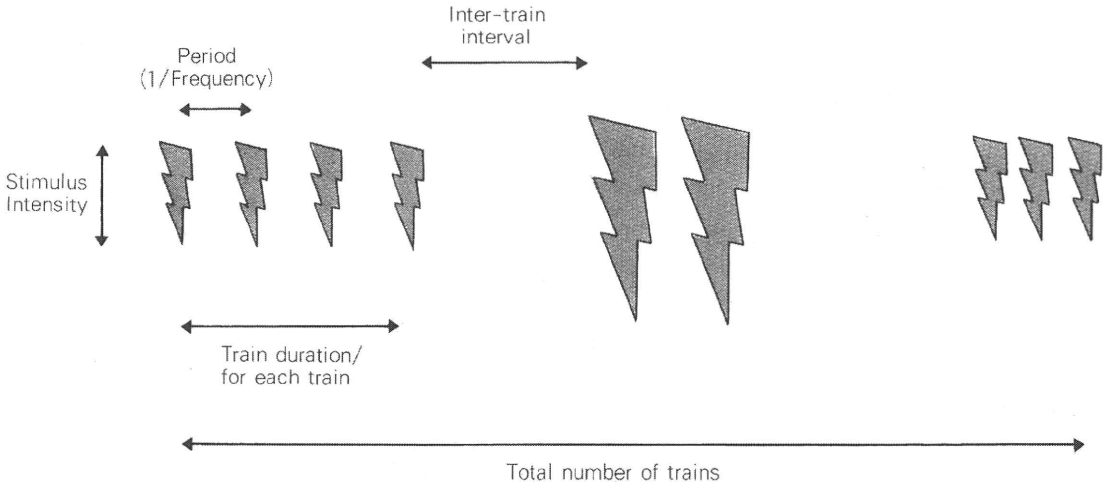

＊通常は刺激強度（カミナリの模式図の大きさ）や刺激頻度は変化させないことが多いが刺激パラメーターの変化が視覚的に理解できるように上記のように記載した

図2　rTMSにおける各種パラメーター

表2　National Institute of Neurological Disorders and Stroke勧告におけるrTMSのsingle trainの最大安全域

Frequency (Hz)	Intensity (% of MT)												
	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	1.6	1	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

表3　20Hz以下のrTMSを10刺激投与する際の各刺激間の時間の推奨安全域

Inter-train interval (s)	Stimulus intensity % of MT			
	100%	105%	110%	120%
5	Safe	Safe	Safe	Insufficient data
1	Unsafe	Unsafe	Unsafe	Unsafe
0.25	Unsafe	Unsafe	Unsafe	Unsafe

に従う．しかしながらrTMSを繰り返す場合，Inter-train intervalの検討が重要であるが，rTMSによる被験者のてんかん発作リスクを考慮し（表4），そのような研究は中止されており詳細は不明確なままである．

運動野におけるTMS刺激方法

脳卒中後の下肢運動麻痺に対する磁気刺激治療の有効性は確立されていないため，上肢の刺激方法のみ記載する．ヒトの運動野における手指の対応部位は，Czから5～6cm外側であり，8の字コイルの中心をその周辺に合わせ刺激を行う（図3）．渦電流が前内側方向であると手指筋に対応する運動野を刺激しやすいため，コイルを前内側方向に設置する（8の字コイルに流れる電流は後外側方向であるが，渦電流はコイルと逆方向に生じるため）．施設間によって異なるが，モニター

表4　てんかんを誘発したrTMS刺激パラメーター

Subject	Intensity (% MT)	Frequency (Hz)	Duration (s)	Inter-train interval (s)
てんかん	＞100	16	10	Long[a]
正常人	250	25	10	Long[a]
正常人	105	15	0.75	0.25
正常人	110	25	0.8	1
正常人	120	15	2.5	Long[a]
正常人	120	15	2.7	＞60
正常人	130	3	7	Long[a]
正常人	200	10	10	300－600
うつ病	110	20	10	60
うつ病	90	10	10	60

Long[a] 間隔は長くてんかんの要因とは考えられていない
(Chen R, et al. 1997, Wassermann EM. 1998, Conca A, et al. 2000より改訂)

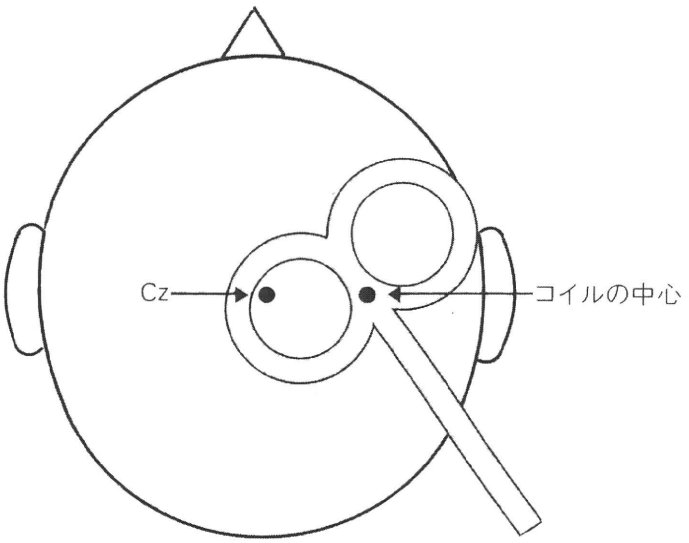

図3　運動野の刺激方法

する筋は第一背側骨格筋が多い．安静時に50μV以上の運動誘発電位が50%以上の確率で得られる刺激強度を安静時運動閾値とよび，閾値より少し大きな刺激強度で少しずつ前後にコイルの中心を移動し，一番大きな運動誘発電位が得られる部位をOptimal siteと定義し刺激部位とする．安静時閾値を基準にrTMSの刺激強度を設定することが多い（詳細な刺激強度は次回に記載）．

rTMSにおける注意点

rTMS実施の重要な注意点はてんかん予防のモニタリングと禁忌事項であり次に示す．

1．生理学的モニタリング

運動野における閾値下での刺激を行う場合，刺激部位に対応する筋からの運動誘発電位を連続的にモニターする．閾値以上の強さで運動野にrTMSを行う場合には，興奮Kindlingの皮質内拡散を見るため，刺激部位に対応する筋以外の筋電図モニターを行う．広範囲での運動誘発電位の存在は興奮の皮質内拡散を示し，てんかんの危険性がある．また可能であれば脳波をモニターすることが推奨されている．

2．rTMSの禁忌

一般的にrTMSの禁忌として頭蓋内の金属，高い頭蓋内圧，妊娠，乳幼児，心臓ペースメーカー，

三環系抗うつ薬，中枢刺激薬，てんかんの家系があげられる．コイル近くの金属製の物体はrTMSにより金属性の物質は加熱されるため，口以外の頭部金属の存在は一般的にrTMSに禁忌であり，長期的な影響が不明なため臨床的恩恵なしに小児，妊婦に対してはrTMSを行うべきではない．三環系抗うつ剤，中枢刺激薬はてんかんの閾値を低下させるため注意が必要である．

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入門講座

経頭蓋磁気刺激を用いた脳卒中リハビリテーション（2）

Stroke rehabilitation using transcranial magnetic stimulation

竹内　直行　　生駒　一憲*
TAKEUCHI Naoyuki　IKOMA Katsunori

・脳卒中後の機能回復は中枢神経系の再構築による可塑性に由来するため，適切な可塑性を引き起こすことが重要である．
・脳卒中後の回復過程には両側半球のバランス変化が影響する．
・大脳皮質の興奮性を変化させるrTMSを用い，脳卒中後の運動麻痺，半側空間無視，失語，嚥下障害，脳卒中後疼痛への治療が報告されている．
・rTMSによって運動麻痺改善が期待できる症例は，分離運動が可能なレベルである．
・rTMS効果増大には運動訓練との併用が重要である．

KEY WORDS 磁気刺激，脳卒中，リハビリテーション

はじめに

脳卒中後の機能回復は中枢神経系の再構築による可塑性に由来し，適切な可塑性を引き起こし機能回復を改善させることが重要である．障害側運動野を中心とした神経再構築が起きると麻痺側の機能回復は良好であるが，機能障害が強い脳卒中患者は健側半球を含めた障害側運動野以外の運動関連領域の動員を必要とする．しかしながら健側半球の過剰な興奮は健側運動野から障害側運動野への脳梁抑制を増加させ障害側運動野機能を抑制し麻痺を悪化させる可能性がある．それゆえ障害側半球の機能だけでなく，両側半球のバランス改善が脳卒中後の回復過程メカニズムに重要である．今回，脳卒中に対する反復経頭蓋磁気刺激（repetitive transcranial magnetic stimulation；rTMS）治療を紹介する．

脳卒中運動麻痺に対するrTMS治療（表1）

1．脳卒中運動麻痺（図1）

左右半球の対立モデルから脳卒中患者の運動麻痺は障害側運動野からの出力減少および健側運動野からの過剰な脳梁抑制によるものと考えられている[1)-3)]．そのため脳卒中後の麻痺側機能改善の戦略として障害側運動野の興奮性増加，健側運動野の興奮性低下を引き起こすことが重要である．上記の理由からrTMSを用い健側運動野を抑制，障害側運動野を興奮させ麻痺側機能を改善させる方法が報告されている．障害側運動野への高頻度rTMS効果及び健側運動野への低頻度rTMSは障

