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厚生労働科学研究費補助金

障害者対策総合研究事業

慢性期脳卒中患者における重度上肢機能障害に対する革新的治療法の実用化研究：ランダム化比較試験によるブレーンマシンインターフェース(BMI)リハビリテーションの効果の検討

平成２６年度　総括研究報告書

研究代表者　藤原俊之

平成２７（２０１５）年　４月

目　　次

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研究代表者
藤原俊之　慶應義塾大学医学部リハビリテーション医学教室　講師

研究要旨
運動イメージを非侵襲的に脳波により感知し、ロボット装具を操作する画期的なブレーンマシーンインターフェース(BMI)リハビリシステムを開発し、脳卒中による重度片麻痺患者の上肢機能リハビリテーションに応用し、実用化を目指すためにランダム化比較試験を施行。参加者は慶應義塾大学病院ならびに東京湾岸リハビリテーション病院で募集。BMI リハビリシステムを用いたリハビリにより、慢性期重度脳卒中片麻痺患者においても上肢運動機能ならびに物品操作能力の改善を認めた。BMI リハビリシステムの応用は、脳卒中リハビリにおいて有用な手段となりうる。

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補永　薫　東京湾岸リハビリテーション病院　医長

Ａ．研究目的

脳卒中患者の総患者数は２８０万人であり、平成22年国民生活基礎調査の概況によると要介護者の介護が必要となった原因のトップは脳血管障害（21.5%）であり、脳卒中後遺症は医療、経済に大きな影響を与えている。特に脳卒中後の片麻痺による上肢機能障害の回復は困難であり、いわゆる回復期のリハビリにおいても実用レベルの上肢機能を獲得できるのは全体の３０％程度とされており（藤原ら，リハ医学 2006）、日常生活における能力低下に上肢機能障害は重大な影響を与えている。しかしながら、上肢機能障害特に手指機能障害に対する効果的なリハビリは殆どないのが現状である(Langhorne P et al, Lancet

Neurol 2009)。我々は脳科学研究戦略推進プログラムにおいて、運動イメージを非侵襲的に脳波により感知し、ロボット装具を操作する画期的なブレーンマシーンインターフェース(BMI)リハビリシステムを開発した。本システムは簡便な脳波システムにより、実験室での限られた使用ではなく、一般の訓練室
での使用が可能である。我々は本システムを用いて、世界に先駆けて臨床におけるBMI治療手技を確立し、従来は代償動作の獲得のみにとどまっていた麻痺手の筋活動を認めない重度片麻痺患者への治療を可能とした(Shindo et al, J Rehabil Med 2011)。すでに30例以上の脳卒中慢性期重度上肢機能障害に用い、運動機能の改善を認めている。しかしながら、質の高いevidenceの獲得には、RCTが必要である。世界的にも未だ少数例でのケース報告のみであり、BMIリハビリに関するRCTは行われていない。本研究ではBMIによるロボット装具による訓練の重度上肢機能障害への効果を明らかとするためにRCTを行い、世界に先駆けてBMIリハビリの効果を明らかにするものである。平成24年度より慶應義塾大学病院、東京湾岸リハビリテーション病院において評価者教育、研究体制の整備を行い、各病院で参加者を募集し、RCTを行った。

Ｂ．研究方法

対象は脳卒中後片麻痺患者とし、参加基準は１）発症後6か月以上経過し、在宅復帰をして、歩行、ADLは自立、２）上肢機能障害が残存し、手は胸の高さまで挙がるが、手指伸展筋群の筋活動を認めない、認知機能障害がなくMini Mental State Examination(MMSE)24点以上とする。対象の募集はリハビリテーション科外来通院患者より行い、倫理委員会申請、臨床試験登録を済ませた時点より募集を開始する。研究デザインはランダム化比較試験(RCT)とし、BMI群では、手指伸展運動イメージ時の運動野における事象関連脱同期を用いて、運動イメージを感知することにより電動ロボット装具を操作してペグの取り外しを行うBMI訓練を40分間、10日間行う。対照群では、同じロボット装具ならびに脳波記録システムを用いてペグの取り外しを行うが、事象関連脱同期をトリガーとせずに行う。クロスオーバーデザインを用い、介入、対照の順序ランダム化して割付を行った。

（倫理面への配慮）

本研究はヘルシンキ宣言ならびに臨床研究に関する倫理指針を遵守する。取り込み基準を満たした患者に対しては、リハビリ科の外来で、当研究についての説明を行い、参加の有無は患者本人が選択する。

参加を選択した場合には、説明文書に従い詳細な説明をもう一度行い、同意を得た段階で、プログラムを開始する。本研究は慶應義塾大学医学部倫理審査委員会にて承認済み（課題番号20120068）であり、UMIN臨床試験登録済み（UMIN試験ID：

UMIN000008468）である。また、東京湾岸リハビリテーション病院倫理審査会でも平成25年度に承認された（受付番号55）。
なおBMI 訓練ならびに対照訓練のどちらも国家資格を有する作業療法士が行うこととした。

C．結果
11 例の解析が終了した。ＢＭＩ群、対照群両群において上肢運動機能の改善を認めたが、ペグの取り外し個数においてはBMI 群の方が大きな改善を認めた。運動機能の改善にはともに運動企図に合わせて手指を動かすことで慢性期の重度片麻痺患者においても改善が認められるが、課題依存性の実際の上肢動作の改善は運動野の活動に同期させて行うBMI の方が効果が高い可能性が示唆された。
D．考察
世界に先駆けて臨床におけるBMI治療手技を確立し、従来は代償動作の獲得のみ
にとどまっていた麻痺手の筋活動を認めない重度片麻痺患者への治療を可能とした(Shindo et al, J Rehabil Med 2011)。すでに30例以上の脳卒中慢性期重度上肢機能障害に用い、運動機能の改善を認めている。しかしながら、質の高いevidenceの獲得には、RCTが必要である。世界的にも未だ少数例でのケース報告のみであり、BMIリハビリに関するRCTは行われていない。本研究ではBMIによるロボット装具による訓練の重度上肢機能障害への効果を明らかとするためにRCTを行い、世界に先駆けてBMIリハビリの効果を明らかにするものである。本研究によりBMIリハビリにより慢性期重度片麻痺患者においても上肢運動機能の改善を認め、さらに手指物品操作性の改善は対照群に比較して有意であったことより、BMIリハビリにより実際のADLにおける実用性を課題依存的に改善させることが可能であることが示唆された。BMIリハビリによる上肢機能障害の改善は、要介護者の介護量軽減が可能となるのみならず、長期療養者ならびに要介護者のQOLの向上に結びつくものと思われる。また世界に先駆けてBMIリハビリの効果を明らかとしたことはまさに「日本発の革新的医療機器の開発と実用化」につながり、この分野で世界をリードすることが可能となる。また、本治療法の実用化が図られれば、マンパワーを必要としない画期的なリハビリ治療手法として病院のみならず、通所介護施設などセラピストが不足している現場においても有効なリハビリ手法として使用が可能となる。これにより介護保険のみでは十分なリハビリを受けることが困難であった長期療養者、在宅患者においても効果的なリハビリを導入することが可能となる見込みである。これは医療・介護サービス提供体制の効率化ならびに機能強化を推進するとともに、長期にわたる要介護者のリハビリの効率化、機能強化、人的資源の効率的な利用に結びつき、医療経済学的にも望ましい効果が期待さ

