Whether or not the detected alteration of the diaphragmatic response in our study is of prognostic significance has yet to be established. Under clinical conditions with a reduced vital capacity in ALS, the voluntary drive from the motor cortex probably plays a significant role to facilitate respiration during a period of disease progression. From this point of view, involvement of the motor cortex may further hasten the clinical deterioration in the later stages of respiratory failure.

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特集 高齢期のパーキンソン病と類縁疾患 各論

KEY WORD
●Hoehn-Yahr 重症度分類 ●運動療法
●作業療法 ●言語療法 ●摂食・嚥下訓練

2．パーキンソン病の治療とケア 2）パーキンソン病のリハビリテーション

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SUMMARY

■パーキンソン病のリハビリテーションには大きく運動療法，作業療法，言語療法，摂食・嚥下訓練がある．外的刺激を利用することで，さらに効果的にリハビリを行える可能性もある．患者1人ひとりの症状はそれぞれ違うことが多いので，リハビリの開始初期から症状に合わせた適切な指導を行うことは非常に重要である．また，パーキンソン病は進行性の疾患のため，1回だけの指導で終わるのではなく，そのステージに合わせたリハビリを継続していく必要がある．

はじめに

パーキンソン病は50～60歳代をピークに発症する神経変性疾患で，日本での有病率は人口10万人当たり100～150人程度であるといわれている．また，日本も含めて世界的に高齢化が進んでおり，その有病率は増加傾向である．

そのような状況にもかかわらず，パーキンソン病を専門とするリハビリテーション(以下リハビリ)療法士は数少なく，運動療法も十分なエビデンスがあるとはいえないのが実情である．しかし，Montgomery[1]らが報告しているように，運動教育や生活指導をすることによって，L-DOPAの増量を遅らせたり，QOLを高めるといった報告は多数ある．

日本のリハビリテーション

日本での医療保険を使用したリハビリは「難病等脳血管疾患」に分類され，現時点では期限などに縛られることなく利用可能である．また，介護保険では2号被保険者に該当する15種類の特定疾患の1つに指定されているため，40歳以上であれば介護保険サービスを利用したリハビリを受けることも可能である．原則的には同一期間に医療保険と介護保険の両方を利用してリハビリを受けることはできない．

われわれの施設では，週に1～2回通院リハビリをするか，普段は介護保険サービスを週に2～3回利用して，年に1回1カ月程度の入院による集中リハビリを行っている患者が多い．

リハビリの目的

パーキンソン病の病期の評価にはHoehn-Yahr重症度分類が最も普及している．これはStage 1～5までであるが，これにStage 1.5と2.5を加えた修正版Hoehn-Yahr重症度分類が使われることも多い．

イギリスのパーキンソン病ガイドライン[2]では，病期によるリハビリの目的を**表1**のように記載している．

リハビリの実際

1．リハビリの種類

1）運動療法

理学療法としては一般に，関節可動域訓練，筋力訓練，バランス訓練，歩行訓練，呼吸リハビリなどが行われる．

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表1　パーキンソン病のリハビリテーションの目的

生活機能障害度	Ⅰ度				Ⅱ度		Ⅲ度
	日常生活，通院にほとんど介助を要しない				日常生活，通院に部分介助を要する		日常生活に全面的な介助を要し，独力では歩行，起立不能
修正版 Hoehn-Yahr 重症度分類	Stage 1	Stage 1.5	Stage 2	Stage 2.5	Stage 3	Stage 4	Stage 5
	一側の障害のみ．機能障害は軽微またはなし	一側の障害に体幹障害が加わる	両側の障害だが，体のバランス障害は伴わない	両側の障害に，自分で立ち直れる程度の突進現象が加わる	姿勢反射障害がみられる．立ち上がるときや歩行時に向きを変えるときにバランスを崩しやすい．身体的にはほとんど独立した生活を遂行できる	症状が進行し，機能障害は高度．かろうじて介助なしで起立および歩行することはできるが，日常生活は高度に障害される	介助がない限り寝たきり，または車いすの生活を余儀なくされる
リハビリの目的		・活動量低下の予防 ・転倒恐怖の予防 ・身体能力の向上			・Ⅰ度の目的に加えて ・以下の動作の維持・向上 移乗 姿勢 手を伸ばして物を取る バランス 歩行　など		・Ⅱ度の目的に加えて ・バイタルの維持 ・褥瘡の予防 ・拘縮の予防

（（文献2より引用し，筆者和訳）

Stage 1 ～ 2 までの段階であれば特別な運動療法ではなく，一般的な運動療法で身体能力の維持・向上を図る．まだ姿勢反射障害が出る前の段階であるが，転倒には気をつける．

Stage 2 くらいから固縮による筋緊張のため，関節可動域制限が出現したり，こわばる感覚が出現してくる．関節可動域の最後まで屈曲・伸展することを意識して行う．可動域訓練は1日2回程度行う方が効果的である．

筋力訓練は，可能であれば少し筋肉痛が生じる程度の負荷をかけて行う．それくらいの負荷が可能であれば，週に2～3回程度行う．負荷をかけることが難しければ，毎日～1日おきに行う．パーキンソン病の患者は，徐々に体幹が前傾してくる．このような患者の筋 CT では，脊柱起立筋や殿筋などに脂肪変性が認められることが多い．早期から背部の筋を意識した筋力訓練を行うことは，前傾姿勢の予防になるかもしれない．

バランス訓練は，能力によって立位・座位・四つ這いの姿勢で行う．立位ではバランスボード，座位ではバランスボールを用いて行う．四つ這いでは図1[3]のような運動を行うが，最初はきちんと姿勢を保持できないことも多いので，理学療法士の指導のもとで行うか，鏡で確認しながら行うのが好ましい．

パーキンソン病では，四肢のみならず体幹機能障害も生じる．しかし，指導や教育を受けたことのない患者は，四肢の運動にだけ目がいきがちである．このため，四肢の筋力は十分保たれているが，体幹機能障害のため著しく活動に制限が生じていることもある．早期から図1のような，体幹機能を意識したリハビリを取り入れることが重要であると思われる．