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表 1　脳卒中後麻痺に対する rTMS 治療報告

報告者	患者人数	障害部位	発症からの期間	刺激部位	刺激方法	刺激回数
Mansur et al. 2005 Neurology	8 人 rTMS 8 人，シャム刺激 8 人	皮質，皮質下梗塞	12ヵ月以上	健側運動野	1 Hz 100% rMT（健側）	600 stimuli
Khedr et al. 2005 Neurology	52人 rTMS 26人，シャム刺激 26人	皮質下，皮質梗塞 （MCA 領域）	5－10日	障害側運動野	3 Hz 120% rMT（健側）	10 trains of 10s ×10 sessions
Takeuchi et al. 2005 Stroke	20人 rTMS 10人，シャム刺激 10人	皮質下梗塞	6－60ヵ月	健側運動野	1 Hz 90% rMT（健側）	1500 stimuli
Kim et al. 2006 Stroke	15人 rTMS 15人，シャム刺激 15人	皮質下，皮質病変 （脳出血，脳梗塞）	6－41ヵ月	障害側運動野	10Hz 80% rMT（障害側）	8 trains of 2s
Fregni et al. 2006 Stroke	15人 rTMS 10人，シャム刺激 5 人	皮質下，皮質梗塞	12－126ヵ月	健側運動野	1 Hz 100% rMT（健側）	1200 stimuli × 5 sessions
Talelli et al. 2007 Clin Neuropysiol	6 人 rTMS 6 人，シャム刺激 6 人	皮質下，皮質梗塞	12－108ヵ月	障害側運動野	intermittent TBS 80% aMT（障害側）	20 trains of 10 bursts（5 Hz）
Kirton et al. 2008 Lancet Neruol	10人（7 歳以上の小児） rTMS 5 人，シャム刺激 5 人	皮質下梗塞	28－160ヵ月	健側運動野	1 Hz 100% rMT（健側）	1200 stimuli × 8 sessions
Izumi et al. 2008 J Rehabil Med	9 人 rTMS 5 人，シャム刺激 4 人	皮質下，皮質梗塞	9－122ヵ月	障害側運動野 （麻痺側随意収縮中に実施）	0.1Hz ＞100 % rMT（障害側）	100 stimmui × 4 sessions

TBS：Theta Burst Stimulation
(1 burst：50Hz，3 stimuli)

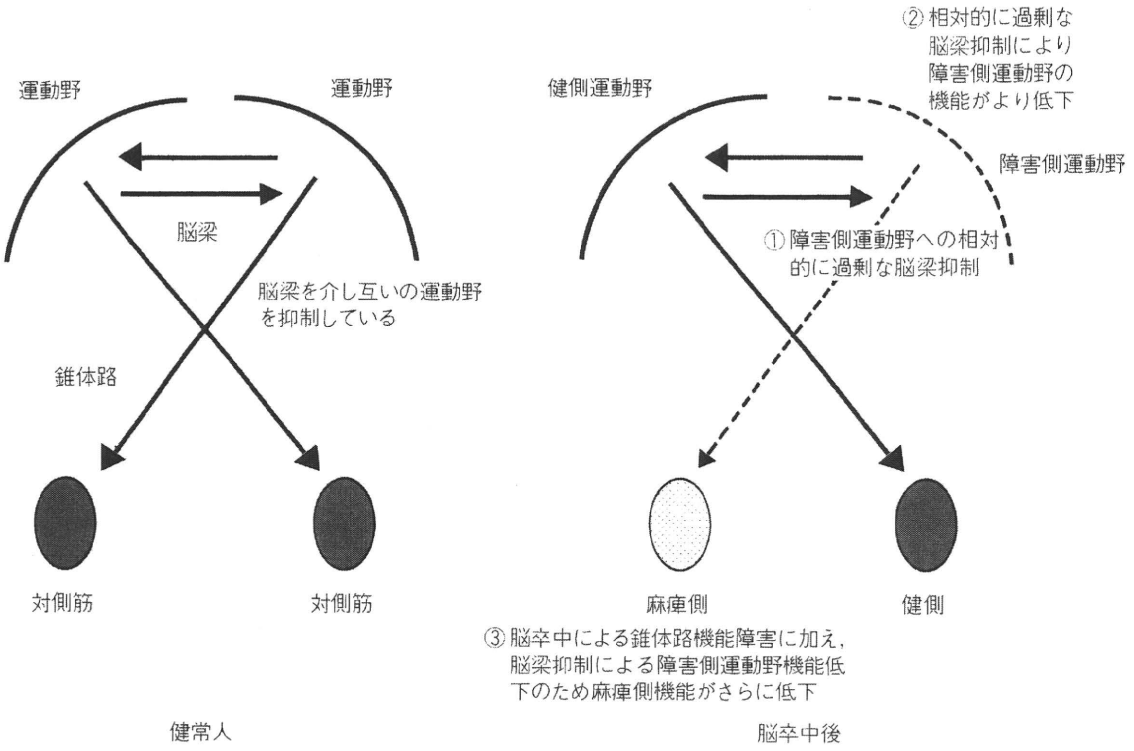

図1　脳卒中後の運動麻痺

害側運動野の興奮性を増加させ錐体路機能の活性化および大脳皮質の可塑性を増大し運動訓練効果が増大すると考えられる[4)5)]．

2．障害側運動野のへの高頻度rTMS（図2）

高頻度rTMSが刺激部位の興奮性を増加させることを利用し，障害側運動野に高頻度rTMSを行い障害側運動野を活性化させる．急性期での報告としては3Hz 120%安静時閾値（rest motor threshold；rMT）の条件で10秒・10トレイン，慢性期では10Hz 80% rMTの条件で2秒・8トレインにて機能改善を得た報告がある．他の方法としてはIntermittent Theta Burst Stimulation（1 burst：50Hz, 3 stimuli）を80%運動時閾値の強度で10 Burst（5Hz）・20トレインを実施した報告がある．一般的に高頻度rTMSはてんかん誘発の可能性が強いため，閾値下にて刺激することが望ましい．

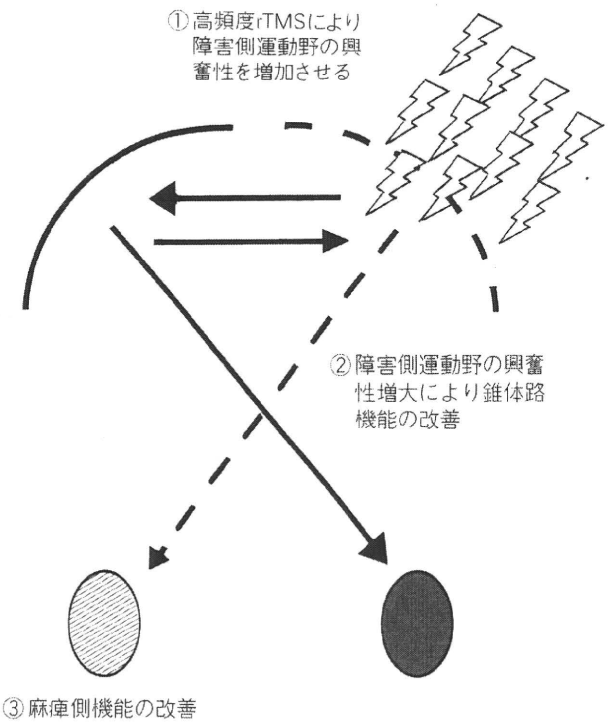

図2　高頻度rTMS

3．健側運動野への低頻度rTMS（図3）

低頻度rTMSが刺激部位を抑制することを利用し，健側運動野に低頻度rTMSを行い健側運動野の興奮性を低下させる．実際には1Hz，90% rMT（または100% rMT）にて10～25分間rTMSを行う．閾値下の刺激は局所的な抑制作用のみにとどまるが，閾値上の刺激は刺激部位だけ

でなく，脳梁抑制の経路を刺激し対側の運動野を抑制する可能性がある．そのため閾値と同レベルまたは閾値下（90% rMT）に刺激を行うことが望ましい．

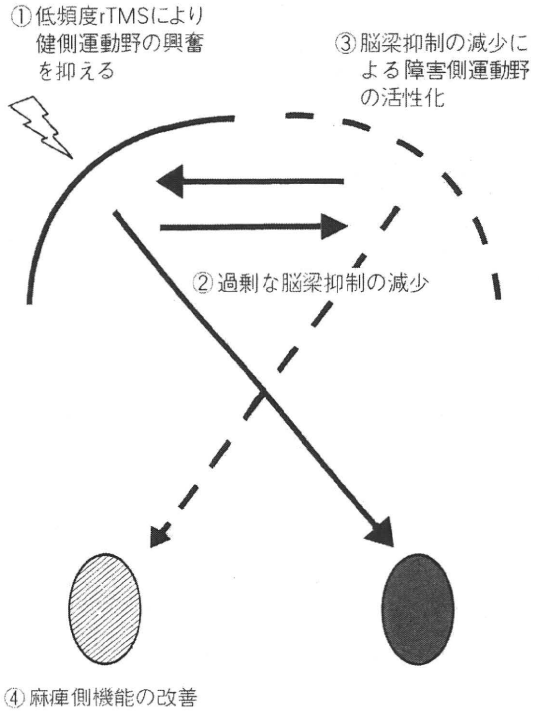

図3　低頻度 rTMS

運動麻痺以外の脳卒中後障害に対する rTMS 治療（図4，表2）

1．半側空間無視

片側半球障害によって引き起こされた半側空間無視は運動麻痺と同じメカニズムで，健側半球（主に左）からの過剰な脳梁抑制にて障害側半球機能が低下すると考え，健側半球へ低頻度 rTMS を行い障害側半球を活性化させる報告が多い．