れる。

E．結論

慶應義塾大学病院ならびに東京湾岸リハビリテーション病院においてBMIリハビリのRCTを行った。BMIによるリハビリテーションにより慢性期の重度上肢機能障害を有する患者においても上肢機能の改善が得られた。本研究によりBMIは脳卒中リハビリテーションにおいて新しい治療法としての応用が可能であることが示された。本手法の実用化により医療・介護サービス提供体制の効率化ならびに機能強化を推進するとともに、長期にわたる要介護者のリハビリの効率化、機能強化、セラピストなどの限られた人的資源の効率的な利用に結びつき、医療経済的にも効果があると思われる。

F．健康危険情報

特記すべきことなし。

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H．知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金（障害者対策総合研究事業）
（分担）研究報告書

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研究分担者　補永　薫　東京湾岸リハビリテーション病院　リハビリテーション部部長

研究要旨

運動イメージを非侵襲的に脳波により感知し、ロボット装具を操作する画期的なブレーンマシーンインターフェース(BMI)リハビリシステムを開発し、脳卒中による重度片麻痺患者の上肢機能リハビリテーションに応用し、実用化を目指すためにランダム化比較試験を施行中である。すでに倫理審査会における承認も得られ、現在参加者を募集中である。

A．研究目的

脳卒中患者の総患者数は280万人であり、平成22年国民生活基礎調査の概況によると要介護者の介護が必要となった原因のトップは脳血管障害（21.5%）であり、脳卒中後遺症は医療、経済に大きな影響を与えている。特に脳卒中後の片麻痺による上肢機能障害の回復は困難であり、いわゆる回復期のリハビリにおいても実用レベルの上肢機能を獲得できるのは全体の30%程度とされており（藤原ら,リハ医学 2006）、日常生活における能力低下に上肢機能障害は重大な影響を与えている。しかしながら、上肢機能障害特に手指機能障害に対する効果的なリハビリは殆どないのが現状である(Langhorne P et al, Lancet Neurol 2009)。我々は脳科学研究戦略推進プログラムにおいて、運動イメージを非侵襲的に脳波により感知し、ロボット装具を操作する画期的なブレーンマシーンインターフェース(BMI)リハビリシステムを開発した。本システムは簡便な脳波システムにより、実験室での限られた使用ではなく、一般の訓練室での使用が可能である。本システムを用いたBMI治療手技による重度片麻痺患者への治療は報告はなされており(Shindo et al, J Rehabil Med 2011)、慶應大学病院リハビリテーション科ではすでに多数の脳卒中慢性期重度上肢機能障害に用い、運動機能の改善を認めている。しかしながら、質の高いevidenceの獲得には、RCTが必要である。世界的にも未だ少数例でのケース報告のみであり、BMIリハビリに関するRCTは行われていない。本研究ではBMIによるロボット装具による訓練の重度上肢機能障害への効果を明らかとするためにRCTを行い、世界に先駆けてBMIリハビリの効果を明らかにするものである。平成24年度より慶應義塾大学病院、東京湾岸リハビリテーション病院、済生会神奈川県病院において評価者教育、研究体制の整備を行い、参加者を募集し、RCTを開始する

B．研究方法

対象は脳卒中後片麻痺患者とし、参加基準は１）発症後6か月以上経過し、在宅復帰をして、歩行、ADLは自立、２）上肢機能障害が残存し、手は胸の高さまで挙がるが、手指伸展筋群の筋活動を認めない、認知機能障害がなくMini Mental State Examination(MMSE)24点以上とする。研究デザインはランダム化比較試験(RCT)とし、BMI群では、手指伸展運動イメージ時の運動野における事象関連脱同期を用いて、運動イメージを感知することにより電動ロボット装具を操作してペグの取り外しを行うBMI訓練を40分間、10日間行う。対照群では、同じロボット装具ならびに脳波記録システムを用いてペグの取り外しを行うが、装具による指の伸展は作業療法士がスイッチを押して行うこととする。クロスオーバーデザインを用い、介入、対照の順序ランダム化して割付を行う。

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本研究はヘルシンキ宣言ならびに臨床研究に関する倫理指針を遵守する。取り込み基準を満たした患者に対しては、リハビリ科の外来で、当研究についての説明を行い、参加の有無は患者本人が選択する。

参加を選択した場合には、説明文書に従い詳細な説明をもう一度行い、同意を得た段階で、プログラムを開始する。本研究は慶應義塾大学医学部倫理審査委員会にて承認（課題番号20120068）された後、東京湾岸リハビリテーション病院倫理審査会でも承認（受付番号55）されている。

なおBMI 訓練ならびに対照訓練のどちらも国家資格を有する作業療法士が行うこととし、訓練環境は通常の訓練と同様に作業療法訓練室を使用する。現在は機器設置を行い、参加者のエントリーを開始している。

C. 研究結果

現在、参加者のエントリーを開始している段階である。

D. 考察および E. 結論

現在、試験途中のため結論は出ていないが、協力病院で行っている同様のシステムでの検討事例を考えると慢性期脳卒中患者において、BMI装置を用いた訓練を取り入れることにより、それまで困難であった手指の随意的な伸展筋活動の改善が期待される。