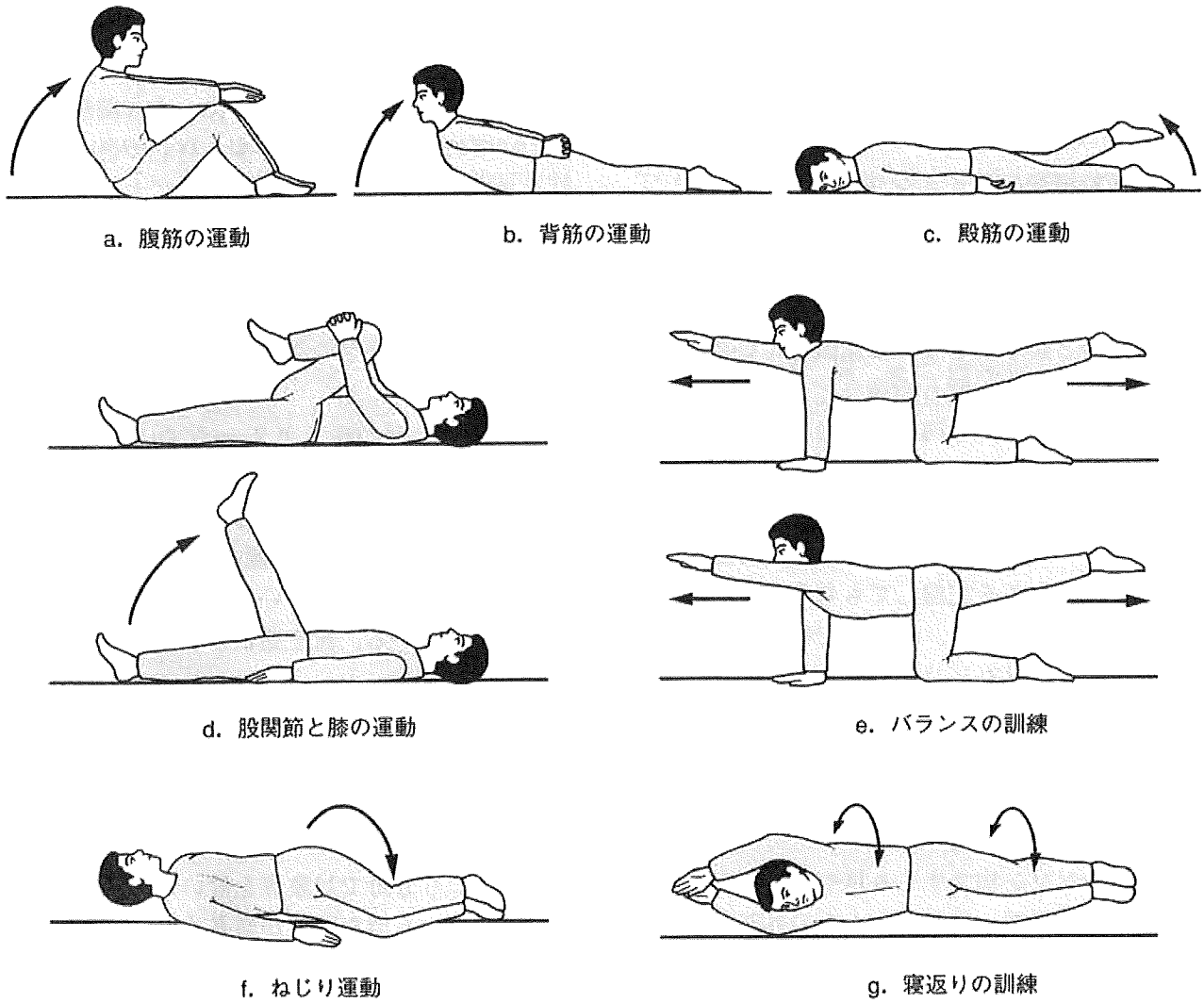

図1　パーキンソン病における運動訓練の例（文献3より引用）

すくみ足や小刻み歩行に対しては，後述するが外部刺激の利用が有効なことがある．トレッドミルは転倒のリスクが高くなるが，歩行訓練として有用である．また，歩行に合わせた一定のリズムでの音刺激や光刺激も歩行訓練に有用である．しかし，外部刺激導入時には良好であったとしても，6週後のフォローアップでは効果が消失したという報告もある[4]．

2）作業療法

作業療法は，小字症に対して書字訓練を行ったり，上肢の巧緻動作障害に対して行うことが多い．上肢の振戦が強い場合は，書字や巧緻動作は難しい．振戦が少ない時間帯に行うか，粗大運動を中心に行う．また，徐々にADLが低下してくるため，生活状況に合わせたADL訓練と環境調整を行う．集団訓練が有用であるという報告もある[5,6]．

3）言語療法

構音障害に対して，開口筋群・舌筋群・口輪筋などのストレッチや筋力訓練を行う．持続発声訓練は呼吸リハビリとしても有用であり，発声しながら壁などを両手で押すpushing exerciseによって，発声持続時間の延長と声量の増大が得られたとする報告がある[7]．

4）摂食・嚥下訓練

パーキンソン病に限らず，一般にこの分野ではまだリハビリのエビデンスは少ない．寡動・無動の症状が強くなると，唾液嚥下も減少する

ため流涎がみられるようになる．Nagaya らは，舌の運動訓練，pushing exercise，頸部周囲の可動域訓練などを行った結果，嚥下反射出現までの時間は有意に短縮したと報告している[8]．

2．運動療法のタイミング

薬物治療が始まると，日内変動が目立つようになる．患者自身は調子が良いときと悪いときがあることは自覚しているが，それがどの時間帯なのかということまでは意識していないことが多い．特に，1度も指導などを受けたことがない患者に，その傾向が顕著に認められる．理論上は，服薬してから1時間後程度が最も動きやすいと思われるが，そのとおりにはならないことも多い．服薬した時間と，時間帯ごとの体の動かしやすさを記録してもらうと，ある程度の傾向が把握できる．できるだけ体を動かしやすい時間帯にリハビリを行うようにする．

また，服薬時間とは無関係に症状が軽快・増悪する on-off 現象があることにも留意する．

3．外的刺激の利用

パーキンソン病ですくみ足や小刻み歩行がみられる際，視覚・聴覚などからの外部刺激によって運動の改善を認めることがある．これを矛盾性運動（kinésie paradoxale）と呼んでいる．Hanakawa らは，この矛盾性運動には外側運動前野が関与していると述べている[9]．感覚入力の影響を受けるこの運動の経路は，小脳-運動前野系といわれており，パーキンソン病の主病変である基底核は関与しない．このため，外的刺激を利用した運動療法は有用である．

トレッドミルでは一定のリズムで歩行できる．また，一定のリズムの光刺激と音刺激では後者の方がより効果があるといわれている[4]．このリズムは，本人が快適で持続可能と感じる歩行速度に合わせて設定する．また，音楽に合わせたダンスなども外国では報告があるが，あまりダンスをする習慣のない日本では馴染まないかもしれない．

また，刺激は外的なものに限定されるので，自分でリズムを取ってもうまくいかないので注意する．

4．そのほか

ベッドサイドや椅子の近くに一定の間隔で線を引いておく．実際には，少し目立つ色のテープを歩幅に合わせて等間隔に貼っておく．これも矛盾性運動を利用したもので，ある程度の効果は得られる．家庭の中でいつも決まった場所ですくみ足が生じるようなら，その場所にテープを貼ったり，小さな障害物を置くのも効果がある．

また，靴の踵の高さが2 cm になると前足部に足圧が集中していくので，歩きにくくなるという報告がある[10]．この報告では，踵の高さを1 cm 程度にすると足圧が踵の方にも分散して，自覚的にも最も歩きやすいと感じる患者が多かったと述べている．靴を選択する際には踵の高さに注意する．

まとめ

Samyra[11]らはレビューの中で，パーキンソン病のリハビリ分野で対象群を置いたエビデンスレベルの高い有望な研究が数多く進められていると報告している．

「運動をするように」という漠然とした指導は受けるが，具体的に何をすればよいのか悩み，結局何もしていないという話を聞くことがある．パーキンソン病専門のリハビリ療法士は少ないため，専門の指導を受けることは難しい．しかし，今後エビデンスレベルの高い報告が増えてくることを考えると，単に運動を行うように促すだけではなく，適切な指導を含めたリハビリが重要である．

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ORIGINAL REPORT

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OVER BILATERAL HEMISPHERES ENHANCES MOTOR FUNCTION AND TRAINING EFFECT OF PARETIC HAND IN PATIENTS AFTER STROKE

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Objective: **The interhemispheric competition model proposes that the functional recovery of motor deficits in patients after stroke can be achieved by increasing the excitability of the affected hemisphere or decreasing the excitability of the unaffected hemisphere. We investigated whether bilateral repetitive transcranial magnetic stimulation might improve the paretic hand in patients after stroke.**
Design: **A double-blind study.**
Patients: **Thirty patients with chronic subcortical stroke.**
Methods: **The patients were randomly assigned to receive 1 Hz repetitive transcranial magnetic stimulation over the unaffected hemisphere, 10 Hz repetitive transcranial magnetic stimulation over the affected hemisphere, or bilateral repetitive transcranial magnetic stimulation comprising both the 1 Hz and 10 Hz repetitive transcranial magnetic stimulation. All patients underwent motor training following repetitive transcranial magnetic stimulation.**
Results: **Bilateral repetitive transcranial magnetic stimulation and 1 Hz repetitive transcranial magnetic stimulation immediately improved acceleration in the paretic hand. Compared with 1 Hz repetitive transcranial magnetic stimulation, bilateral repetitive transcranial magnetic stimulation decreased the inhibitory function of the affected motor cortex and enhanced the effect of motor training on pinch force. Moreover, this effect of motor training lasted for one week. On the other hand, 10 Hz repetitive transcranial magnetic stimulation had no effect on the motor function.**
Conclusion: **Bilateral repetitive transcranial magnetic stimulation improved the motor training effect on the paretic hand of patients after stroke more than unilateral stimulation in pinch force; this might indicate a new neurorehabilitative strategy for stroke.**

Key words: repetitive transcranial magnetic stimulation, motor training, stroke, neuronal plasticity, rehabilitation.

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INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method that can change the excitability of the human cortex for at least several minutes. The nature of the after-effect depends on the frequency, intensity, and pattern of stimulation. High-frequency rTMS (more than 5 Hz) increases cortical excitability, whereas low-frequency rTMS (1 Hz or less) leads to suppression of cortical excitability (1).

The interhemispheric competition model proposes that motor deficits in patients after stroke are due to a reduced output from the affected hemisphere and excess transcallosal inhibition of the affected hemisphere from the unaffected hemisphere (2, 3). Therefore, improvement of motor deficit could be achieved by increasing the excitability of the affected hemisphere or decreasing the excitability of the unaffected hemisphere by using rTMS. Research has demonstrated that low-frequency rTMS over the unaffected hemisphere decreased the excitability of the unaffected hemisphere and improved the motor function of the paretic hand in patients after stroke (4, 5). High-frequency rTMS over the affected hemisphere also improved the motor function of the paretic hand by increasing the excitability of the affected motor cortex (6). Moreover, low-frequency rTMS over the unaffected hemisphere improved the motor training effect (7). Therefore, the application of rTMS has been proposed to promote functional recovery of the paretic hand in stroke patients owing to the induced neuroplasticity.

Considering the interhemispheric competition model of patients after stroke, adding high-frequency rTMS over the affected hemisphere along with low-frequency rTMS over the unaffected hemisphere might improve the motor function of the paretic side in the patients after stroke by a greater degree than would unilateral rTMS alone. To our knowledge, there is no report that has combined both high-frequency and low-frequency rTMS in patients after stroke. In the present study, we hypothesized that bilateral rTMS might improve the motor training effect on the paretic hand in patients after stroke.