2．失　　語

左半球言語領域周囲または右半球の病巣対側部位など，患者間によって機能代償部位が異なるため個々の症例にあわせ刺激部位を決定する必要がある．安保らは言語タスク時の機能画像を利用し，賦活部位の対側半球に低頻度 rTMS を行い言語機能の回復が得られたこと報告している[6]．

3．嚥 下 障 害

障害側半球への高頻度 rTMS および健側半球への低頻度 rTMS の報告がある．急性期および慢性

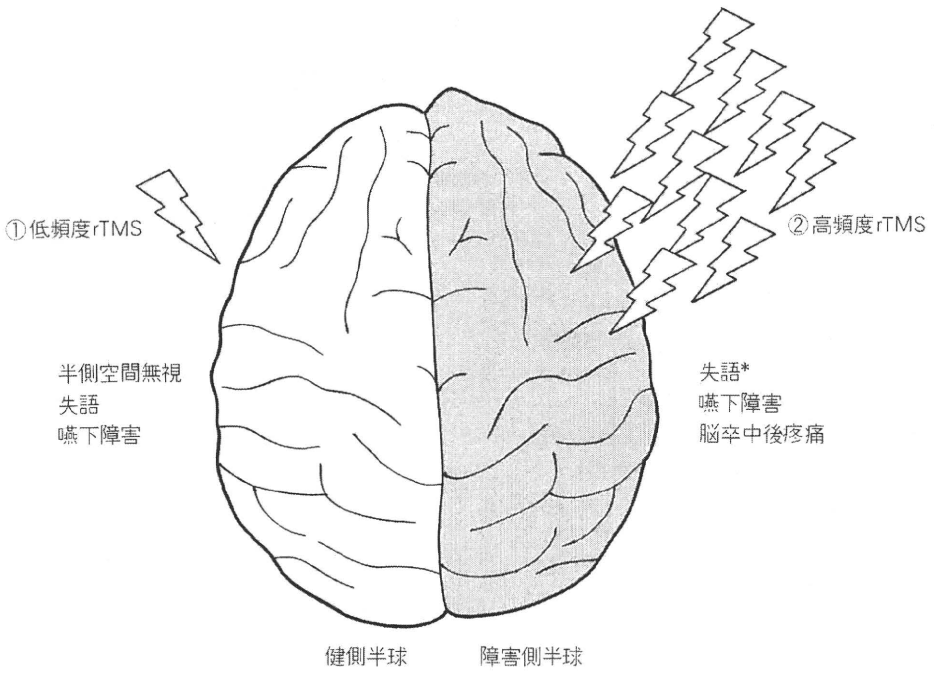

図4　運動麻痺以外に対する rTMS 治療

① 低頻度 rTMS によって健側半球の機能を低下させ，脳梁抑制を介し，障害側半球の活性化を引き起こす．
② 高頻度 rTMS によって直接，障害側半球の活性化を引き起こす．
*障害側半球へ低頻度および高頻度 rTMS の報告がある．

表 2　運動機能以外の症状に対する rTMS の応用

報告者	障害名	患者人数	発症からの期間	刺激部位	刺激方法	刺激回数
Oliveri et al. 2001 Neurology	半側空間無視	7人 rTMS 7人，シャム刺激7人	1－48週間	P5 or P6 （健側半球）	25Hz 115% rMT（健側）	10 stimuli
Brighina et al. 2003 Neurosci Lett	半側空間無視	3人 コントロール無し	3－5ヵ月	P5 （健側半球）	1 Hz 90% rMT（健側）	900 stimuli × 7 sessions
Shindo et al. 2006 J Rehabil Med	半側空間無視	2人 コントロール無し	6ヵ月	P5 （健側半球）	0.9Hz 95% rMT（健側）	900 stimuli × 6 sessions
Naeser et al. 2005 Brain Lang	失語	4人 コントロール無し	5－11年	右ブローカ部位 （健側半球）	1 Hz 90% rMT（健側）	1200 stimuli × 10 sessions
Khedr et al. 2009 Acta Neurol Scand	嚥下障害	26人 rTMS14人、シャム刺激12人	5－10日	障害側運動野	3 Hz 120% rMT(健側)	10 trains of 10s × 5 sessions
Verin et al. 2009 Dysphagia	嚥下障害	7人 コントロール無し	11－132ヵ月	健側運動野	1 Hz 120% rMT（健側）	120 stimuli × 5 sessions
Khedr et al. 2005 J Neurol Neurosug Psychiatry	脳卒中後疼痛	24人 rTMS14人，シャム刺激10人	18±17ヵ月	障害側運動野	20Hz 80% rMT（障害側）	10 trains of 10s ×5 sessions
Andre-Obadia et al. 2006 Clin Neuropysiol	脳卒中後疼痛	10人 rTMS10人，シャム刺激10人	6.9±4.0年	障害側運動野	20Hz 90% rMT（障害側）	20 trains of 4s
Hirayama et al. 2006 Pain	脳卒中後疼痛	12人 rTMS12人，シャム刺激12人	1.3－16年	障害側運動野	5 Hz 90% rMT（障害側）	10 trains of 10s
Goto et al. 2008 Pain	脳卒中後疼痛	17人 コントロール無し	1.0－8.8年	障害側運動野	5 Hz 90% rMT（障害側）	10 trains of 10s

期ともに改善した報告を認めるが，急性期においては自然回復の可能性（コントロール群よりは改善を認めているが）の問題点がある．また嚥下機能は両側支配の報告が多いため健側半球機能を低下させることによる嚥下機能悪化の可能性も否定できない．

4．脳卒中後疼痛

障害側運動野へ高頻度rTMSを行う報告が多い．疼痛改善のメカニズムは不明であるが，以前より大脳皮質電気刺激にて除痛が得られた報告があり，共通のメカニズムが推測されている．一つの仮説としては脳卒中後の慢性疼痛は障害側運動野での脱抑制に関連があると考えられており，それをrTMSにて是正することによって除痛効果があるかもしれない[7]．

臨床応用のポイント

ここでは報告の多い運動麻痺に対するrTMS治療のポイントを記載する．

1．適応患者

発症からの期間にてrTMS効果の差は認めないが，rTMSの効果は健側運動野刺激および障害側運動野刺激ともに，障害側運動野の活性化を目的とするため運動野に病巣がある症例は効果が少ないと考えられる．また麻痺側が共同運動レベルではrTMSの効果が少なく，効果がある症例は錐体路機能がある程度保たれている必要がある．7歳以上の小児脳卒中患者でrTMS治療による麻痺の改善が報告されているが[8]，6～7歳以下の小児は脳梁がまだ未発達なために，過剰な脳梁抑制を低下させる健側rTMS治療は効果が少ないと考えられる．

2．効果増強方法

rTMSによる効果の持続及び増強については，追加刺激，刺激後の運動訓練を組み合わせることが重要と考えられる[4][9]．特に強制使用との併用が効果増大に期待できる．強制使用は麻痺のためあまり使用していない状態の麻痺側上肢を強制的に使用することによって運動機能を改善する方法であるが，健側上肢を抑制することによって健側半球興奮性を低下させる側面を持つ．そのため強制使用は障害側運動野を活性化させ，健側運動野の興奮性を低下させるrTMS治療と共通点があり，相乗効果が期待できる．

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歩行障害

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はじめに●

歩行(ambulation, walk)とは下肢を用いた移動を指す．歩行時の姿勢や四肢の運動パターンを表すときは，歩容(gait または gait pattern)という言葉を用いて，歩行と区別する．ただし，慣例的に歩行と歩容を厳格に区別していないことが多く，「歩行障害」には移動能力の障害と歩容の障害の二つの意味が含まれる．ここでは，慣例に従って「歩行」と表記する．以下においては正常歩行と歩行障害について述べた後，高齢者の転倒とその予防についても述べる．

正常歩行●

歩行周期を**図1**[1]に，歩行に関する用語について**表1**に示す．

接地のときは踵から降ろし立脚期が始まる．爪先が最後に離れて空中に出て遊脚期になる．立脚期と遊脚期の比率は約6：4，単脚支持期と両脚支持期の比率は約4：1である．歩行が速くなると遊脚期が長くなり，両脚支持期が短くなる．歩