H. 知的財産権の出願・登録状況

現在行っていない。

厚生労働科学研究費補助金（障害者対策総合研究事業）
（分担）研究報告書

臨床利用できるブレーンマシンインターフェースシステムの構築と実践に関する研究

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研究要旨
ブレーンマシーンインターフェース(BMI)リハビリテーションのための電動装具について、臨床的な有用性の高い設計をおこない、臨床環境で簡便に装脱着が可能なデザインの装具を開発した。また、電動装具に組み込んだ筋電気刺激装置の中枢神経系に対する作用を検討するため、単一パルス経頭蓋磁気刺激法を用いて皮質脊髄路の活性評価をおこない、特定のパルス幅、パルス周波数で筋電気刺激を与えることが運動出力を促進することにつながることを明らかにした。このことは、BMI リハビリテーション効果を説明する神経生理学的機序のひとつとして有用であった。

A．研究目的

脳卒中片麻痺は、患者本人の生活動作を大きく阻害し、日常生活や社会参画を阻む要因となっているが、手指の機能障害に対する効果的なリハビリはほとんど存在しない (Langhorne et al., 2011)。一方、神経科学の発展により、神経系における感覚運動ループの活動を健全に保つことが、正常な運動制御能の維持向上に役立つことが分かってきており、ヒトの成熟脳においても同様な機能可塑性が備わっていることが明らかになりつつある（ex. Ishida et al., Behav Brain Res 2015）。

我々はこれまでに、文部科学省脳科学研究戦略推進プログラムにおいて、随意運動関連脳活動を非侵襲的に頭皮脳波から感知し、その信号の健常性に応じてロボット装具を操作するブレーンマシーンインターフェース(BMI)リハビリシステムを開発し、これによって神経系における感覚運動ループの活動を強制的にうながすことで、脳卒中片麻痺患者の運動機能回復をうながすことに成功した（Kasashima et al., in press; Ono et al., 2015; 2014)。本事業では、医学的見地からその有効性と安全性を検証するために、ランダム化比較試験を実施しているが、麻痺手に装着して利用するBMI用電動装具に関しては、重量のある据え置き型タイプか、装着性に難のある簡易グローブタイプのものしか存在せず、実臨床に即した機能的デザインを有するBMI装具の開発が求められていた。

そこで、本研究では、四指の集団伸展と屈曲が可能な一自由度のプラスチック把持

装具を設計し、母指を痙性抑制肢位に保持しつつつまみ動作を可能にする機能装具を作成した。また、装具の前腕部には電気刺激用表面電極を組み込む設計とし、総指伸筋に対して機能的電気刺激が与えられる改良を施した。電気刺激が中枢神経系におよぼす影響については、単一パルス経頭蓋磁気刺激法を用いて皮質脊髄路の活性評価によって実施し、その有用性を確認した。

B. 研究方法

本研究では、まずリハビリテーション専門医2名ならびに作業療法士2名にヒアリングをおこない、BMIリハビリテーションの対象疾患である脳卒中重度片麻痺患者の上肢に対する装具療法の臨床的ポイントについて洗い出しをおこなった。その結果、約7割の対象患者が手指および手関節の屈曲位を呈する痙性麻痺を呈しており、母指が対立位に保持できない非機能的肢位にあったことから、装具は母指を対立位に固定する形状とし、痙性麻痺に拮抗して四指を集団伸展することを可能とするために金属プレートによる指支持構造とした。対象患者によって屈曲角度や母指位置が異なったものの、将来的な量産化を視野にいれるため、共通デザインで利用可能な母指対立装具の作製をおこなった。具体的には母指を入れるスペースは大きく確保し、被験者の母指サイズに応じて補助材でその間隙を埋めるセミカスタム仕様とした。ペグ把持訓練を実施可能とするために、手関節の屈曲角度は、10度から30度まで、10度ごとに3段階用意し、その機能評価から10度屈曲位のものを最終デザインとして選定した。また、前腕伸筋側には電気刺激パッドを組み込み、麻痺側総指伸筋に対する機能的電気刺激が与えられるようにした。

次に、機能的電気刺激が中枢神経系への及ぼす修飾作用を同定するために、健常成人を対象として二種類の刺激パターンで機能的電気刺激を与え、その皮質脊髄路に及ぼす促通効果を分析した。刺激パターンはいずれも単極性の矩形パルスとし、一方は1msパルス幅100Hz（高周波刺激）、もう一方は0.3msパルス幅20Hz（低周波刺激）とした。どちらの刺激パターンにおいても、手関節角度が30度に維持される刺激強度に調節し、その際に対側一次運動皮質へ単一パルス経頭蓋磁気刺激を与えて、皮質脊髄路の興奮性を評価した。通常は誘発筋電図によってその興奮量をプローブするが、今回は筋に機能的電気刺激を与えていて計測が不可能だったことから、その代替として手関節の誘発角度変化をゴニオメータで計測することとした。今回は、誘発角度変化が2度になる磁気刺激強度を興奮閾値と定め、その際の刺激強度の大小によって皮質脊髄路の興奮性を判断した。すなわち、刺激強度が小さくて済むほど、皮質脊髄路は高い興奮性を呈していると判断した。

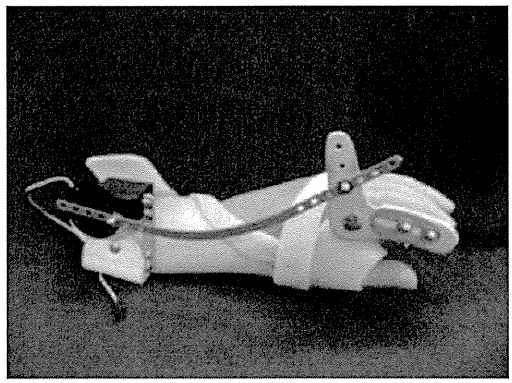
C. 研究結果

設計したBMI用装具を図1に示す。これまでに20名を超える脳卒中片麻痺患者で試用をおこない、疼痛や怪我の発生事象なく、設計通りの運用が可能であった。

機能的電気刺激による皮質脊髄路の評価を図2に示す。7名の被験者に対する結果から、低周波刺激の場合でも高周波刺激の場合でも、通常安静状態に比べて高い興奮性を示していたほか、高周波刺激の場合のほ

うが低周波刺激の場合よりも興奮性が上昇傾向にあることが示された。

(a)



(b)