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METHODS

The study population comprised 30 patients after stroke. The inclusion criteria were as follows: (*i*) first-time stroke of more than 6 months duration; (*ii*) only subcortical lesion confirmed by magnetic resonance imaging (MRI); (*iii*) motor deficits of the unilateral upper limb that had improved to the extent that patients could perform pinching tasks; and (*iv*) normal Mini-Mental State Examination score. The exclusion criteria included the following: (*i*) severe internal carotid artery stenosis; (*ii*) seizure; and (*iii*) an intracranial metallic implant. Participants were randomly divided into 3 groups (Table I). The unaffected rTMS group received rTMS over the unaffected hemisphere, the affected rTMS group received rTMS over the affected hemisphere, and the bilateral rTMS group received rTMS over both the unaffected and affected hemispheres. All the subjects gave their written informed consent, and the protocol was approved by the local ethics committee of the Hokkaido University Graduate School of Medicine.

The measurements for assessing the motor function (acceleration and pinch force) were performed at pre-rTMS and post-rTMS (Post 1: immediately after the rTMS; Post 2: after motor training; and Post 3: 7 days after rTMS). The parameters of TMS (i.e. resting motor threshold (rMT), amplitude of motor evoked potentials (MEPs), and intracortical inhibition (ICI)) were evaluated at pre-rTMS, Post 1, and Post 3. We did not evaluate the rMT, MEPs, and ICI immediately after motor training (Post 2) because the motor performance modulates the excitability of the motor cortex and ICI (9). Patients and the experimenter performing the evaluations were blinded to the type of stimulation.

Single-pulse TMS was performed using a 70-mm figure-of-8 coil and Magstim 200 (Magstim Co., Dyfed, UK), and rTMS was applied using the same coil and a Magstim Rapid stimulator (Magstim Co.). The coil was placed tangentially over the motor cortex at an optimal site for the first dorsal (FDI) muscle. The optimal site was defined as the location where stimulation at a slightly suprathreshold intensity elicited the largest MEPs in the FDI. This position was marked on the scalp and used throughout the experiment. The rMT was determined separately for each stimulator and defined as the lowest stimulator output that could produce MEPs with a peak-to-peak amplitude greater than 50 microvolts in at least half of the 10 trials. The peak-to-peak amplitude of 10 averaged FDI responses obtained at 120% rMT was also determined by using the Magstim 200 (Magstim Co.).

Paired-pulse stimulation was performed to investigate ICI in the affected motor cortex. To apply paired pulses, a figure-of-8 coil was connected to a Bistim device (Magstim Co.) that triggered 2 magnetic stimulators. The stimulus intensity of the first conditioning shock was 80% rMT and that of the second pulse was 120% rMT. We performed the tests at interstimulus intervals (ISI) of 2 and 3 msec. Ten trials were recorded for each ISI, and unconditioned trials (controls) were recorded during complete relaxation. The paired stimulation with each ISI was randomly mixed with the control stimulation. The MEPs amplitudes obtained by paired-pulse stimulation were expressed as a percentage of the mean control MEPs amplitude, and the ICI was then calculated by averaging these values. We obtained ipsilesional TMS data from 19 patients. The exclusion of patients with no ipsilesional TMS data might have weakened the power of the ipsilesional TMS parameter analysis. However, we excluded patients who did not display MEPs in the affected hemisphere from the ipsilesional TMS study section, i.e. patients in whom MEPs were not induced even at 100% stimulator output (4 patients in bilateral rTMS group, 3 patients in unaffected rTMS group, and 4 patients, affected rTMS group).

We alternatively applied the 1 Hz rTMS over the unaffected hemisphere and 10 Hz rTMS over the affected hemisphere by using 2 Magstim Rapid stimulators (Magstim Co.). This was because it was difficult to apply rTMS over the affected and unaffected hemispheres simultaneously due to the mechanical limitation of the overlap of the 2 figure-of-8 coils in the patient's head. Fig. 1 shows the rTMS protocols. In the bilateral rTMS group, the patients were stimulated at 90% rMT, 1 Hz, and 50 sec train duration over the unaffected hemisphere (50 stimuli) alternating with 90% rMT, 10 Hz, and 5 sec train duration over the affected hemisphere (50 stimuli), with an interval of 5 sec for 20 times, resulting in 1000 stimuli for each hemisphere. High-frequency rTMS protocols with a lower stimulator intensity are desirable for preventing seizures in patients after stroke (10). The rMT of the affected hemisphere is often higher than that of the unaffected hemisphere in patients after stroke. Therefore, we used the stimulation power according to the rMT of the unaffected hemisphere at both the 1 Hz and 10 Hz rTMS in order to avoid a risk of seizure. In the event that MEPs of the affected hemisphere could not be elicited at the maximal stimulator output, the coil was fixed at a location over the affected hemisphere that was homologous to the optimal site of the unaffected hemisphere. In the unaffected rTMS group, active rTMS was applied over the unaffected hemisphere and sham stimulation was applied over the affected hemisphere at the same frequency and intensity used for bilateral rTMS. Sham stimulation was applied over the optimal site by positioning the coil perpendicular to the scalp (11). Similarly, in the affected rTMS group, active rTMS was applied over the affected hemisphere and sham stimulation was applied over the unaffected hemisphere. After rTMS, the patients performed a pinching task for 15 min as motor training, as described in a previous report (12). During the pinching task, the patients were asked to perform a metronome-paced pinch of their index finger and thumb of the affected hand as fast as possible (frequency individualized between 0.3 and 0.5 Hz). For assessing the motor function, we checked the pinch force and acceleration as described previously (5). In each session, 10 pinch force values and 15 acceleration values were averaged. The patients were allowed to familiarize themselves with this motor evaluation on the previous day of the rTMS experiment.

The clinical characteristics data (Table I) were compared between the bilateral rTMS, unaffected rTMS, and affected rTMS groups by analysis of variance (ANOVA) or the χ^2 test, depending on the variable type. The effects of rTMS and motor training were evaluated using an ANOVA for repeated measures with TIME as a within-subjects factor and CONDITION (bilateral rTMS, unaffected rTMS, and affected rTMS) as a between-subjects factor. A *post-hoc* analysis was performed with Bonferroni's correction. Any possible correlation between the changes in the various parameters was determined by Pearson's correlation coefficient test as an exploratory analysis. All data were normalized by conversion to percentage change from the mean values of pre-rTMS.

Table I. *Clinical characteristics of patients after stroke*

	Bilateral rTMS group $n=10$	Unaffected rTMS group $n=10$	Affected rTMS group $n=10$
Age, years, mean (SD)	60.9 (12.4)	58.1 (12.3)	59.0 (12.7)
Gender, *n*			
Male	8	7	7
Female	2	3	3
Paretic side, *n*			
Right	6	7	5
Left	4	3	5
Duration after stroke, months, mean (SD)	26.1 (28.0)	24.7 (28.9)	35.6 (38.7)
Fugl-Meyer scale, mean (SD)			
Total, %	66.4 (17.5)	71.8 (17.3)	66.2 (21.5)
Hand, %	67.1 (26.2)	71.7 (23.9)	64.4 (24.2)

Fugl-Meyer scale (8) (percentages of maximum points in the upper limb (66 points) and in hand (24 points)).
rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation.

RESULTS

The subjects did not report any adverse side-effects during the course of the study. No difference was observed between the bilateral, affected, and unaffected rTMS groups with regard

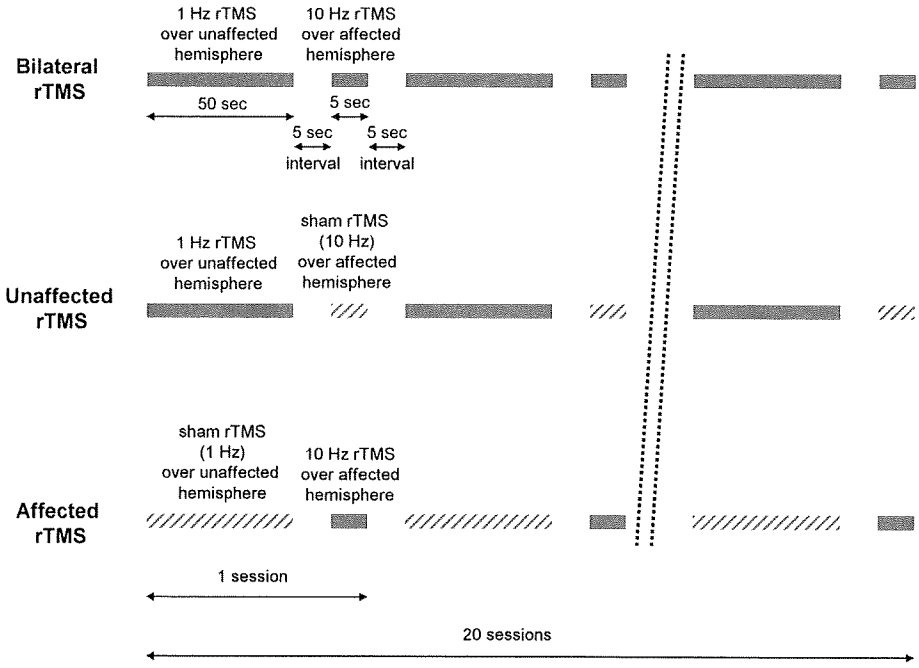

Fig. 1. The protocol of repetitive transcranial magnetic stimulation (rTMS). In the bilateral rTMS group, the patients were stimulated at 1 Hz and 50 sec train duration over the unaffected hemisphere, alternating with 10 Hz and 5 sec train duration over the affected hemisphere, with an interval of 5 sec for 20 times. In the unaffected rTMS group, active rTMS (*solid grey bar*) was applied over the unaffected hemisphere and sham stimulation (*hashed grey bar*) was applied over the affected hemisphere at the same frequency and intensity used for bilateral rTMS. Similarly, in the affected rTMS group, active rTMS was applied over the affected hemisphere and sham stimulation was applied over the unaffected hemisphere.