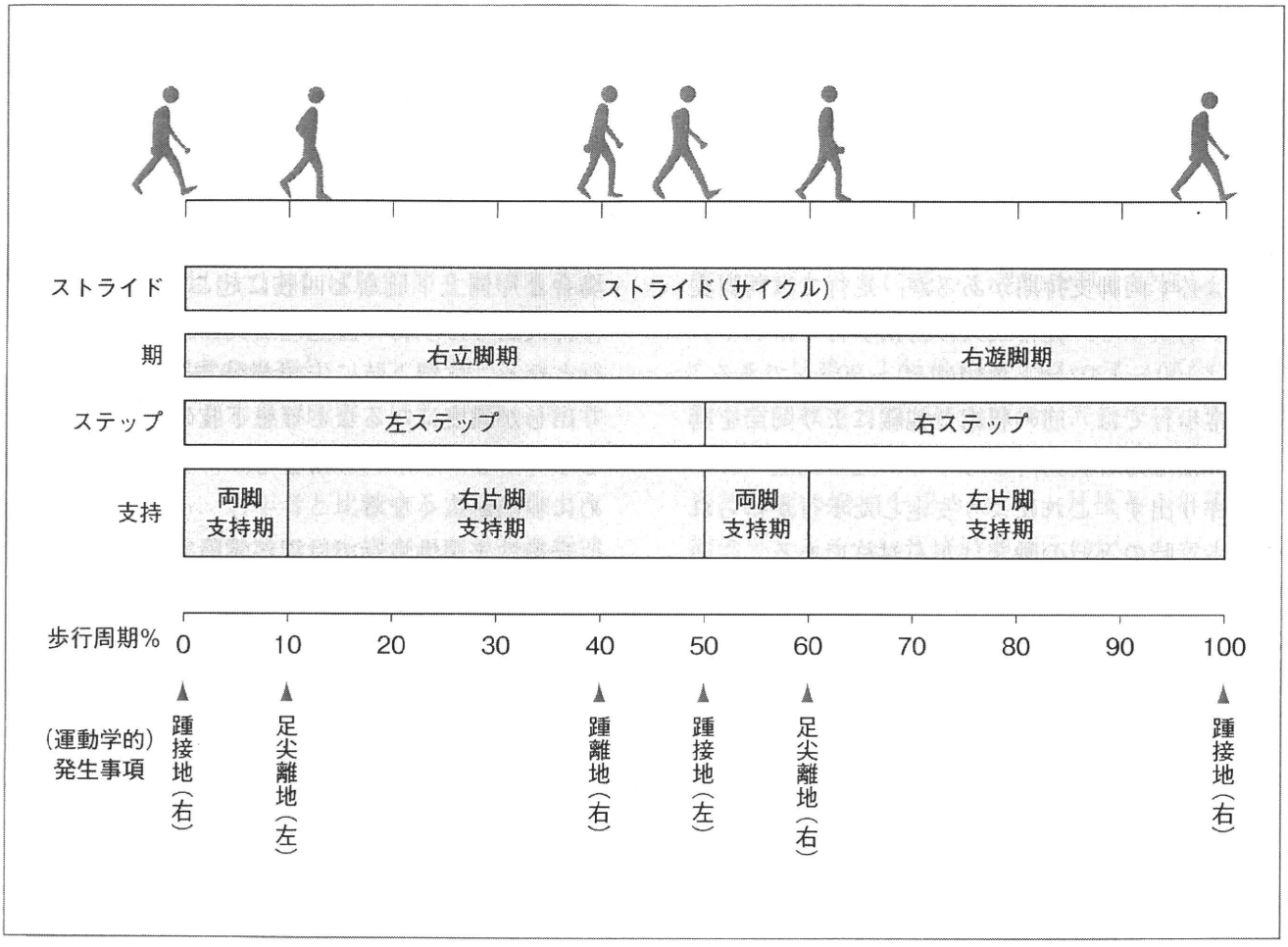

図1　歩行周期
(文献1)を改変引用)

0910-1551/10/￥100/頁/JCOPY

●痙性片麻痺性歩行では分回し歩行となり，尖足，反張膝を伴う．
●パーキンソン歩行では前傾姿勢で小刻み歩行となり，突進現象やすくみ足を伴う．
●失調性歩行では酩酊様歩行となり，歩隔が拡大する．

表1　歩行に関する用語

ステップ（step：歩）	右ステップなら左踵接地から右踵接地まで，左ステップなら右踵接地から左踵接地まで
歩幅（step length）	ステップの長さ
歩隔（step width）	両足の左右方向の距離（両踵の間隔）
ケイデンス（cadence：歩調）	単位時間あたりのステップ数
ストライド（stride：重複歩）またはサイクル（cycle）	一側の踵接地から再び同側の踵が接地するまで
立脚期	足が地面についている時期
遊脚期	足が空中にある時期
単脚支持期	一側の脚で体を支持する時期
両脚支持期	両脚で体を支持する時期

行では必ず両脚支持期があるが，走行では両脚支持期が消失する．健常成人の自由歩行ではケイデンスは100～120/分，歩幅は50～80cmである．

正常歩行では，筋の収縮と弛緩により関節を動かし，推進力と制動力をもった一定の運動パターンを作り出す．これにより安定した歩行が得られる．歩行時の下肢の動きは左右対称である．

主な歩行障害とその特徴●

1.　痙性片麻痺性歩行 spastic hemiparetic gait

片麻痺の原因として多いのは脳卒中である．痙性麻痺のため伸筋共同運動が優位となり，下肢の屈曲運動が円滑に出現しないため，遊脚期に下肢を十分挙上できない．股関節が外転し外から円を描くように回して麻痺側下肢を前方に振り出す．これを分回し歩行という．さらに尖足も加わるため，麻痺側下肢を引きずることも多い．また，接地時には尖足のため足尖から接地し，立脚期に膝関節は過伸展（これを反張膝という）する．

2.　パーキンソン歩行 parkinsonian gait

パーキンソン病の歩行では前傾姿勢で歩幅が小さい（小刻み歩行）．腕の振りは減少するか消失する．歩行しているうちに歩行速度が徐々に速まり小走り状態となって止まれなくなる（突進現象）こともある．さらに，最初の一歩を出すことができずに地面に足が貼りついたようになることもある．これをすくみ足という．すくみ足では，地面に横線を描いてそれをまたがせるなど，視覚刺激を入れると第一歩を容易く出すことができるようになる．この現象を矛盾性運動 paradoxical movement という．姿勢反射障害のため転倒しやすい．

3.　失調性歩行（運動失調性歩行）ataxic gait

小脳障害，脊髄障害，前庭障害による3種類の失調性歩行がある．

小脳性失調性歩行では運動失調が体幹に起こる場合と片側上下肢など四肢に起こる場合がある．体幹失調では歩行の直進性が失われ，酩酊様の歩行となる．片側下肢に失調が起こった場合は，振り出しが過度になるなど罹患下肢の運動制御ができなくなる．いずれの場合も，バランスをとるために歩隔が広くなる．

脊髄性失調性歩行では深部覚障害のため下肢の位置情報がフィードバックされないため，振り出す足の制御ができず，地面に投げ出すように足を出す．歩隔は広く，体幹は動揺する．視覚による代償ができない暗所などでは，体幹の動揺は激しくなり，歩行不能に陥ることもある．

前庭性失調性では歩行の方向が障害側へ偏位するのが特徴であるが，障害が両側性の場合は小脳性体幹失調の場合と同様な歩行となる．

4.　鶏歩 steppage gait

総腓骨神経麻痺による前脛骨筋麻痺などにより

- 高齢者の歩行では，歩幅や関節の動きは減少し，立脚期の比率が増大する．
- 高齢者の転倒では，つまずきの有無よりバランスを崩したときの立ち直り機能が重要である．

下垂足が起こると，踵から接地できなくなる．足尖が地面にひっかからないように遊脚期に足を高く上げ，大きく振り下ろすように接地する．

5. あひる歩行 waddling gait

筋ジストロフィ，多発筋炎など近位筋の筋力低下を起こす疾患でみられることが多く，両側の中殿筋の筋力低下のため，体幹を左右に揺すって歩く状態をいう．中殿筋の筋力低下により骨盤が立脚時に水平を保てず遊脚側に傾くが，これを代償するために体幹を立脚側に傾ける．大殿筋の筋力低下が同時にみられることが多く，腰椎が前彎し股関節を前方に突き出した姿勢をとることも多い．

6. 骨関節障害による歩行障害

障害された関節およびその程度により，歩行障害はさまざまである．股関節の拘縮は骨盤の運動で代償できることが多い．膝関節の屈曲拘縮では立脚期に膝が伸展しないため踵接地が早くなる．脚長差は3cm以内であれば股関節を下げることで代償できることが多い．

7. 健常高齢者の歩行[2)]

これは疾病による歩行障害ではないが，高齢者に転倒が多いことを考慮すると，理解しておくことは重要である．若年者と比較すると以下のような特徴がある．高齢者では歩幅が小さく，歩行速度の増大は歩幅よりケイデンスを増加させて得る．立脚期の比率が増大する．股関節，膝関節の動きは少なく，骨盤の回旋は小さい．足関節は足尖離地のときの最大底屈が小さい．遊脚期の足趾の上がりには大きな差はない．

高齢者の転倒

高齢者は一般に転倒しやすいとされるが，前項で述べた健常高齢者の歩行がそのまま転倒につながるのではない．転倒の原因としてつまずきがよく指摘されるが，重要なことはつまずきの有無ではなく，バランスを崩したときの立ち直り機能である[2)]．高齢者は骨関節疾患や脳血管障害などが加わっている可能性は高く，これらの病的要因が加わるとさらにバランス機能は低下する．高齢者の転倒リスクを軽減するためには，バランス訓練，筋力強化などが必要である．

転倒に対するリハビリテーション

転倒には個人的要素である内的要因と生活環境などの外的要因が関係する．外的要因の除去については，家屋のバリアフリー化，路面の整備，照明の設置などの対策がある．内的要因に対しては，バランス訓練，筋力強化を含めた歩行訓練が必要になる．