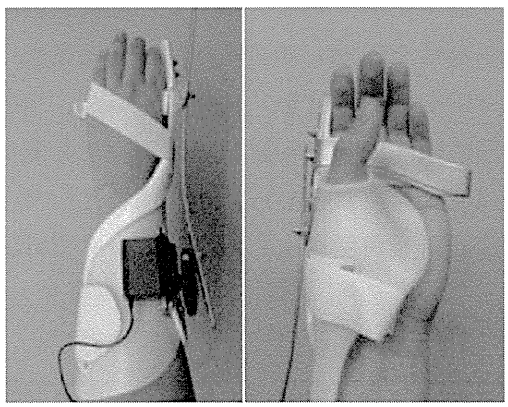


図１　開発した BMI 用電動装具

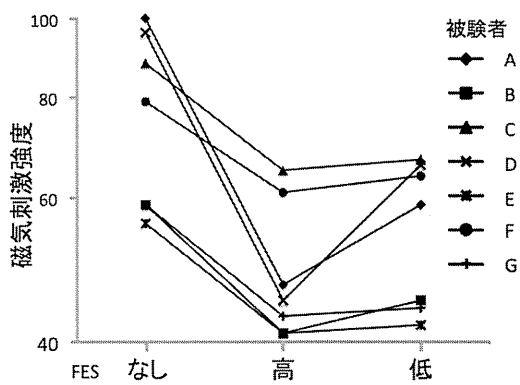


図２　経頭蓋磁気刺激による皮質脊髄路の興奮性評価

D. 考察

今回開発した BMI 用電動装具は、臨床的に十分利用可能なものであると実験的に確認された。また、装具に組み込むべき機能的電気刺激のパラメータは、1ms パルス幅 100Hz のほうがより中枢神経系に対する機能修飾効果が期待された。

E. 参考文献

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研究成果の刊行に関する一覧表

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ORIGINAL REPORT

BRAIN–COMPUTER INTERFACE TRAINING COMBINED WITH TRANSCRANIAL DIRECT CURRENT STIMULATION IN PATIENTS WITH CHRONIC SEVERE HEMIPARESIS: PROOF OF CONCEPT STUDY

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Objective: **Brain–computer interface technology has been applied to stroke patients to improve their motor function. Event-related desynchronization during motor imagery, which is used as a brain–computer interface trigger, is sometimes difficult to detect in stroke patients. Anodal transcranial direct current stimulation (tDCS) is known to increase event-related desynchronization. This study investigated the adjunctive effect of anodal tDCS for brain–computer interface training in patients with severe hemiparesis.**

Subjects: **Eighteen patients with chronic stroke.**

Design: **A non-randomized controlled study.**

Methods: **Subjects were divided between a brain–computer interface group and a tDCS- brain–computer interface group and participated in a 10-day brain–computer interface training. Event-related desynchronization was detected in the affected hemisphere during motor imagery of the affected fingers. The tDCS-brain–computer interface group received anodal tDCS before brain–computer interface training. Event-related desynchronization was evaluated before and after the intervention. The Fugl-Meyer Assessment upper extremity motor score (FM-U) was assessed before, immediately after, and 3 months after, the intervention.**

Results: **Event-related desynchronization was significantly increased in the tDCS- brain–computer interface group. The FM-U was significantly increased in both groups. The FM-U improvement was maintained at 3 months in the tDCS-brain–computer interface group.**

Conclusion: **Anodal tDCS can be a conditioning tool for brain–computer interface training in patients with severe hemiparetic stroke.**

Key words: event-related desynchronization; upper extremity motor function; stroke; rehabilitation; electroencephalography; brain stimulation; brain–machine interface.

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INTRODUCTION

More than half of patients with stroke cannot achieve full recovery from motor impairment. (1). Various treatments have been developed to facilitate motor recovery of the paretic upper extremity (UE) in stroke patients. However, functional recovery depends on the severity of motor impairment (2). Langhorne et al. (3) performed a meta-analysis of multiple clinical trials and found that few treatments consistently improved hand motor function. The prognosis of functional motor recovery for severely affected UEs is poor. More recently, some newer interventions have been applied for UE rehabilitation, such as constraint-induced movement therapy (CIMT) (4), robot-assisted arm training (5), hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy (6) and brain–computer interface (BCI) training (7–11). BCI training, in particular, can be a revolutionary method for patients with severe hemiparesis who have undergone few effective treatments (9).

BCI technology can directly translate brain signals into commands for the control of external devices (12). BCI systems estimate a patient's motor intention based on the amplitude modulation of the mu rhythm (7), which is typically found over the sensorimotor cortex with a frequency of 8–13 Hz and is attenuated by movement execution and imagery. This phenomenon is referred to as event-related desynchronization (ERD). The ERD of the mu rhythm, termed mu ERD, is interpreted as the desynchronized activities of the activated neurones. The mu ERD is known to appear in the motor area during motor execution, preparation or imagery (13). However, the application of BCI in patients with severe motor disabilities has been limited because it is sometimes difficult to detect a sufficiently strong ERD (14). If ERD can be potentiated, it would be easier to utilize BCI in patients with severe motor disabilities.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that can modulate cortical excitability by inducing a weak current on the scalp (15). Anodal tDCS increases motor cortex excitability, whereas cathodal tDCS decreases it (15). Some studies have reported that combining tDCS with rehabilitation may potentiate the effect

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of rehabilitation (16, 17). Furthermore, it has been suggested that motor recovery following stroke or motor relearning of the paretic limb is maximized by anodal tDCS (18).

Matsumoto et al. (19) reported that anodal tDCS increased the magnitude of mu ERD induced by motor imagery in healthy subjects. They found that the magnitude of mu ERD was related to motor cortex excitability. Kasashima et al. (14) showed that anodal tDCS over the affected hemisphere increased the magnitude of mu ERD during paretic finger motor imagery in stroke patients. Therefore, it was assumed that anodal tDCS would potentiate ERD for BCI applications.

The hypothesis of this study was that the application of anodal tDCS could potentiate the effects of BCI training in stroke patients. This study explored the adjunctive effect of tDCS for BCI training and the long-lasting effects of BCI training in patients with chronic severe hemiparetic stroke.

MATERIAL AND METHODS

A non-randomized, controlled, cohort before–after, single-blind trial was conducted in patients with chronic hemiparetic stroke.

