accuracy between gyral and intrasulcal ECoG. a: The percents correct of the classification were compared between seven electrode groups of each patient: all available electrodes ('all', 20–28 electrodes), all gyral electrodes ('gyral', 12–20 electrodes), intrasulcal electrodes on the motor side ('sulcal M1', four electrodes), those on the sensory side ('sulcal S1', four electrodes), the mean of all the combinations of four gyral electrodes ('gyral (4) – mean of all combinations' or 'gyral (4) – mean'), four gyral electrodes with the highest average *F*-values ('gyral (4) – highest F', blue circles in Fig. 4), and four gyral electrodes with the highest classification performance ('gyral (4) – best combination' or 'gyral (4) – best'). A dotted line indicates the chance level for each patient (33.3% or 50%). b: Classification performance was compared between the seven groups. Each bar shows the mean kappa coefficients for all patients (error bar, standard error). A paired *t*-test was applied among the equally-sized ECoG groups ('sulcal M1', 'sulcal S1', 'gyral (4) – mean of all combinations', and 'gyral (4) – highest F') and 'gyral (4) – best combination'. The number of electrodes in each group is presented below each bar.

Further, the four gyral electrodes with the highest average *F*-values were selected ('gyral (4) – highest F', blue circles in Fig. 4), and were compared with the intrasulcal electrodes. As shown in Fig. 4, most of the 'gyral (4) – highest F' electrodes were located around the precentral gyrus, the gyral portion of M1. Finally, the performance of the best combination of four electrodes was calculated to estimate the upper bound of the classification performance obtained with four gyral electrodes ('gyral (4) – best combination'; see Subjects and methods).

Fig. 5a shows the classification performance for individual patients. The performance largely exceeded the chance level for all electrode groups and all patients, reaching 86.6±5.8% correct (mean±SD for patients 1–3, who performed actual movements) and 85.5±17.2% correct (mean±SD for patients 4 and 5, who imagined movement) with the 'all' ECoG. These results are comparable with those of a