長屋ら[3)]は**図2**のような転倒予防教室を転倒またはつまずきを経験した高齢者に対して行った．理学療法士がマンツーマンで1週間に1回，運動機能評価とそれに続いて運動指導を実施し，8週目に自宅で運動を続けるように指導を行い終了した．6ヵ月後と1年後にフォローアップをした．転倒予防教室8週間終了直後の評価では，大腿四頭筋の筋力増強，反応時間の短縮，握力の増強，歩行速度の増加を認めた．6ヵ月後と1年後の長期効果をみると，反応時間は元に戻ったが，大腿四頭筋筋力と握力の増加は維持されていた．転倒予防プログラム開始前の1年間の転倒既往は76.9%の参加者でみられたのに対し，プログラム終了1年後の転倒は18.9%に減少し，転倒予防教室の効果が認められた．

このような中身の濃いリハビリテーションプログラムを実施できる施設は少ないと思われるが，転倒に対する運動指導の有用性は否定できないところである．言葉だけで自主的な運動訓練をすすめても転倒予防の効果は乏しいと考えられ，要所

●転倒予防にはリハ介入とともに，運動訓練に対する意識づけが重要である．

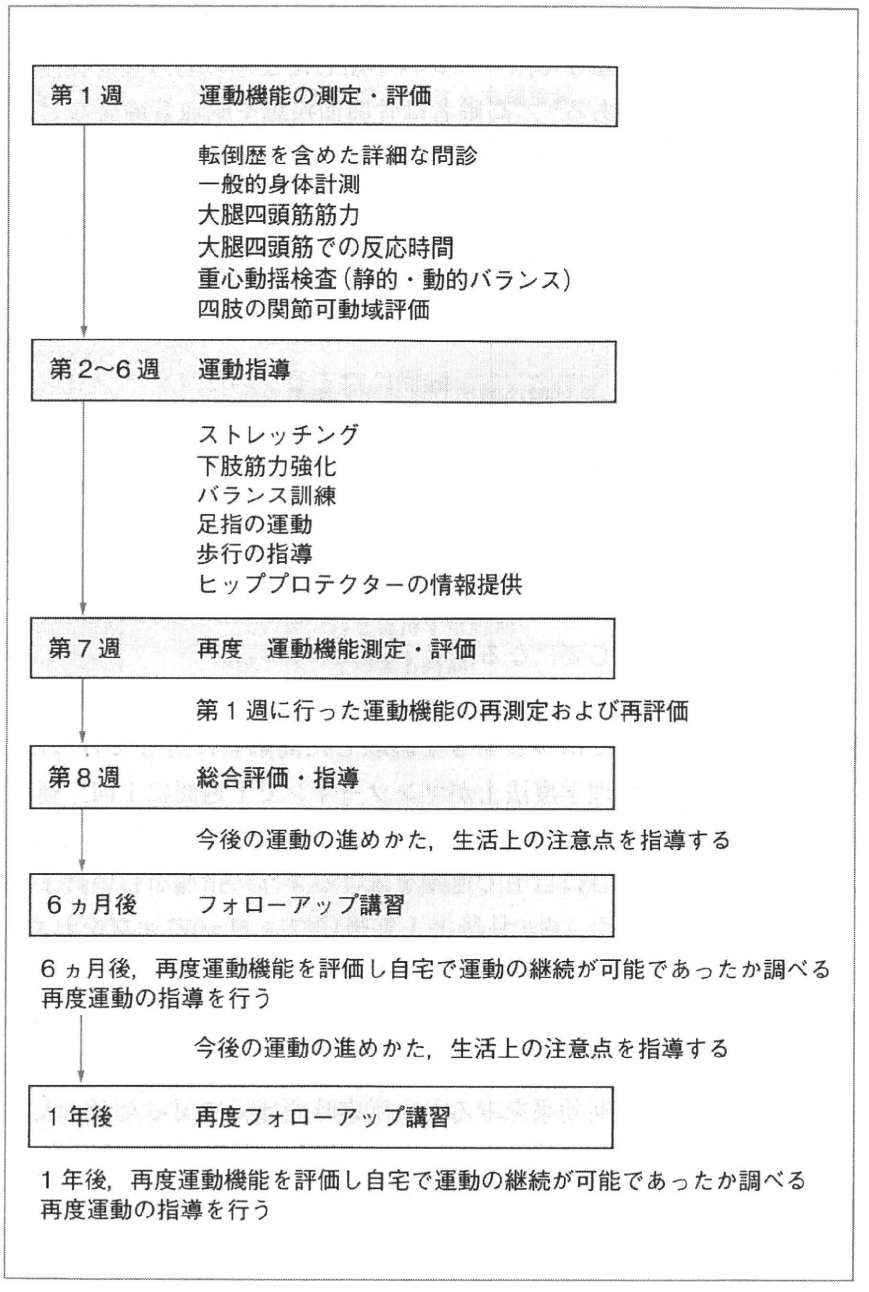

図２　転倒予防教室の例
（文献３）より引用）

での実地指導を含めたリハビリテーション介入が必要であろう．

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ORIGINAL REPORT

CORRELATION OF MOTOR FUNCTION WITH TRANSCALLOSAL AND INTRACORTICAL INHIBITION AFTER STROKE

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Objective: **The inhibitory role of neuronal networks in motor recovery after stroke remains to be elucidated. We examined the influence of transcallosal inhibition and short intracortical inhibition on motor recovery after stroke. We also investigated the correlation between transcallosal inhibition and mirror activity.**

Design: **A cross-sectional study.**

Subjects: **Thirty-eight chronic stroke patients.**

Methods: **Transcallosal inhibition was evaluated using single transcranial magnetic stimulation, and short intracortical inhibition was assessed using paired-pulse transcranial magnetic stimulation. Mirror activity was measured during tonic contraction of the contralateral hand.**

Results: **Transcallosal inhibition from the contralesional to the ipsilesional motor cortex correlated positively with motor function of the paretic hand; in contrast, transcallosal inhibition to the ipsilesional motor cortex correlated negatively with mirror activity of the paretic hand in both cortical and subcortical stroke patients. Short intracortical inhibition of the ipsilesional motor cortex correlated negatively with motor function of the paretic hand in only the subcortical stroke patients.**

Conclusion: **Transcallosal inhibition from the contralesional to the ipsilesional motor cortex may inhibit mirror movements in stroke patients with good motor function. The weak transcallosal inhibition in patients after stroke with poor motor function may be ineffective for inhibiting mirror movement; however, it may have the advantage of facilitating motor recovery.**

Key words: stroke; rehabilitation; reorganization; mirror movement; transcallosal inhibition; intracortical inhibition.

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INTRODUCTION

Stroke alters the neuronal function of the motor cortex adjacent to or distant from the lesion through neuronal networks (1). Transcranial magnetic stimulation (TMS) has been used to detect changes in neuronal function after stroke. Several studies have reported the loss of inhibition in the ipsilesional and the contralesional motor cortex of stroke patients using TMS (2, 3). A decrease in the inhibition contributes to the cortical reorganization by unmasking the latent networks (4); however, whether the disinhibition after stroke is caused by the lesion, whether it reflects a compensatory mechanism, or both, is still poorly understood (1). The change in transcallosal inhibition (TCI) after subcortical stroke has also been assessed using TMS (5). While a recent study has examined the changes in both TCI and intracortical inhibition after stroke (6), it remains unknown whether these neurophysiological parameters are correlated with motor function in both cortical and subcortical stroke and whether the parameters of cortical stroke differ from those of subcortical stroke.

In this study, we evaluated TCI and short intracortical inhibition (SICI) to determine whether these TMS parameters influence motor recovery in both cortical and subcortical stroke. It has been demonstrated previously that although SICI may be reduced in appearance, the inhibitory function may be normal if the excitability function increases (7). Therefore, we measured not only SICI but also short interval cortical excitability (SICE) to evaluate inhibitory and excitatory function in more detail. In addition, we investigated the correlation between TCI from the contralesional to the ipsilesional motor cortex and the mirror activity of the paretic hand. We hypothesized that the change in TCI to the ipsilesional motor cortex after stroke could influence the mirror activity of the paretic hand during non-paretic hand movement.

METHODS

The study population comprised 38 first-time chronic stroke patients. Motor function was evaluated using the upper limb subset of the Fugl-Meyer scale (FMS) (8). All the subjects gave written informed consent, and the experimental protocol was approved by the local ethics committee of Hokkaido University Graduate School of Medicine. The patients were classified into the following two subgroups according to brain computed tomography (CT) or MRI findings (Table I): (*i*) the cortical group, which had stroke lesions involving the sensorimotor cortex or both sensorimotor cortex and subcortical structure; and (*ii*) the subcortical group, which had lesions located caudal to the *corpus callosum*, indicating that the *corpus callosum* was intact.