to age, gender, paretic side, the duration after stroke, or the Fugl-Meyer scale (Table I). There was no difference between the bilateral, affected, and unaffected rTMS groups with regard to acceleration, pinch force, amplitude of the contralesional MEPs, amplitude of the ipsilesional MEPs, ICI of the affected hemisphere, rMT of unaffected hemisphere, or rMT of affected hemisphere in pre-rTMS (Table II).

Fig. 2 shows the change in motor function after rTMS and motor training. A repeated-measures ANOVA showed a significant interaction between TIME and CONDITION with respect to acceleration ($F6,81=2.743$, $p=0.018$) and pinch force ($F6,81=5.539$, $p<0.001$). It also showed a significant effect of TIME on both acceleration ($F6,81=21.014$, $p<0.001$) and pinch force ($F6,81=31.191$, $p<0.001$). The *post-hoc* test revealed an improvement in acceleration immediately after bilateral rTMS (pre-rTMS vs Post 1: $p=0.002$) and unaffected rTMS (pre-rTMS vs Post 1: $p=0.008$). The motor training did not induce an additional improvement in acceleration after bilateral rTMS or unaffected rTMS. These improvements in acceleration lasted for one week after bilateral rTMS (pre-rTMS vs Post 3: $p<0.001$) and unaffected rTMS (pre-rTMS vs Post 3: $p<0.001$). Compared with unaffected rTMS, bilateral rTMS increased the acceleration during all the sessions, albeit not significantly. In the affected rTMS group, the *post-hoc* test did not show a significant improvement in acceleration after rTMS or motor training. Bilateral rTMS (Post 1: $p=0.034$; Post 2: $p<0.001$; Post 3: $p=0.001$) and unaffected rTMS (Post 2: $p<0.001$; Post 3: $p=0.022$) resulted in a greater increase in acceleration than affected rTMS.

The *post-hoc* test did not show a significant improvement in pinch force immediately after bilateral rTMS or unaffected rTMS. However, the motor training induced an improvement in pinch force after bilateral rTMS (pre-rTMS vs Post 2: $p<0.001$; Post 1 vs Post 2: $p<0.001$) and unaffected rTMS (pre-rTMS vs Post 2: $p=0.008$). These improvements in pinch force also lasted for one week after bilateral rTMS (pre-rTMS vs Post 3: $p<0.001$) and unaffected rTMS (pre-rTMS vs Post 3: $p=0.009$). The effect of motor training after rTMS on pinch force was more enhanced by bilateral rTMS than by unaffected rTMS (Post 2: $p=0.004$; Post 3: $p=0.010$). In the affected rTMS group, the *post-hoc* test did not show a significant improvement in pinch force after rTMS or motor training. Bilateral rTMS increased the pinch force compared with affected rTMS (Post 2: $p<0.001$; Post 3: $p<0.001$).

Table II. *Physiological parameters of pre-repetitive transcranial magnetic stimulation (rTMS)*

	Bilateral rTMS group	Unaffected rTMS group	Affected rTMS group
Acceleration, m/sec^2, mean (SD)	1.9 (1.7)	1.9 (1.2)	2.2 (1.4)
Pinch force, N, mean (SD)	25.7 (10.3)	27.7 (10.2)	30.1 (14.2)
Amplitude of contralesional MEPs, μV, mean (SD)	696.3 (619.7)	797.4 (828.8)	664.6 (585.5)
Amplitude of ipsilesional MEPs, μV, mean (SD)	337.0 (293.2)	401.3 (320.7)	432.0 (307.3)
ICI of affected hemisphere, %, mean (SD)	59.2 (16.6)	63.4 (24.7)	70.7 (28.3)
rMT of unaffected hemisphere, %, mean (SD)	48.1 (7.4)	48.3 (14.5)	50.5 (8.3)
rMT of affected hemisphere, %, mean (SD)	62.0 (12.5)	55.3 (14.4)	56.0 (16.1)

ICI: intracortical inhibition; MEPs: motor evoked potentials; rMT: resting motor threshold: SD: standard deviation.

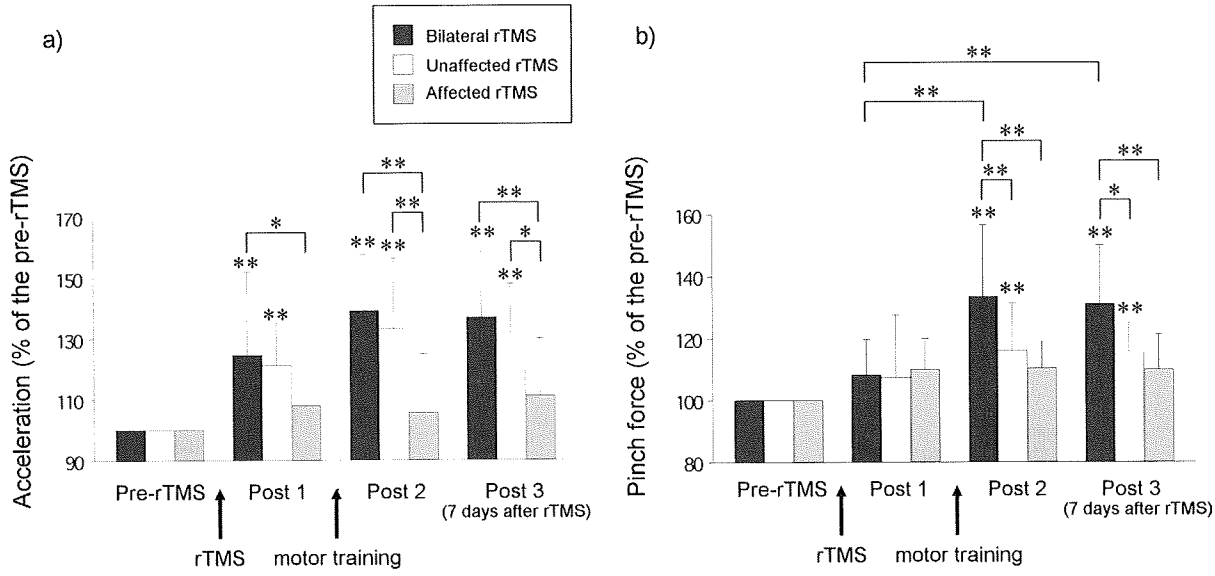

Fig. 2. The effects of repetitive transcranial magnetic stimulation (rTMS) and motor training; (a) acceleration; (b) pinch force. Bilateral and unaffected rTMS improved the acceleration of the paretic hand (pre-TMS vs Post 1: bilateral, $p=0.002$; unaffected, $p=0.008$) and this improvement in acceleration lasted for one week after rTMS and motor training (pre-TMS vs Post 3: bilateral, $p<0.001$; unaffected, $p<0.001$). The motor training improved the pinch force of the paretic hand after bilateral rTMS (pre-rTMS vs Post 2: $p<0.001$; Post 1 vs Post 2: $p<0.001$) and unaffected rTMS (pre-rTMS vs Post 2: $p=0.008$). This improvement in pinch force also lasted for one week after rTMS and motor training (pre-rTMS vs Post 3: bilateral, $p<0.001$; unaffected, $p=0.009$). The effect of motor training on pinch force was more enhanced by bilateral rTMS than by unaffected rTMS (Post 2: $p=0.004$; Post 3: $p=0.010$). *$p<0.05$; **$p<0.01$ (asterisk without a line indicates a p-value comparison with pre-rTMS); error bar, standard deviation.