Participants

Participants were recruited from an outpatient rehabilitation clinic of a university hospital. Patients were included in the study if they met the following criteria: (*i*) a first unilateral subcortical stroke not involving the sensorimotor cortex as confirmed by brain magnetic resonance imaging (MRI) or computed tomography (CT); (*ii*) time from stroke onset of more than 180 days; (*iii*) ability to raise the paretic hand to the height of the nipple; (*iv*) inability to extend the paretic fingers; (*v*) no motor improvement during the 30 days prior to starting the intervention as confirmed by both the patients and their physicians; (*vi*) ability to walk independently in their daily lives; (*vii*) no severe cognitive deficits as determined by a Mini Mental State Examination score > 25; (*viii*) no severe pain in the paretic UE; (*ix*) no pacemaker or other implanted stimulator; and (*x*) no history of seizures within the past 2 years and no use of anticonvulsants at 1 month before the intervention.

From August 2009 to March 2011, 24 patients visited the outpatient clinic to join this study. Six patients were excluded because they did not meet the inclusion criteria, and 18 patients were enrolled in the study. The study purpose and procedures were explained to the participants, and written informed consent was obtained from each. No patient had a history of seizures. Two patients, who had brain surgery in the acute stroke phase, and 5 patients, who had used anticonvulsants until more than 1 month before the intervention, were assigned to the BCI group in order to avoid adverse events due to brain stimulation. The others were assigned to the BCI combined with tDCS group (tDCS-BCI group). No changes were made in medications, such as anti-spastic drugs, from 1 month before until 3 months after the intervention. No participant received any pharmacological therapies to enhance or modify motor recovery during the same period. The study was approved by the institutional ethics review board and was registered at the UMIN Clinical Trial Registry (UMIN000002121).

Electroencephalographic recording

Electroencephalography (EEG) was performed with Ag–AgCl electrodes (1 cm in diameter), with a right ear reference at C3 in patients with right hemiparesis and at C4 in patients with left hemiparesis, according to the international 10–20 system. An additional electrode was placed at a position 2.5 cm anterior to C3 or C4. A ground electrode was placed on the forehead, and the reference electrode was placed on either A1 or A2 (ipsilateral to the affected hemisphere). EEGs were recorded in a bipolar manner and were filtered with a bandpass of 2–100 Hz. The signals were digitized at 256 Hz using a biosignal amplifier (g.USBamp, g. tec medical engineering GmbH, Austria). Surface electrodes were placed bilaterally on the skin overlying the extensor digitorum communis (EDC) muscle to confirm the absence of electromyographic (EMG) activity during motor imagery tasks and to avoid unexpected muscle contraction (1024 Hz sampling with a bandpass of 10–512 Hz).

Event-related desynchronization quantification

As a feature representing the participant's motor imagery, mu ERD, which is a diminution of the alpha band (8–13 Hz) of the mu rhythm amplitude, was used to control the BCI. The ERD was expressed as the percentage of the power decrease related to the 1-s reference interval before the direction of imagery. The ERD at a certain frequency was calculated for each time and frequency according to equation (1):

$$\mathrm{ERD}\ (f, t) = \{(R(f) - A(f, t)) / R(f)\} \times 100\ (\%); \quad (1)$$

where $A(f, t)$ is the power spectrum density of the EEG at a certain frequency band f [Hz] and time t [s] since the imagery task was started, and $R(f)$ is the power spectrum at the same frequency f [Hz] of the baseline period.

Brain–computer interface training

Motor imagery-based BCI training was carried out for approximately 45 min a day, 5 times a week, for a total of 10 days. All participants received 40 min of standard occupational therapy per day, which consisted of gentle stretching exercises, active muscle re-education exercises and introduction to bimanual activities in their daily lives.

Details of the training protocol are described in detail elsewhere (8). A brief overview is given here. The participants were seated in a comfortable chair with their arms supported and relaxed on the armrest in pronation. They were facing a 15.4-inch computer monitor placed approximately 60 cm in front of their eyes. A motor-driven orthosis with a servomotor (9.5 kg·cm for output torque at 4.8 V supply; S9351, Futaba Sangyo, Tokyo, Japan) was attached to the affected hand to achieve finger extension–flexion movement at the metacarpophalangeal joints (Fig. 1).

A star-shaped cursor began to move at a fixed rate from left to right across the monitor over a 10-s period. Participants were instructed to rest for 6 s and then to either imagine extending their affected fingers or remain relaxed for the next 4 s, depending on the task cue on the monitor. If the mu ERD was detected after the cue instruction to imagine finger extension, the star-shaped cursor moved down on the screen as a visual feedback, and then the motor-driven orthosis extended their affected fingers for 5 s (Fig. 1). Each trial was performed at 30-s intervals. One training session consisted of 10 trials of motor imagery and 10 trials of relaxation, presented in a randomized order. Daily BCI training consisted of 3 training sessions.

A calibration session was performed before the training session to adjust the EEG classification parameters, as described elsewhere (20). In a randomized order, the participants were asked either to imagine extension of their paretic fingers or to remain relaxed for 4 s. Each task was repeated 20 times.

Transcranial direct current stimulation (tDCS)

Participants in the tDCS-BCI group received anodal tDCS over the affected hemisphere before BCI training. The tDCS was applied through rectangular, saline-soaked sponge electrodes (50 × 70 mm) with a battery-driven stimulator (CX-6650, Rolf Schneider Electronics, Gleichen, Germany). The position of the primary motor cortex (M1) of the affected hemisphere was determined as a site symmetrically opposite to the unaffected M1 side. This was confirmed by induction of the largest motor-evoked potential (MEP) in the unaffected EDC muscle with constant stimulus intensity using transcranial magnetic stimulation (TMS) with a figure-of-eight stimulation coil connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, UK). The MEPs were used on the unaffected M1 because the MEPs on the affected M1 were not evoked well in all patients. The anode electrode