TCI was performed using a 70-mm figure-8 coil and Magstim 200 (Magstim Company, Dyfed, UK), and paired-pulse TMS was applied

Table I. *Clinical characteristics*

	Age, year Mean (SD)	Gender Male *n*	Gender Female *n*	Paretic side Right *n*	Paretic side Left *n*	Duration after stroke, month Mean (SD)	Fugl-Meyer scale, Mean (SD)	*EMG activity of first dorsal interosseous Non-paretic, μV Mean (SD)	*EMG activity of first dorsal interosseous Paretic μV Mean (SD)
Cortical group (n=20)	61.7 (10.1)	12	8	12	8	46.3 (34.2)	68.0 (23.4)	350.8 (210.2)	155.0 (140.8)
Subcortical group (n=18)	61.6 (10.3)	11	7	10	8	56.9 (51.9)	63.9 (21.7)	395.4 (220.1)	154.6 (155.5)

*Mean rectified EMG activity during maximal tonic contraction.
SD: standard deviation; EMG: electromyography.

using the same coil and a Bistim device (Magstim Company) that triggered two magnetic stimulators. The coil was placed tangentially over the motor cortex at an optimal site for the first dorsal interosseous (FDI) muscle. The optimal site was defined as the location where stimulation at a slightly suprathreshold intensity elicited the largest motor-evoked potentials (MEPs) in the FDI. The resting motor threshold (rMT) was determined separately for each stimulator and defined as the lowest stimulator output that could activate MEPs with a peak-to-peak amplitude greater than 50 μV in at least half of the 10 trials. We excluded patients for whom MEPs were not detected in the ipsilesional hemisphere from the ipsilesional TMS study section, i.e. patients in whom MEPs were not induced even at 100% stimulator output.

We performed paired-pulse TMS at inter-stimulus intervals (ISIs) of 2, 3, 10 and 15 ms. The intensity of the first conditioning stimulus was 80% rMT and that of the test stimulus was 120% rMT. Ten trials were performed 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 mean peak-to-peak amplitude of the control MEPs and paired MEPs at each ISI was calculated. The mean amplitudes of paired MEPs at ISIs of 2 and 3 ms were averaged to obtain a representative value for SICI and that at ISIs of 10 and 15 ms intervals for intracortical facilitation (ICF). SICI is expressed as the percentage of the degree of inhibition (1 − (paired/control)), and ICF is expressed as the percentage increase (paired/control) in MEPs amplitude. SICE was measured using paired-pulse TMS at an ISI of 2 ms. The intensity of the conditioning stimulus varied between 30% and 80% of MT and was administered randomly at 10% increments; whereas, the intensity of the test stimulus was the same as that for the SICI measurement. MEPs amplitudes at each conditioning stimulus in SICE were expressed as a percentage of the mean amplitude of the control MEPs.

In the TCI procedure, each hemisphere was stimulated 20 times (intensity, 150% rMT) during unilateral maximal tonic contraction of the ipsilateral FDI, while keeping the contralateral upper limb relaxed as described previously (9). Twenty electromyography (EMG) signals of the FDI were rectified and averaged for evaluation of TCI. The mean amplitude of EMG signals prior to the stimulus for 100 ms was defined as the background activity. TCI was quantified by the period of relative EMG suppression after the stimulus, i.e. from the point at which the EMG activity clearly decreased below the background activity to that at which the EMG activity again increased to equal the background activity. The area of suppressed EMG activity was also averaged. TCI was then defined as the percentage of this mean suppressed activity in the background activity. This indicates that the greater the EMG activity suppression, the greater the TCI.

Mirror activity was calculated from the data in the TCI section to avoid the fatigue of stroke patients by additional tests. We rectified and averaged 20 EMG signals of the contralateral FDI muscles (mirror condition) prior to TMS for 100 ms during a maximal tonic contraction of the FDI muscle (active condition). Finally, mirror activity was expressed as a percentage of the mean amplitude of the mirror condition in the mean amplitude of the active condition at the same FDI.

Clinical data were compared between the cortical and subcortical groups by using the Mann-Whitney U test or the χ^2 test, depending on the type of variable assessed. For the comparison of TMS parameters, the Kruskal-Wallis test was used. The changes in SICE were evaluated using analysis of variance (ANOVA) for repeated measures, with INTENSITY as a within-subjects factor and STIMULATION SITE as a between-subjects factor. A *post-hoc* analysis was performed with Bonferroni's correction. Possible correlations among the various parameters were determined using the Spearman's correlation test.

RESULTS

There was no significant difference between the cortical and subcortical groups with regard to age, gender, paretic side, duration after stroke, FMS, EMG activity of non-paretic, or EMG activity of paretic (Table I). Table II shows TMS parameters of each hemisphere in the subcortical and cortical groups. We obtained ipsilesional TMS data from 9 patients in the cortical group and 9 patients in the subcortical group. There was no significant difference between the 4 stimulation sites with regard to rMT, amplitude of MEPs, SICI, ICF, or TCI (Table II).

Table III shows the correlations between TMS parameters and motor function of the paretic hand. SICI of the ipsilesional motor cortex was negatively correlated with the FMS score

Table II. *Transcranial magnetic stimulation parameters*

Stimulation site	rMT, % Mean (SD)	Amplitude of MEPs, μV Mean (SD)	SICI, % Mean (SD)	ICF, % Mean (SD)	TCI, % Mean (SD)
Ipsilesional hemisphere in cortical group (n=9)	52.8 (12.2)	921.9 (463.6)	38.4 (50.6)	169.2 (71.8)	50.1 (14.0)
Ipsilesional hemisphere in subcortical group (n=9)	50.9 (9.7)	556.8 (348.7)	23.6 (41.7)	182.6 (160.8)	53.7 (14.3)
Contralesional hemisphere in cortical group (n=20)	51.9 (9.1)	895.0 (451.7)	25.7 (65.8)	192.2 (93.6)	46.2 (15.1)
Contralesional hemisphere in subcortical group (n=18)	52.9 (8.6)	813.6 (670.0)	22.0 (49.6)	239.6 (139.5)	58.7 (14.6)

rMT: resting motor threshold; MEPs: motor evoked potentials; SICI: short intracortical inhibition; ICF: intracortical facilitation; TCI: transcallosal inhibition; SD: standard deviation.

Table III. *Correlations between transcranial magnetic stimulation parameters (TMS) and Fugl-Meyer scale (correlation coefficient and* p*-values)*

	Fugl-Meyer scale			
	Ipsilesional hemisphere (stimulation site)		Contralesional hemisphere (stimulation site)	
TMS parameters	Cortical (n=9)	Subcortical (n=9)	Cortical (n=20)	Subcortical (n=18)
rMT	–0.497 (0.173)	–0.033 (0.933)	0.038 (0.873)	0.143 (0.570)
MEPs	0.267 (0.488)	–0.183 (0.637)	–0.251 (0.285)	–0.060 (0.813)
SICI	–0.483 (0.187)	–0.783 (0.013)*	–0.121 (0.612)	–0.162 (0.521)
ICF	0.300 (0.433)	0.550 (0.125)	0.403 (0.078)	0.054 (0.832)
TCI	–0.200 (0.606)	–0.250 (0.516)	0.502 (0.024)*	0.649 (0.004)**

*p<0.05; **p<0.01.
rMT: resting motor threshold; MEP: motor-evoked potentials; SICI: short intracortical inhibition; ICF: intracortical facilitation; TCI: transcallosal inhibition.

of the paretic hand in the subcortical (Fig. 1a; r=–0.783, p=0.013), but not the cortical group (r=–0.483, p=0.187). TCI from the contralesional to the ipsilesional motor cortex was positively correlated with the FMS score of the paretic hand in both the cortical (Fig. 1b; r=0.502, p=0.024) and the subcortical groups (Fig 1c; r=0.649, p=0.004). There was a negative correlation between TCI to the ipsilesional motor cortex and mirror activity of the paretic hand in both the cortical (Fig. 2a; r=–0.508, p=0.022) and the subcortical groups (Fig 2b; r=–0.600, p=0.009). There was no significant correlation between TCI from the ipsilesional to the contralesional motor cortex and mirror activity of the non-paretic hand in either group.

Fig. 3 shows the change in SICE in the cortical and the subcortical group. A repeated-measures ANOVA for SICE showed no significant interaction between INTENSITY and STIMULATION SITE (F (15, 260)=0.884, p=0.582) or STIMULATION SITE (F (3, 52)=0.142, p=0.935), but a significant effect of INTENSITY (F (5, 260)=21.462, p<0.001), reflecting that SICE had not been influenced by the stimulation site. *Post-hoc* analysis revealed that a strong conditioning stimulus could reduce SICE (Fig. 3).

DISCUSSION

This study revealed that the inhibitory function of the ipsilesional motor cortex correlated negatively with motor function of the paretic hand in subcortical stroke patients. The inhibition from the contralesional to the ipsilesional motor cortex correlated positively with motor function of the paretic hand; in contrast, the inhibition from the contralesional to the ipsilesional motor cortex correlated negatively with mirror activity of the paretic hand in both cortical and subcortical stroke patients.