Fig. 3 shows the change in the corticospinal excitability after rTMS. A repeated measures ANOVA for MEPs showed a significant interaction between TIME and CONDITION (contralesional MEPs: $F4,54=3.277$, $p=0.018$; ipsilesional MEPs: $F4,32=3.654$, $p=0.015$) and a significant effect of TIME on MEPs (contralesional MEPs: $F4,54=4.188$, $p=0.020$; ipsilesional MEPs: $F4,32=9.012$, $p<0.001$). The *post-hoc* test revealed that a decreased amplitude of contralesional MEPs was produced immediately by unaffected rTMS ($p=0.001$) but not by bilateral rTMS or affected rTMS. The *post-hoc* test revealed that an increased amplitude of ipsilesional MEPs was produced immediately by unaffected rTMS ($p<0.001$)

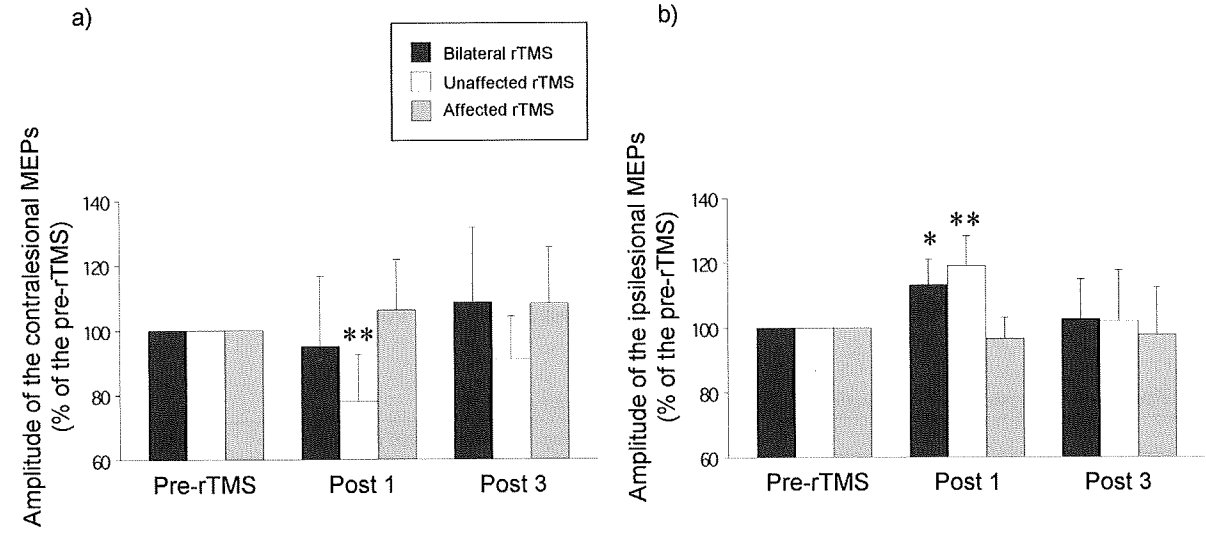

Fig. 3. The change in the corticospinal excitability after repetitive transcranial magnetic stimulation (rTMS). (a) Amplitude of the contralesional MEPs. (b) Amplitude of the ipsilesional motor evoked potentials (MEPs). Unaffected rTMS decreased the amplitude of contralesional MEPs (pre-rTMS vs Post 1: $p=0.001$) and increased the amplitude of ipsilesional MEPs (pre-rTMS vs Post 1: $p<0.001$). Bilateral rTMS increased the amplitude of ipsilesional MEPs (pre-rTMS vs Post 1: $p=0.021$). However, the changes induced by rTMS were observed to be diminished at 7 days after rTMS. *$p<0.05$; ** $p<0.01$; error bar, standard deviation.

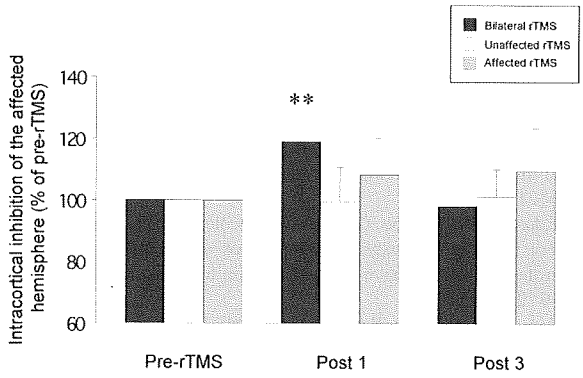

Fig. 4. The change in the intracortical inhibition after repetitive transcranial magnetic stimulation (rTMS). A decreased intracortical inhibition of the affected hemisphere was produced by bilateral rTMS (pre-rTMS vs Post 1: $p=0.002$). However, the change induced by rTMS was observed to be diminished at 7 days after rTMS. $^{**}p<0.01$; error bar, standard deviation.

and bilateral rTMS ($p=0.021$), but not by affected rTMS. There was no significant difference in the ipsilesional MEPs changes between bilateral rTMS and unaffected rTMS. The MEPs changes diminished at 7 days after bilateral rTMS and unaffected rTMS.

Fig. 4 shows the change in the inhibitory function of affected hemisphere after rTMS. A repeated measures ANOVA for ipsilesional ICI showed a significant interaction between TIME and CONDITION ($F4,32=3.021$, $p=0.032$) and a significant effect of TIME on ipsilesional ICI ($F4,32=3.398$, $p=0.046$). The *post-hoc* test revealed that a decreased ipsilesional ICI was produced immediately by bilateral rTMS (pre-rTMS vs Post 1: $p=0.002$) but not by unaffected rTMS or affected rTMS. However, the ICI change diminished at 7 days after bilateral rTMS.

A repeated-measures ANOVA for contralesional and ipsilesional rMT did not show a significant interaction between TIME and CONDITION; furthermore, no significant effect of CONDITION or TIME was observed. In both the bilateral and unaffected rTMS groups, the improvement in the motor function after rTMS (Post 1) or motor training (Post 2) showed no significant correlation with the age, duration after stroke, the Fugl-Meyer scale, and the changes in ipsilesional MEPs and ICI.

DISCUSSION

This study reports that bilateral rTMS and unaffected rTMS therapy can improve the motor training effect in the paretic hand of patients after stroke. Moreover, bilateral rTMS could improve the motor function more than unaffected rTMS. Our study results suggest that stimulating the affected hemisphere along with inhibition of the unaffected hemisphere by bilateral rTMS appears to improve the motor function of the paretic side in patients after stroke, while the procedure remains safe and well tolerated.

We found that 1 Hz rTMS over the unaffected hemisphere increased the corticospinal excitability of the affected hemisphere; this result is in agreement with previous reports (7). The inhibition of the excitability of the unaffected hemisphere by 1 Hz rTMS would result in a decrease in the transcallosal inhibition from the unaffected to the affected hemisphere and an increase in the excitability of the affected hemisphere (5, 7). The enhancement of motor cortex excitability appeared to be a necessity for motor learning (13). Therefore, artificially increasing cortical excitability with rTMS could facilitate motor learning and recovery after stroke (6, 7). However, bilateral rTMS could increase the corticospinal excitability of the affected hemisphere as well as could unaffected rTMS, despite the fact that bilateral rTMS could improve the motor training effect in the paretic hand more than unaffected rTMS. Therefore, in addition to increasing the cortical excitability of the affected hemisphere, bilateral rTMS might have another mechanism that could improve the motor function. By this other mechanism, the disinhibition induced by bilateral rTMS might contribute to the functional improvement of the paretic hand. Kobayashi et al. (14) have reported that 1 Hz rTMS over the motor cortex induced the disinhibition of the contralateral motor cortex, which might be induced by the disruption of transcallosal inhibition (14). High-frequency rTMS could also induce the disinhibition of the stimulated motor cortex (15). In this study, only affected rTMS or unaffected rTMS caused no change in the inhibitory function of the affected hemisphere, but bilateral rTMS could decrease the inhibitory function of the affected hemisphere by using 2 rTMS protocols that had the ability to induce disinhibition. A decrease in the inhibition unmasks the pre-existing, functionally latent neural networks around the lesion, thereby contributing to cortical reorganization (16). Based on these findings, the increased excitability and decreased inhibitory function of the affected motor cortex after bilateral rTMS might contribute to a more suitable environment for reorganization of the affected motor cortex by motor training.

A previous study (6) reported that high-frequency rTMS over the affected hemisphere improved the motor function of a paretic hand. However, in the present study, 10 Hz rTMS over the affected hemisphere had no effect on motor function. There are several possible reasons for this, as follows. First, we did not use a stereotactic system with integrated MRI data to stimulate the affected motor cortex; this might have resulted in inadequate stimulation because of the anatomical changes that occur after stroke. Secondly, we conducted a sham stimulation to ensure that the conditions between affected rTMS and bilateral rTMS were as similar as possible. However, it is possible that the patients could differentiate between the active and sham stimulations based on the physical scalp sensations; this might influence the results of affected rTMS. Thirdly, the stimulation power according to the rMT of the unaffected hemisphere might be too weak to increase the cortical excitability by only affected rTMS. This is because the rMT of the unaffected hemisphere is often lower than that of the affected hemisphere in stroke patients. Thus, the fact that affected rTMS had no effect on the motor function might also be because of the insufficient stimulation power.