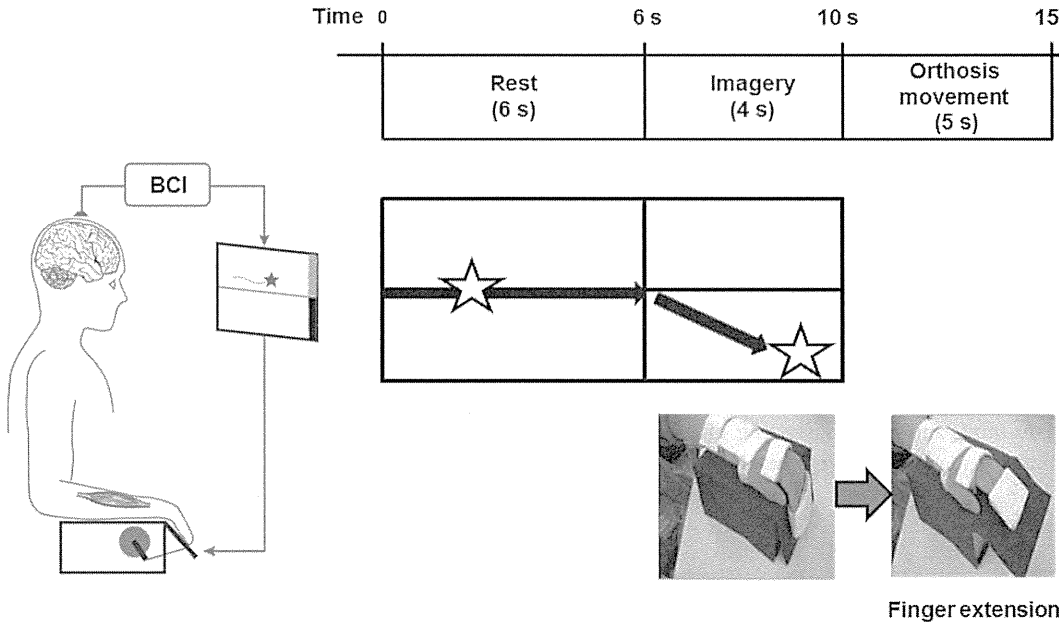

Fig. 1. Brain–computer interface (BCI) system. The participant is seated in front of a screen that displays the task and visual feedback. The paretic hand is placed on the motor-driven orthosis, which extends the paretic fingers. The task cue shows "Rest" for 6 s and "Imagine" for 4 s. The imagery task indicates that the participant should imagine extension of the paretic fingers. The star-shaped cursor moves from left to right on the screen. When event-related desynchronization is detected with electroencephalography, the star-shaped cursor moves downward on the screen, and then the motor-driven orthosis extends the paretic fingers for 2 s and returns them to the rest position for 3 s.

was placed over the M1 of the affected hemisphere, and the cathode was placed over the contralateral supraorbital area. tDCS was applied for 10 min with a current intensity of 1 mA. Participants were awake and sat in an upright position in a comfortable armchair during stimulation.

The positions of EEG electrodes were established before tDCS. For placing the stimulation electrodes, the EEG electrodes over the stimulus sites were removed after marking the scalp. After the tDCS stimulation, the EEG electrodes were placed in the same position as before, and this procedure took less than 1 min.

Outcome measures

The following clinical assessments and the measurement of mu ERD were conducted 1 day before (before) and after the intervention (post-), as described below. The accuracy rate of BCI training was also calculated on each day. To determine the long-term effects, the clinical evaluations were also assessed 3 months after the intervention (3 months) (Fig. 2).

Clinical assessments

UE motor function was assessed with the Fugl-Meyer Assessment UE motor score (FM-U) (66 points, total score) (21). The FM-U includes 33 items and consists of test A (shoulder/elbow/forearm: 36 points, A score), test B (wrist: 10 points, B score), test C (hand/finger: 14 points, C score) and test D (coordination: 6 points, D score). The D score was excluded because all patients in this study could not touch their noses with their index finger fully extended and had no remaining finger extension. The FM-U was assessed according to the scoring manual (22), and the validity and reliability of this method has been previously confirmed (23). Spasticity was measured with the Modified Ashworth Scale (MAS) (24) for finger, wrist and elbow flexors.

The FM-U and the MAS were scored by an independent assessor who was blinded to the allocation of the participants. This assessor scored all patients with stroke who were admitted to the department during the study period, including patients not recruited for this study.

The brain lesions were assessed with MRI or CT. The volumes of haemorrhage were calculated by the ABC/2 method, where A is the greatest haemorrhage diameter by MRI, B is the diameter 90° to A, and C is the approximate number of slices with haemorrhage multiplied by the slice thickness (25).

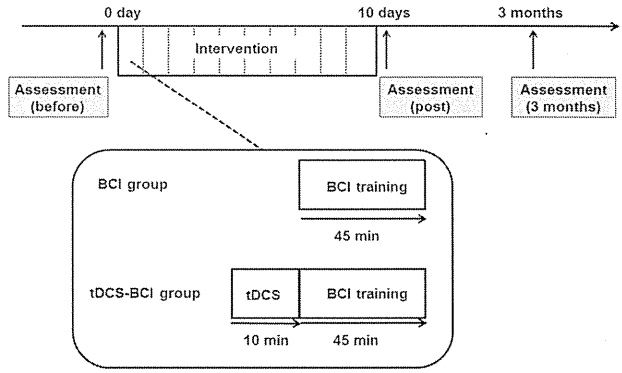

Fig. 2. Experimental design. All participants received the intervention of 10 days of training, which consisted of 1 × 45-min brain–computer interface (BCI) training session per day. The participants in the transcranial direct current stimulation (tDCS)-BCI group received anodal tDCS (1 mA, 10 min) over the affected motor cortex immediately prior to every BCI training session. Clinical examinations were performed 1 day before (before), 1 day after (post), and 3 months after the intervention (3 months).

Assessment of mu event-related desynchronization

The values of mu ERD during motor imagery of extension of the affected fingers were assessed 1 day before and 1 day after the 10-day intervention. The detail method was described previously (14) and is summarized in Appendix S1[1].

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-1925

Table I. *Clinical characteristics of participants*

	tDCS-BCI group ($n=11$)	BCI group ($n=7$)	p-value
Age, years, mean (SD)	53.5 (12.4)	48.0 (9.7)	0.441
TFO, months, mean (SD)	46.2 (20.2)	56.4 (36.4)	0.389
Gender, M/F, n*	9/2	4/3	0.225
Type of stroke*			0.629
Ischaemic, n	6 (1 lacunar)	3 (1 lacunar)	
Haemorrhagic, n	5	4	
Volume of lesion* (mm^3), mean (SD)	8,000 (7,282)	34,083 (29,795)	0.268
Paretic side, right/left, n*	6/5	5/2	0.417
Lesion, n*			
Putamen	4	3	0.398
Corona radiata	0	1	
Putamen-corona radiata	6	3	
Thalamus	1	0	
FM-U	27.6 (11.2)	23.4 (13.8)	0.487
MAS, median (min-max)**			
Finger flexors	1+ (1, 2)	2 (1+, 3)	0.038
Wrist flexors	2 (1, 3)	2 (1, 3)	0.845
Elbow flexors	1+ (1, 2)	1+ (1, 2)	0.316

p-values were calculated with Student's t-test, χ^2 tests* or Mann-Whitney U test**. TFO: time from onset of stroke; FM-U: Fugl-Meyer Assessment upper extremity motor score; MAS: Modified Ashworth scale; tDCS: transcranial direct current stimulation; BCI: brain–computer interface; M: male; F: female.