Several studies have reported disinhibition of the ipsilesional motor cortex in the acute stage of both cortical and subcortical stroke (2, 10). However, whether the inhibitory function of the ipsilesional motor cortex normalizes or remains decreased in the chronic stage remains controversial (11, 12). The correlation between inhibitory function and motor function is also poorly understood. In this study, we have revealed that the inhibitory function of the ipsilesional motor cortex was correlated negatively with the motor function of the paretic hand in only

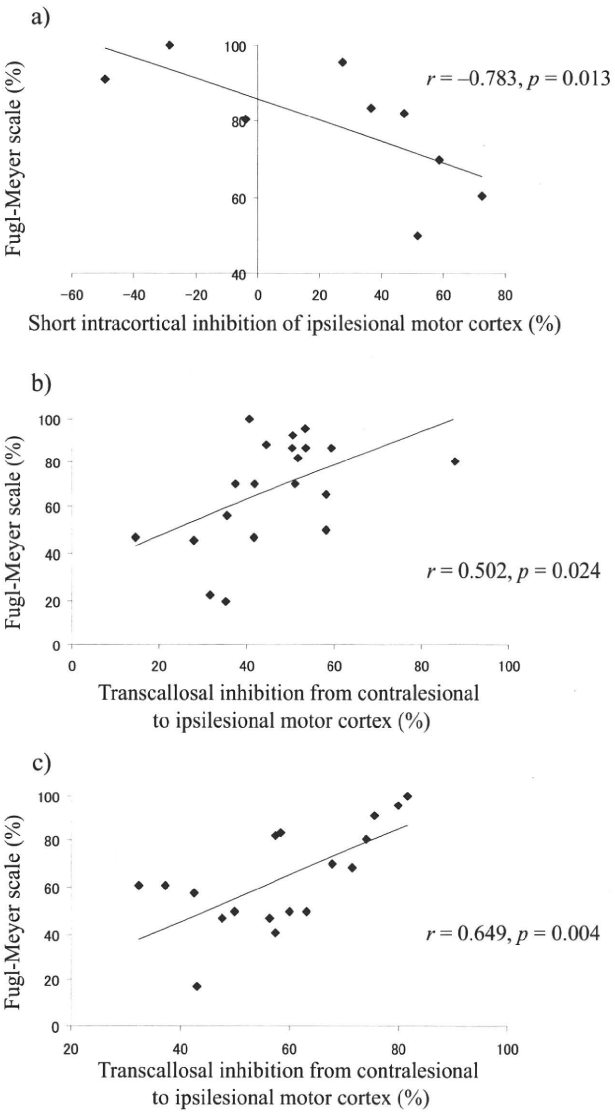

Fig. 1. Correlation between inhibitory function and motor function. (a) There was a negative correlation between intracortical inhibition of the ipsilesional motor cortex and the Fugl-Meyer Scale score in the subcortical group. There was a significant positive correlation between transcallosal inhibition from the contralesional to the ipsilesional motor cortex and the Fugl-Meyer Scale score in both (b) the cortical and (c) the subcortical groups.

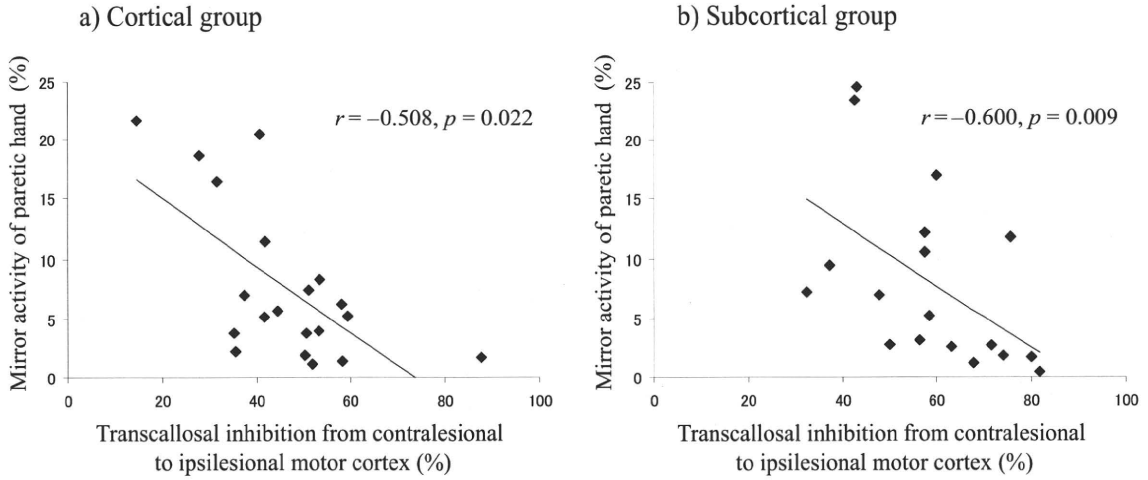

Fig. 2. The correlation between transcallosal inhibition and mirror activity of the paretic hand. There was a negative correlation between transcallosal inhibition from the contralesional to the ipsilesional motor cortex and mirror activity of the paretic hand in both (a) the cortical and (b) the subcortical groups.

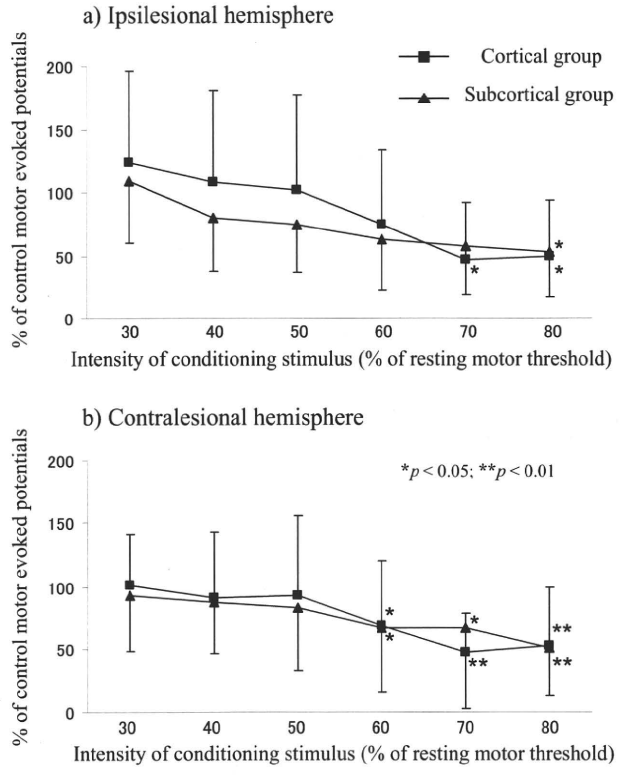

Fig. 3. Short interval cortical excitability. The strong conditioning stimulus reduced the amplitude of motor evoked potentials (MEPs) in short interval cortical excitability in all groups. A significant reduction in the amplitude of the MEPs is indicated by asterisks. Error bar: standard deviation.

subcortical stroke patients, but not cortical stroke patients, in the chronic stage. Considering these findings, the continuous disinhibition of the ipsilesional motor cortex in subcortical stroke patients may promote the best possible recovery of motor function by facilitating the plasticity of the non-damaged motor cortex in the ipsilesional hemisphere (4); in contrast, the inhibitory function of the ipsilesional motor cortex in cortical stroke patients may be influenced more by direct cortical damage than compensatory mechanisms in the chronic stage.

The problem with the SICI methods is that it was difficult to decide whether a reduced SICI indicated weak inhibitory or strong excitatory cortical function solely on the basis of the SICI paradigm. To avoid this problem, we used the SICE paradigm that could evaluate the inhibitory and excitatory circuits in more detail. The influence of the excitatory function has been shown to be superior to that of the inhibitory function at a strong conditioning stimulus in the SICE paradigm (7). If only the excitatory function increases and the inhibitory function remains unchanged, the amplitude of SICE is small at a weak conditioning stimulus and large at a strong conditioning stimulus (7). However, the amplitude of SICE was reduced according to the intensity of the conditioning stimulus in this study. Therefore, the reduction in SICI of the ipsilesional motor cortex implies the loss of inhibitory function and not an epiphenomenon caused by modified neuronal circuits shifting toward excitatory activity.

TCI from the contralesional to the ipsilesional motor cortex was more prominent in patients with greater motor function during movement. This finding is not consistent with that of previous study, which reported a negative correlation between TCI at pre-movement and the motor function of the paretic hand (5). These differences may have resulted from the differing methods and TCI mechanisms employed in our and previous study (13). A recent study reported that TCI could inhibit unwanted mirror activity during intended unimanual motor tasks (14). Consistent with this report, TCI to the ipsilesional motor cortex was correlated negatively with the mirror activity of the paretic hand in our study. Therefore, TCI to the ipsilesional motor cortex during movement may play a neurophysiological role in the inhibition of mirror movement of the paretic hand. To clarify this hypothesis, further studies are required to evaluate the change in mirror activity when TCI to the ipsilesional motor cortex is reduced by using inhibitory repetitive TMS over the contralesional motor cortex (14). We propose that TCI to the ipsilesional motor cortex may

be important for mirror movement of the paretic hand; however, we agree with the hypothesis that TCI to the ipsilesional motor cortex may inhibit motor function in some stroke patients (5). Considering these findings, TCI to the ipsilesional motor cortex may be influenced by a balance between motor function and mirror movement in the paretic hand during the process of reorganization after stroke. That is to say, TCI to the ipsilesional motor cortex may be strong to inhibit mirror movement in patients with good motor function; in contrast, TCI in patients with poor motor function may be weak to improve motor function without inhibition of mirror movement.