Nevertheless, the method used in our study has some advantages. First, the use of a low-power stimulation for the affected hemisphere increased the safety of bilateral rTMS. Theoretically, compared with unaffected rTMS, bilateral rTMS involving direct high-frequency stimulation of the affected hemisphere can increase the excitability of the affected hemisphere to a greater extent; this is because high-frequency rTMS is known to increase the cortical excitability (1). However, there was no significant difference in the excitability of the affected hemisphere between bilateral rTMS and unaffected rTMS. Thus, bilateral rTMS may be a safe and well-tolerated procedure because it does not cause excessive excitability of the affected hemisphere. The fact that we did not perform affected rTMS and unaffected rTMS simultaneously is another advantage of our study. Nitsche et al. (17) had demonstrated that homeostatic plasticity acted when both excitability-changing protocols were applied simultaneously. If affected rTMS and unaffected rTMS are applied simultaneously, homeostatic plasticity might work to maintain the global network function within the normal physiological range, thereby nullifying the effects of both affected rTMS and unaffected rTMS. Future studies should therefore aim to clarify whether homeostatic plasticity can develop with simultaneous application of rTMS and transcranial direct current stimulations, which can stimulate small areas and can alter the cortical excitability as efficiently as rTMS.

In conclusion, our results have demonstrated that the combination of 1 Hz rTMS over the unaffected hemisphere and 10 Hz rTMS over the affected hemisphere could lead to an improvement in the motor function of the paretic hand of patients with chronic stroke. These findings will probably be pertinent to the design and optimization of neurorehabilitative strategies for stroke.

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ABSTRACT: Needle electromyography (EMG) of the tongue is traditionally used as a key to the diagnosis of amyotrophic lateral sclerosis (ALS), although relaxation of the tongue is often difficult to achieve. Recently, frequent abnormalities in the EMGs of the sternocleidomastoid (SCM) and upper trapezius muscles in ALS have been reported. To elucidate the diagnostic utility of these muscles we performed a multicenter prospective study to examine EMGs of the tongue (genioglossus), SCM, and trapezius in 104 ALS or suspected ALS patients. We also examined EMGs of the SCM and trapezius in 32 cervical spondylosis (CS) patients. We mainly evaluated fibrillation potentials/positive sharp waves (Fib/PSWs) and fasciculation potentials. Complete relaxation was achieved in 85% of ALS patients in the trapezius, but in only 6% of patients in the tongue. Fib/PSWs were observed in 8%, 13%, and 45% of ALS patients in the tongue, SCM, and trapezius, respectively, whereas fasciculation potentials were observed in 1%, 7%, and 39%, respectively. Abnormal spontaneous activity of any type was found in 9%, 17%, and 63% of patients, respectively. The high frequency of abnormal spontaneous activity in the trapezius was similar among the different diagnostic categories, and even 72% of clinically suspected ALS (progressive muscular atrophy) patients showed them in their trapezius. We did not observe Fib/PSWs or fasciculation potentials in any of our CS patients, thus these findings have excellent specificity. Tongue EMG added little utility over the clinical sign of tongue atrophy. Abnormal spontaneous activity in the trapezius would be more useful for the early diagnosis of ALS.
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UTILITY OF TRAPEZIUS EMG FOR DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurological disorder that involves both the upper motor neuron (UMN) and the lower motor neuron (LMN), and therefore diagnostic testing must be sufficiently sensitive and specific. Needle electromyography (EMG) plays an important role in the diagnosis of ALS both by confirming LMN dysfunction in clinically affected regions and detecting evidence of LMN dysfunction in clinically uninvolved regions. The revised El Escorial Criteria (EEC)[4] for the diagnosis of ALS include electrophysiologic criteria that require evidence of denervation and reinnervation in at least two of four regions of the neuraxis (cranial, cervical, thoracic, and lumbosacral) to assure widespread LMN involvement.

One drawback of the EEC is its rather low sensitivity in early stages of the disease.[2,29,35] One reason

Abbreviations: ALS, amyotrophic lateral sclerosis; CS, cervical spondylosis; EEC, revised El Escorial criteria; EMG, electromyography; Fib/PSW, fibrillation potentials and/or positive sharp waves; LMN, lower motor neuron; MUP, motor unit potential; PMA, progressive muscular atrophy; SCM, sternocleidomastoid; UMN, upper motor neuron

Key words: amyotrophic lateral sclerosis; needle electromyography; upper trapezius; tongue; sternocleidomastoid

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for this low sensitivity is the low frequency of EMG abnormalities in the cranial nerve region.[10,28] EMG of the tongue (usually genioglossus) has been traditionally considered an important key for documentation of bulbar involvement in ALS,[26] and it is frequently performed in clinical practice. However, achieving relaxation of the tongue is often difficult, and thus an evaluation of spontaneous activity may be difficult in this muscle.[10,14,27,39] Very limited data are available on how frequently patients can actually relax the tongue muscles to allow for accurate determination of spontaneous activity.[14,30] Accordingly, whether EMGs of the tongue are helpful in documenting subclinical LMN involvement remains controversial.[1,13,23]

Recently, some investigators have reported frequent abnormalities in EMG of the sternocleidomastoid muscle (SCM) or the upper trapezius muscle in ALS patients.[6,19,27] However, the relative utility of these muscles in comparison with the tongue in the diagnosis of ALS has not been investigated fully, nor is it clear whether these muscles can be relaxed more easily than the tongue. In order to clarify these issues we conducted a multicenter prospective study to compare the EMG findings of these three muscles in a large number of patients with ALS or suspected ALS. Because one of the important roles of EMG of cranial muscles in ALS is the exclusion of cervical spondylosis,[1,19,30] we evaluated the specificity of the EMG findings in the trapezius and SCM by examining these muscles in patients with cervical spondylosis (CS) who presented with overt atrophy of upper-limb muscles.

MATERIALS AND METHODS

Patients and Clinical Evaluation. Consecutive patients with ALS or CS were enrolled from 1 February 2007 to 31 January 2008 at EMG clinics of eight tertiary medical centers and related institutes (The Tokyo Metropolitan Neuromuscular Electrodiagnosis Study Group). All patients gave informed consent to the study design and experimental procedures.

For the ALS group, we made a clinical diagnosis of ALS or suspected ALS after full neurological examinations and standard systemic needle EMG examinations. Other diagnoses were excluded by appropriate imaging studies, laboratory tests, and nerve conduction studies. We classified each ALS patient into the following diagnostic categories according to the EEC: clinically definite, probable, probable laboratory supported, possible, and suspected. The EMG findings of the tongue were considered in determining the EEC category, but those of the SCM and trapezius were not, because these muscles have been considered to have both cranial and cervical innervations.[6,27] The "clinically suspected" category had been defined in the first version of the El Escorial criteria,[42] corresponding to pure lower motor neuron disease, or progressive muscular atrophy (PMA). This category was deleted in the revised EEC, but we continued to use this term in this study for convenience. We included patients with such a lower diagnostic certainty because we wanted to investigate the possible role of EMGs of these muscles for the early diagnosis of ALS. For the clinically suspected category, we required that all of the following conditions be met: (1) a history of relentlessly (in months) progressive muscle weakness; (2) LMN involvement suggested clinically or electrophysiologically in at least two body regions; and 3) other diagnoses were excluded by the appropriate tests. Patients in the clinically possible or clinically suspected categories were followed up as long as possible. A rise in the category to clinically probable (including laboratory supported) or higher, the development of respiratory dysfunction requiring artificial ventilation, or the need for a gastrostomy feeding tube were regarded as validating the diagnosis of ALS. The other clinical information recorded for the ALS patients included the duration of illness, the site of symptom onset (bulbar or nonbulbar), and the presence or absence of tongue atrophy as a marker for bulbar, and not pseudobulbar, signs.

The inclusion criterion for the CS patients was that the patient presented with overt atrophy and weakness of the upper limb muscles due to CS with confirmation by clinical features and corresponding magnetic resonance imaging (MRI) findings. They usually had sensory symptoms and long-tract signs suggestive of cervical myelopathy, but some of them lacked both and presented with a pure LMN syndrome typical of CS amyotrophy. The latter is mainly reported in Japan.[18,20,31,37] Such cases would be the most confused with ALS because of the lack of sensory symptoms. In the patients with CS amyotrophy, the clinical course was abortive and often showed a slight improvement, but it never showed the typical relentlessly progressive course of ALS. The muscle atrophy and EMG changes of these patients were strictly confined to a segmental distribution even within the upper limb muscles.