Accuracy rate of brain–computer interface training

The numbers of successful performances (i.e. moving the orthosis after imagery cues and not moving after the resting cues) were counted, and the accuracy rate was calculated as the number of successful performances divided by the number of trials. The mean accuracy rates on the first day and the last day of BCI training were compared.

Data analysis

Student's t-test was used to compare the baseline data of age, time from stroke onset and FM-U total score/subscores of the 2 groups. The Mann–Whitney U test was used to compare the baseline data of volumes of haemorrhage and MAS scores. The normality of the distribution of these variables was confirmed with the Kolmogorov–Smirnov test. A χ^2 test was used to compare categorical variables (gender, type of stroke, paretic side and lesion) of the 2 groups. Differences were considered significant if $p<0.05$.

A 2-factor mixed factorial analysis of variance (ANOVA) was used to compare the FM-U and MAS scores with the between-subjects factor of Intervention (BCI and tDCS-BCI groups) and the within-subjects factor of Time (before, post- and 3 months). The mu ERD and accuracy rate were also analysed using a 2-factor mixed factorial ANOVA with the between-subjects factor of Intervention (BCI and tDCS-BCI groups) and the within-subjects factor of Time (before and post for the mu ERD; the first and last trials for the accuracy rate). If the difference within the subjects was significant, *post-hoc* analysis was performed with a paired t-test in the FM-U, mu ERD and accuracy rate, and the Wilcoxon signed-rank test in the MAS. All statistical analyses were performed with SSPS version 18.0J (SPSS Japan, Japan).

RESULTS

All participants finished the intervention without experiencing any adverse effects. Table I shows the clinical characteristics of the participants. There were no significant differences between the 2 groups in any of the clinical evaluation items (age, time from onset of stroke, gender, type of stroke, paretic side, lesion and FM-U) before the intervention, except for the MAS of the finger flexors (Table I).

In the clinical assessment, 2 participants were not assessed at 3 months. One in the BCI group received different treatment after the intervention, and 1 in the tDCS-BCI group did not show up. The changes of the FM-U and MAS are shown in Table II. The 2-factor mixed factorial ANOVA showed no significant interaction effect between Intervention and Time in the total FM-U score ($F(2,28)=2.43$, $p=0.107$), the A score ($F(2,28)=2.96$, $p=0.068$), the B score ($F(2,28)=0.18$, $p=0.833$) and the C score ($F(2,28)=1.56$, $p=0.228$). It showed a significant main effect of Time in the total FM-U score ($F(2,28)=17.42$, $p<0.001$), the A score ($F(2,28)=8.19$, $p=0.002$) and the C score ($F(2,28)=10.94$, $p<0.001$), but not in the B score ($F(2,28)=3.02$, $p=0.065$). A *post-hoc* paired t-test showed significant differences in the total, A and C scores between before and post- ($p<0.001$, $p=0.004$ and $p=0.011$,

Table II. *Clinical assessment scores*

	tDCS-BCI group			BCI group			Interaction	Main effect of time
	Before ($n=11$)	Post ($n=11$)	3 months ($n=10$)	Before ($n=7$)	Post ($n=7$)	3 months ($n=6$)	p	p
FM-U, mean (SD)								
A	21.64 (7.32)	23.91 (7.20)**	26.10 (6.49)**	18.29 (8.98)	22.00 (8.19)	21.17 (9.56)	0.068	0.002
B	1.55 (1.86)	2.73 (2.61)	2.40 (1.58)	1.43 (2.51)	2.29 (2.75)	2.67 (2.42)	0.833	0.65
C	4.45 (2.54)	7.00 (2.76)*	7.90 (2.23)**	3.71 (2.75)	5.71 (2.98)*	5.67 (1.51)	0.228	<0.001
Total	27.64 (11.17)	33.64 (10.91)**	36.40 (8.72)**	23.43 (13.79)	30.00 (12.48)*	29.50 (12.23)	0.107	<0.001
MAS, median (min–max)								
Finger	1+(1, 2)	1 (0, 2)*	1 (0, 1+)**	2 (1+, 3)	1+ (1, 3)*	1 (1, 2)*	0.663	<0.001
Wrist	2 (1, 3)	1+ (0, 3)	1 (0, 2)*	2 (1, 3)	1+ (1, 3)	1~1+ (1, 1+)	0.230	<0.001
Elbow	1+ (1, 2)	1 (1, 1+)*	1 (0, 1+)*	1+ (1, 3)	1+ (1, 2)	1 (0, 1+)	0.608	<0.001

*$p<0.05$, **$p<0.01$ compared with the score of before; post-hoc paired t-test for the FM-U, Wilcoxon signed-rank test for the MAS. tDCS: transcranial direct current stimulation; BCI: brain–computer interface; FM-U: Fugl-Meyer Assessment upper extremity motor score; A: shoulder/elbow/forearm, 36 points; B, wrist, 10 points; C: hand/finger, 14 points; MAS: Modified Ashworth scale; finger: finger flexors; wrist: wrist flexors; elbow: elbow flexors; SD: standard deviation.

respectively), and between before and 3 months ($p=0.001$ for all) in the tDCS-BCI group. In contrast, in the BCI group, there were significance differences between before and post- in the total and C scores ($p=0.027$, $p=0.038$, respectively), and a not significant but slight improvement in the A score ($p=0.056$). There was no significant difference in all of the scores between before and 3 months (total score: $p=0.093$, A score: $p=0.376$, C score: $p=0.139$).