The neurophysiological results of this study may help improve individualized rehabilitation strategies after stroke. Recent study has reported that inhibitory neuromodulation of the contralesional motor cortex could improve the motor function of the paretic hand by a reduction in TCI to the ipsilesional motor cortex (9). Therefore, inhibitory neuromodulation of the contralesional motor cortex may be especially effective for stroke patients with good motor function who had strong TCI, although the mirror activity of the paretic hand may increase. In addition, for subcortical stroke patients with disinhibition of the ipsilesional motor cortex, intense use of the paretic limb, such as constraint-induced movement therapy, may promote motor recovery by inducing use-dependent reorganization (15). In contrast, inhibitory neuromodulation of the contralesional motor cortex may be less effective in stroke patients with poor motor function, because these patients already have weak TCI before the neuromodulation interventions. The functional imaging study has reported that the contralesional motor cortex is engaged during paretic hand movements in stroke patients with poor motor function (16). Therefore, therapy aimed at increasing the excitability of the contralesional motor cortex may be effective for motor recovery of stroke patients with poor motor function. However, to our knowledge, there is no report that a neuromodulatory approach that increases the excitability in only the contralesional motor cortex can enhance motor recovery, ignoring the importance of the balance between bilateral hemispheres (17). If excitability is increased only in the contralesional motor cortex, the weak TCI to the ipsilesional motor cortex in stroke patients with poor motor function may become strong and inhibit the function of the ipsilesional motor cortex. Therefore, bilateral movement training that engages and balances both hemispheres may be effective for stroke patients with poor motor function (18).

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Research Report

The effect of smoking on pain-related evoked potentials

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ABSTRACT

The effects of human tobacco smoking and nicotine on pain-related brain activities were investigated. EEG responses evoked by a painful laser beam (laser evoked potentials; LEPs), and the plasma nicotine concentration (PNC) were measured. There were two sessions, one after smoking (Smoking session), and the other in no smoking (Control session). Subjective ratings of pain perception were also measured using the visual analog scale (VAS). Two major components, N2 and P2 of LEPs, were recorded. The amplitude of P2 was significantly smaller in the Smoking session than in the Control session. A significant negative correlation was found between PNC and the amplitude of N2 as well as P2. The results were consistent with the hypothesis that smoking and/or nicotine have an antinociceptive effect, which supports most non-human studies and some human studies. Smoking of a single tobacco cigarette did not show a subjectively perceivable extent of reduction in the intensity of evoked pain.

1. Introduction

Nicotine has been demonstrated to have various psychophysiological effects in humans. The effects of smoking or nicotine on event related potentials (ERPs) have been explored by numerous groups (Friedman et al., 1974; Houlihan et al., 2001; Knott et al., 1999; Woodson et al., 1982; for reviews, Knott et al., 1995 and Pritchard et al., 2004). Most of these studies reported increased amplitudes and/or decreased latencies supporting the notion that nicotine enhances brain processing.

On the other hand, non-human studies demonstrated an antinociceptive effect of nicotine. Mattila et al. (1968) reported that nicotine injected subcutaneously increased the threshold of pain in mice and rabbits. The antinociceptive effect of nicotine was shown to involve nervous systems with various neurotransmitters including μ-opioid (Berrendero et al., 2002; Biala and Weglinska, 2006), serotonin, and epinephrine (Cucchiaro et al., 2005; Cucchiaro et al., 2006; Iwamoto, 1991).

The effect of nicotine on pain perception in humans has also been explored by some groups, but the results of these studies have not been consistent. Pomerleau et al. (1984) reported that smoking increased the pain threshold time for arm immersion into ice water, whereas Mueser et al. (1984) found no significant effect of smoking on the perception of painful electric stimulation. Scott et al. (2007) explored effect

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of smoking on μ-opioid receptor-mediated neurotransmission using positron emission tomography (PET). They reported that tobacco smoking enhanced μ-opioid receptor-mediated neurotransmission in the right anterior cingulate cortex and suppressed in the left amygdala, left ventral basal ganglia, and right thalamus after tobacco smoking, suggesting a possible role of smoking and nicotine on pain perception in humans through these brain areas, which are important in pain processing (Kakigi et al., 2005).

Pain-related evoked potentials are commonly used in studies that objectively evaluate pain-related brain activities in humans. N2 and P2 are the two major components constantly recorded in pain-related evoked potentials. They are thought to reflect the activities of operculoinsular and cingular cortices, respectively (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996; Iannetti et al., 2003; Kakigi et al., 2005). Their amplitudes are shown to be correlated to the magnitude of subjectively perceived pain (Kakigi et al., 1989; Bromm and Treede, 1991; García-Larrea et al., 1997). Knott (1990) and Knott and De Lugt (1991) recorded pain-related evoked potentials after electrical stimulation, but the results did not consistently support the notion that smoking attenuates their amplitude.

In the present study, we measured evoked potentials after painful laser stimulation (laser evoked potentials; LEPs) in smoking and non-smoking conditions. Painful laser stimulation activates Aδ fibers but not Aβ fibers; electrical stimulation activates both. Laser stimulation enables one to evaluate the brain activities related to Aδ fiber mediated pain information without confounded by Aβ fiber mediated tactile information. To evaluate the effect of smoking on LEPs over time, LEPs were measured in five runs in each of the two sessions on separate days (Smoking and Control sessions), which followed a 12-hour abstinence from smoking. Subjects smoked one cigarette after the first run in the Smoking session. Plasma nicotine and cotinine concentration (PNC and PCC) were also measured just before each run. We tested the correlation between amplitudes of LEPs and PNC, which rapidly decrease after smoking. Cotinine is the main metabolite of nicotine, which remains in the plasma with a $t_{1/2}$ of about 18 hours. It is used to assess current smoking status of subjects. To our knowledge, there have been no reports on the effect of smoking or the plasma nicotine concentration on laser-evoked potentials (LEPs).

2. Results

2.1. *Plasma nicotine and cotinine concentrations*

For all the 10 subjects, the PNC in the Control session and Pre in the Smoking session was less than 7 ng/ml, indicating that all the subjects had been abstinent from smoking before each session as instructed. Mean values and standard errors are shown in the results. The mean PNC for each run averaged over subjects was highest at 5 min after smoking in the Smoking session (29.8±6.9 ng/ml) and decreased as time passed in the following runs.

The mean PCC at Pre in the Control and Smoking sessions averaged over all subjects was 61.9±24.3 ng/ml and 74.0±23.1 ng/ml, respectively. The PCC in 4 of the 10 subjects was below the limit of detection in the Control session. For three of these four subjects, the PCC at Pre was also below the limit of detection in the Smoking session.

2.2. *Amplitudes and latencies of N2 and P2*

Fig. 1 shows superimposed waveforms of a representative subject in each run in each session. The N2 and P2 components of LEPs were consistently observed in each subject with a peak latency at around 200 and 300 ms, respectively. Fig. 2 shows the grand-averaged LEP waveforms for each run in the Smoking and Control sessions. The mean amplitudes of N2 and P2 averaged over subjects for each run are shown along with the PNC in Figs. 3a and b. The mean N2 amplitude, N2 latency, P2 amplitude, and P2 latency averaged over all subjects and all runs were 10.6±0.6 μV, 216±2 ms, 16.6±0.7 μV, and 330±2 ms, respectively. The amplitude of N2 is shown as a positive value.

In a two-way repeated-measures ANOVA (Session and Run) on the amplitude of P2, we found a significant interaction ($F(4, 36)=3.1$, $p=0.049$) and a significant main effect of Session ($F(1, 9)=11.0$, $p=0.01$). In a post hoc paired t-test for each run, the amplitude of P2 was found to be smaller in the Smoking session than in the Control session for the run 5 min after smoking ($t(9)=3.5$, $p=0.03$). The difference in the P2 amplitude between Runs in the Smoking session was not significant in a one-way repeated measures ANOVA ($F(4, 36)=2.53$, $p=0.10$). We did not find a significant interaction of Session and Run, or a significant main effect of Session or Run on the amplitude of N2 ($F(4, 36)=1.7$, $p=0.19$, $F(1, 9)=0.96$, $p=0.35$, and $F(4, 36)=2.7$, $p=0.07$, respectively), or on the latency of N2 or P2 in two-way repeated measures ANOVAs (Session and Run). PNC was negatively correlated to N2 amplitude ($R=-0.29$, $p<0.01$, Fig. 4a) and P2

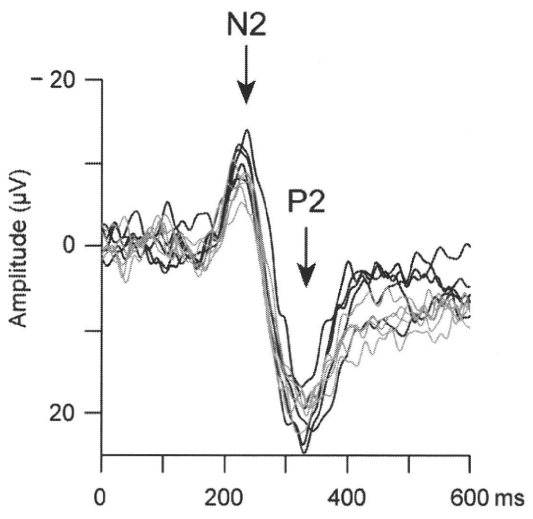

Fig. 1 – Superimposed waveforms of a representative subject in each run in the Control (black) and Smoking (gray) sessions. The waveforms of 600 ms from stimulus onset are shown. Each sweep represents the averaged waveform of 10 artifact-free epochs in a run. Each waveform is adjusted using the 100-ms prestimulus period as a baseline. N2 and P2 deflections (labeled with arrows) were constantly recorded throughout the experiment.