Electromyography. All of the EMG examiners were board-certified neurologists and were proficient electromyographers with at least 10 years of professional EMG experience. Concentric needle EMG examinations were performed in standard settings us-

ing EMG machines at each institute. Three muscles, the tongue (genioglossus), SCM, and upper trapezius (hereafter simply called "trapezius") were examined in all patients from the ALS group, whereas the SCM and trapezius were examined for the CS patients.

For the tongue examination the needle was inserted through the submandibular triangle with the patient in the supine position. Thus, to be accurate, we investigated the genioglossus muscle, but we call this muscle the "tongue" hereafter for simplicity. Special care was taken to relax this muscle, which may be the best possible tactic for this purpose (Jun Kimura, personal communication). Specifically, we told the patient that we would examine "the muscle under the jaw," and not the tongue itself, in order to draw his or her attention away from the tongue. In addition, we instructed the patient to freely swallow saliva when he or she noticed its pooling.

For each muscle, spontaneous activity was explored in at least 10 different sites. Only regularly firing potentials that lasted more than 3 s were accepted as fibrillation potentials or positive sharp waves (Fib/PSWs). These activities were judged to be pathological only when they were identified at a minimum of two different sites within the muscle. Fasciculation potentials were defined as motor unit potential (MUP)-shaped potentials that fired in a highly irregular pattern, often with a clustering of discharges.[32] We observed a completely relaxed muscle for at least 30 s to determine the presence or absence of fasciculation potentials. Any persistence of voluntary MUPs was considered to render the identification of fasciculation potentials impossible.

The level of relaxation achieved for each muscle was classified into three grades: complete relaxation (no remaining voluntary MUPs), partial relaxation, and no relaxation. Partial relaxation indicated that some voluntary MUPs remained, but identification of Fib/PSWs was possible by paying attention to the regularly firing sound. Fasciculation potentials were evaluated only for complete relaxation, whereas Fib/PSWs were evaluated for complete and partial relaxation.

In this study we relied primarily on observation of spontaneous activity as evidence of abnormality. Voluntary activity was also evaluated for each muscle using ordinary methods of qualitative assessment. We regarded the following features as abnormal signs that indicated LMN dysfunction: (1) giant MUPs, (2) reduced recruitment pattern, and (3) polyphasic and unstable MUPs.[4]

Statistical Analysis. The frequency of specific EMG parameters was compared between different patient groups using the Chi-square test for independence or Fisher's exact probability test. For comparisons regarding three or more categories with rank order, such as relaxation levels or diagnostic categories, we used the two-sample Wilcoxon test.

RESULTS

Clinical Features. One hundred and four ALS patients were included. They consisted of 56 men and 48 women ranging in age from 45 to 83 years (mean, 66.5 years). At the time of examination the duration of illness ranged from 3–52 months (median 11 months). The region of symptom onset was bulbar (including pseudobulbar) in 40 and nonbulbar in 64 (upper limb in 40, lower limb in 20, respiratory muscles in two, thoracic in one, neck muscles in one). Tongue atrophy was evident in 41 patients. The number of patients in each diagnostic category was as follows: clinically definite, 6; clinically probable, 21; clinically probable-laboratory supported, 18; clinically possible, 34; and clinically suspected, 25. Among the 59 patients in the clinically possible or suspected categories, sufficient follow-up information for more than 3 months was available in 47 patients, and the diagnostic category rose to clinically probable (including laboratory supported) or higher in 16 patients. Nine additional patients developed respiratory failure that caused death or required ventilatory support or gastrostomy tube feeding. Six of these 25 patients died. For the remaining 22 patients the diagnostic level did not reach clinically probable or higher, and they did not develop such critical problems over 3–14 months of follow-up.

For the CS group, 32 patients were included, they consisted of 29 men and 3 women ranging in age from 33–85 years (mean, 62.2 years). The distribution of weakness was mainly proximal (C5–C6 innervation) in 21 patients, mainly distal (C7–T1 innervation) in nine patients, or a combination of both in two patients.

Electromyography. The levels of relaxation achieved for each muscle are presented in Table 1. The trapezius had the highest level of complete relaxation (85% of ALS and 97% of CS patients). Similar levels of relaxation were achieved in 43% of ALS patients for the SCM and only 6% for the tongue. A level of relaxation that enabled identification of Fib/PSWs was achieved in all patients for the trapezius, but it was achieved in slightly more than half of ALS pa-

Table 1. Relaxation level and summary of EMG findings.

	Tongue	SCM	Trapezius
Amyotrophic lateral sclerosis (n=104)			
Relaxation level			
Complete	6 (6%)	45 (43%)‡	88 (85%)§
Partial	54 (52%)	50 (48%)	16 (15%)
No relaxation	44 (42%)	9 (9%)	0 (0%)
EMG findings			
Fib/PSWs	8 (8%)	13 (13%)	47 (45%)§
Fasciculation potentials	1 (1%)	7 (7%)‡	41 (39%)§
Any abnormal spontaneous activity*	9 (9%)	18 (17%)	65 (63%)§
MUP changes†	52 (50%)	62 (60%)	67 (64%) ‖
Both Fib/PSWs and MUP changes (Revised El Escorial criteria)	8 (8%)	11 (11%)	40 (38%)§
Both abnormal spontaneous activity and MUP changes (Awaji criteria)	9 (8%)	16 (15%)	50 (48%)§
Cervical spondylosis (n=32)			
Relaxation level			
Complete	not done	14 (44%)	31 (97%)
Partial	not done	18 (56%)	1 (3%)
No relaxation	not done	0 (0%)	0 (0%)
EMG findings			
Fib/PSWs	not done	0 (0%)	0 (0%)
Fasciculation potentials	not done	0 (0%)	0 (0%)
Any abnormal spontaneous activity*	not done	0 (0%)	0 (0%)
MUP changes†	not done	2 (6%)	6 (19%)

Fib/PSWs, fibrillation potentials and/or positive sharp waves; SCM, sternocleidomastoid.
**Any abnormal spontaneous activity, either Fib/PSWs or fasciculation potentials, or both.*
†MUP changes, changes in the shape or recruitment of the motor unit potentials (MUPs).
‡$p < 0.05$ for tongue vs. SCM (Wilcoxon's two sample test was used for comparisons between the ranked relaxation levels of any two muscles).
§$P < 0.05$ both for tongue vs. trapezius and SCM vs. trapezius.
‖ $P < 0.05$ only for tongue vs. trapezius.

tients for the tongue. The differences in the relaxation level between the different muscles were highly significant.

The EMG findings of the patients are also summarized in Table 1. The frequency of abnormal spontaneous activity in the ALS patients was markedly different between the three muscles. Both Fib/PSWs and fasciculation potentials were much more frequently identified in the trapezius than in the tongue or SCM. Any type of abnormal spontaneous activity was observed in 62% of the ALS patients for the trapezius, but it was observed in only 17% of patients for the SCM and 8% for the tongue. In contrast, the frequency of MUP changes (changes in the MUP shape or recruitment) was not very different between the three muscles.

The frequency of abnormal spontaneous activity for each ALS subgroup is summarized in Table 2. In general, there was little difference in frequency between the different subgroups; significant differences were observed only for the tongue. Patients who had tongue atrophy or were in categories with a higher diagnostic certainty had a significantly higher frequency of Fib/PSWs in the tongue, although even patients with overt tongue atrophy had a rather low frequency of Fig/PSWs (15%). Notably, the findings for the trapezius, in which abnormal spontaneous activity was most frequently observed, were similar between the different subgroups, particularly between the different diagnostic categories. Even clinically suspected ALS patients presented with a similarly high frequency of Fib/PSWs, fasciculation potentials, or any type of abnormal spontaneous activity (72%) as compared to the higher diagnostic categories.

The EMG findings of the CS patients are also shown in Table 1. Neither Fib/PSWs nor fasciculation potentials were observed in any CS patient, although MUP changes were infrequently observed.

DISCUSSION

Methods of the EMG Assessment. Usually, LMN dysfunction in ALS is confirmed by the presence of both Fib/PSWs and MUP changes.[4] In the present study, however, we relied primarily on spontaneous activity, including fasciculation potentials. We also recorded changes of MUP shape and recruitment, but we did not use them as a primary marker for abnormality. Qualitative assessment remains the most popular method employed for the evaluation of voluntary activity in daily EMG practice. Many previous studies that investigated EMGs of the cranial muscles in ALS also employed qualitative assessment[3,27,30] or gave no detailed description on the method of evaluation for voluntary activities.[5,6,10,28] A qualitative method would be sufficiently reliable if performed by a trained examiner,[7,12] but it would not be free from subjective biases. In contrast, the judgment of spontaneous activity is a clear-cut dichotomy: it is either present or absent, and is sufficiently reliable, particularly because we employed strict definitions to identify spontaneous activity. We admit that establishing the neurogenic nature of the overall disease process by evaluating MUP shape and recruitment is mandatory for the diagnosis of ALS, but this is usually achieved in the limb muscles for most cases.

There remains controversy regarding the significance of fasciculation potentials in the diagnosis of ALS. One conventional view is that fasciculation po-

Table 2. Frequency of abnormal spontaneous activities for ALS subgroups.

	Fib/PSWs			Fasciculation potentials			Any abnormal		
spontaneous activity*	Tongue	SCM	Trapezius	Tongue	SCM	Trapezius	Tongue	SCM	Trapezius
Bulbar onset (n = 40)	3 (8%)	5 (13%)	16 (40%)	0 (0%)	2 (5%)	13 (33%)	3 (8%)	6 (15%)	22 (55%)
Non-bulbar onset (n = 64)	5 (8%)	8 (13%)	31 (48%)	1 (2%)	5 (8%)	28 (44%)	6 (9%)	12 (19%)	43 (67%)
Tongue atrophy									
Present (n = 41)	6 (15%)†	8 (20%)	22 (54%)	0 (0%)	3 (7%)	15 (37%)	6 (15%)	10 (24%)	27 (66%)
Absent (n = 63)	2 (3%)	5 (8%)	25 (40%)	1 (2%)	4 (6%)	26 (41%)	3 (5%)	8 (13%)	38 (60%)
Diagnostic category according to the Revised E1 Escorial criteria									
Definite (n = 6)	1 (17%)‡	1 (17%)	5 (83%)	0 (0%)	0 (0%)	1 (17%)	1 (17%)	1 (17%)	5 (83%)
Probable (n = 21)	3 (14%)	4 (19%)	7 (33%)	0 (0%)	1 (5%)	9 (43%)	3 (14%)	5 (24%)	12 (57%)
Probable-laboratory supported (n = 18)	3 (17%)	1 (6%)	12 (67%)	0 (0%)	1 (6%)	8 (44%)	3 (17%)	1 (6%)	13 (72%)
Possible (n = 34)	0 (0%)	3 (9%)	12 (35%)	1 (3%)	3 (9%)	12 (35%)	1 (3%)	6 (18%)	17 (50%)
Suspected (PMA; n = 25)	1 (4%)	4 (16%)	11 (44%)	0 (0%)	2 (8%)	11 (44%)	1 (4%)	5 (20%)	18(72%)

Fib/PSWs, fibrillation potentials and/or positive sharp waves; SCM, sternocleidomastoid; PMA, progressive muscular atrophy.
**Any abnormal spontaneous activity, either Fib/PSWs or fasciculation potentials, or both.*
†$P < 0.05$ (present vs. absent).
‡$P < 0.05$ (Wilcoxon's two sample test on whether the categories with higher diagnostic certainty had a higher incidence of abnormality).

tentials are nonspecific findings, since they occur not only in various disorders but also in normal individuals.[8,23] Other authors, including the present authors, however, have argued that fasciculation potentials have an important role for diagnosis, given their high specificity for ALS.[9,32,33,39] The recent Awaji criteria, which were proposed as the revised criteria for ALS diagnosis,[11] gave fasciculation potentials a similar significance as Fib/PSWs. In the present study we observed no fasciculation potentials in the SCM or trapezius muscles in any CS patients. The specificity of fasciculation potentials was excellent in this regard, and these results support the new Awaji criteria.

Limitations of Tongue EMG. The present results clearly revealed the limitations of tongue EMG. The probability of obtaining complete relaxation was very low, and even partial relaxation was achieved in only approximately half of the subjects. Fib/PSWs were identified in only 8% of ALS patients, and fasciculation potentials were even less. Difficulty in relaxing the tongue has been mentioned by several authors,[10,14,27,39] but few reports have presented the actual frequency of this problem. Preston et al.[30] reported that the relaxation of the tongue was insufficient in two out of 21 ALS cases. Finsterer et al.[15] stated that they found any type of spontaneous activities in the tongue in 60%–63% of patients, and they could not accurately assess spontaneous activity in the remaining patients. We believe our high frequency of nonrelaxation was not due to poor technique, but rather it was due to the fact that we gave greater attention to this issue with an effort to maintain adequate quality control to standardize our findings.

We identified Fib/PSWs in the tongue in only 3% of the subjects who lacked overt tongue atrophy and in 15% of the subjects with atrophy. Thus, contrary to prevalent belief,[1,13,15] tongue EMGs rarely detected subclinical LMN involvement of the bulbar muscles,[23] and they provided little additional utility over the clinical sign of tongue atrophy.

Most previous studies reported a higher frequency of Fib/PSWs or fasciculation potentials in the tongue than the present study.[5,15,27,30] The earlier clinical stage in our study may be the reason for the lower frequency,[10] but it is unlikely to be the main reason. The frequency of abnormal spontaneous activity in patients with a higher diagnostic certainty was also low in the present study (Table 2). We hypothesize that the more rigorous conditions we used to identify abnormal spontaneous activity must be the major reason for our lower figure, because small voluntary MUPs may be difficult to distinguish from fibrillation potentials in the cranial nerve muscles.[10,14] De Carvalho et al.[10] found no Fib/PSWs in bulbar muscles (masseter, tongue, or SCM) of 68 ALS patients. However, one drawback of their study may be that they looked for spontaneous activity in only four different sites in each muscle. We explored at least 10 different sites, which must be a minimum requirement as the standard EMG technique.[34]

Utility of the Trapezius EMG. Our results revealed that it was easier to achieve complete relaxation in the upper trapezius muscle, and the frequency of Fib/PSWs and fasciculation potentials in ALS patients was by far the highest in this muscle among the three muscles investigated. A similar superiority of the trapezius muscle has been reported by Cho et al.[6] in a smaller number of subjects, although they did not differentiate between abnormalities in spontaneous activity and those in voluntary activity.

We observed abnormal spontaneous activity far more frequently in the trapezius than in the SCM, in spite of the fact that both muscles are innervated by the spinal accessory nerve.[16,21,41] Similarly, low frequency of fibrillation potentials in the SCM have been reported by other authors.[10,27] This discrepancy between the trapezius and SCM cannot be completely explained by better relaxation in the trapezius because a relaxation level that enabled identification of Fib/PSWs was achieved for most patients even in the SCM. A study in the rat demonstrated that the SCM was innervated rostrally from C1 to C3 motoneurons, whereas the trapezius was innervated caudally from C3 to C5.[22] However, it is hard to explain the observed discrepancy by a different location of neuronal soma, because there was no difference in the findings between patients with bulbar-onset (caudal progression) and nonbulbar onset (rostral progression). A similar preferential involvement or appearance of fibrillation potentials in ALS has been described for other muscles such as the tibialis anterior, thenar muscles, or first dorsal interosseus muscle.[24,25,36,38,40] Although the pathophysiological basis for such selectivity is unknown, the upper trapezius should be added to the list of muscles that are preferentially affected in ALS, at least regarding spontaneous activity.

In the present study we observed no abnormal spontaneous activity in the SCM or trapezius muscles in any of the 32 CS patients. In CS patients, normal EMGs of the SCM have been reported by a few authors,[19,27] but we could not find any previous reports for trapezius EMG. Considering the location of the motoneurons for the SCM and upper trapezius, as mentioned above, the SCM may well be spared in CS patients, but the trapezius, with cell bodies at C3 to C5, may be involved because the C3–4 vertebral level (C4–5 spinal level) is the upper limit of cord compression in cervical spondylotic myelopathy.[17] Some of the cervical spondylotic amyotrophy cases may be actually motor radiculopathies,[20,31] and the spinal accessory nerve ascending within the spinal canal would not be affected by the radiculopathy. In addition, the anterior portion of the upper trapezius muscle, which we usually select as the needle insertion site during the examination in the supine position, may be innervated by the rostral group of the spinal motoneurons for this muscle.[22] In any case, we can conclude from the present results that the abnormal spontaneous activity in the upper trapezius (and SCM) indicates widespread LMN involvement that is rarely seen in CS and is highly suggestive of ALS.

We observed abnormal spontaneous activity, including fasciculation potentials, in the trapezius in clinically possible or even "suspected" ALS patients (PMA patients) as frequently as in patients with a higher diagnostic certainty. More than half (25/47) of patients with such lower diagnostic categories for whom sufficient follow-up information was available later went up to the higher categories or developed life-threatening respiratory dysfunction or dysphagia despite rather short follow-up periods. Traynor et al.[35] reported that patients who were initially classified into lower diagnostic categories showed no better prognosis than those who were classified into higher diagnostic categories, and 67% of them eventually fulfilled higher categories. A further 15% remained trial ineligible until death. These facts suggest that most patients classified into lower diagnostic categories in the present study actually suffered from ALS. In this regard, observation of abnormal spontaneous activity in the trapezius will contribute to the early diagnosis of ALS.

Considering the predominantly high-to-middle cervical location of motoneurons for the SCM and trapezius, it is not appropriate to classify these muscles as bulbar muscles.[10,14] However, we can at least define them as cervical muscles, and examination of the trapezius EMG with its high frequency of abnormality would contribute to reducing the number of muscles examined until the EEC regarding the cervical region is satisfied.

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