The 2-factor mixed factorial ANOVA showed no significant interaction between Intervention and Time ($p>0.05$), and a significant main effect of Time ($p<0.001$) in the MAS of the finger, wrist and elbow flexors. The Wilcoxon signed-rank test showed a significant decrease in the MAS of the finger flexors in both groups between before and post- (tDCS-BCI group: $p=0.011$, BCI group:$p=0.038$) and between before and 3 months ($p=0.004$, 0.024, respectively). There were also tendencies toward decrease in the MAS of the elbow and wrist flexors in both groups between before and post- (tDCS-BCI group: $p=0.025$ and 0.059, BCI group: $p=0.102$ and 0.102, respectively) and between before and 3 months ($p=0.016$ and 0.010, $p=0.059$ and 0.102, respectively).

The changes in the mu ERD values are shown in Fig. 3. The 2-factor mixed factorial ANOVA showed a significant interaction between Intervention and Time ($F(1,16)=6.94$, $p=0.018$), and a significant main effect of Time ($F(1,16)=14.68$, $p=0.001$). The *post-hoc* paired *t*-test showed a significant increase in the mu ERD values between before and post- in the tDCS-BCI group ($p<0.001$), but not in the BCI group ($p=0.483$).

The mean accuracy rate in the tDCS-BCI group increased from 49.91±7.92% to 58.68% (SD 8.62), whereas it increased in the BCI group from 52.10% (SD 9.39) to 55.76% (SD 4.42). The 2-factor mixed factorial ANOVA showed no significant interaction between Intervention and Time ($F(1,16)=2.34$, $p=0.145$), and a significant main effect of Time ($F(1,16)=14.12$, $p=0.002$). The *post-hoc* paired *t*-test showed a significant improvement between the first and last trials in the tDCS-BCI group, but not in the BCI group (tDCS-BCI group: $p=0.001$, BCI group: $p=0.220$).

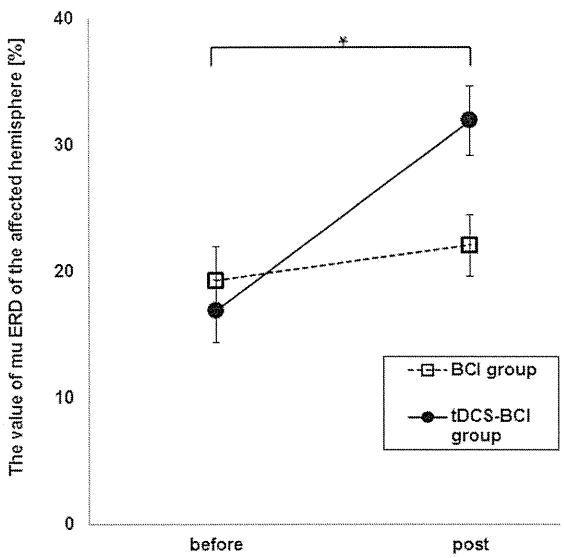

Fig. 3. The change in mu event-related desynchronization (ERD). The means of the mu ERD values of the transcranial direct current stimulation (tDCS)-brain–computer interface (BCI) group (square) and the BCI group (round) are plotted before and one day after the intervention (post). Error bars indicate standard error. Asterisks indicate significant differences from the baseline value with the *post-hoc* Student's *t*-test (*$p<0.01$).

DISCUSSION

The present study demonstrated that a 10-day BCI training improved motor function in patients with chronic severe hemiparetic stroke. Although there was a significant increase in ERD only in the tDCS-BCI group, no significant difference was found in improvement in motor function between the 2 groups. The tDCS-BCI group, however, showed a slightly longer-lasting improvement in motor function compared with the BCI group.

BCI training may produce an increase in appropriate brain activity and lead to the restoration of function through neuroplasticity (12). Shindo et al. (8) showed that BCI training increased the motor cortex excitability of the affected hemisphere, as confirmed with TMS. Functional MRI showed that BCI training increased ipsilesional motor cortex and premotor cortex activities (9). The combination of a coincident movement of the paretic fingers and the volitional brain signals by BCI training may induce sensorimotor integration and increase the recruitment of descending corticospinal fibres. These increments of excitability of motor pools may induce neural plasticity or neural compensation, leading to improvement in motor function.

Anodal tDCS increases cortical excitability (15) because of the increase in spontaneous neurone firing (26, 27) and the modulation of resting membrane potential (26, 28). Anodal tDCS is known to facilitate immediate production of mu ERD in healthy subjects and stroke patients (14, 19). Anodal tDCS could help to improve decoding of brain signals during BCI training by immediately increasing mu ERD, which might lead to an additional increase in mu ERD even after the BCI training was completed. It has been reported that ERD was correlated with M1 excitability (29) and blood-oxygen-level-dependent (BOLD) response (30). An increase in mu ERD in the tDCS-BCI group may be related to neural excitation in the affected hemisphere. Although tDCS could lead to an increase in ERD, we could not find a clear difference in motor improvement between the tDCS-BCI and BCI groups in this study. There was no interaction effect between Intervention and Time. It is possible that anodal tDCS improves motor function (31), but the effect may be limited only to patients with milder paresis (32). There was no substantial difference in the accuracy rate in this study. This could mean that the number of doses offered in successful trials of BCI training was not high enough to improve motor function. However, a more extensive change in brain signals (i.e. ERD) could result in a more significant long-term effect.

We found a reduction in spasticity in both groups. This may be due to the increase in awareness and learning of relaxation that comes through BCI training. It is difficult for patients with severe motor impairment to recognize their affected hand. BCI training can help patients concentrate on their affected hand, resulting in increases in awareness and use of the affected UE in their activities of daily living (8). In addition, the sequential training between relax and imagery may enable patients to learn how to decrease involuntary muscle activity (8). These effects of BCI training could have an impact on the whole UE, leading to improvements in proximal, as well as distal, portions. All participants received occupational therapy for 40 min per day in addition to the intervention. Occupational therapy may also contribute to the improvement. However, the change in the FM-U from baseline to post-intervention was 6.6 ± 6.0 points in our BCI group. This improvement was better than the changes in the FM-U only by conventional therapy for severe chronic patients with stroke in previous studies, showing that conventional therapies for 6–8 weeks resulted in 1.2–2.2 point improvements in the FM-U (5, 33, 34).

Study limitations

Several limitations must be considered regarding this study. First, the method of group allocation could have given rise to bias. The allocation of participants to the tDCS-BCI and BCI groups was controlled, but not randomized, with different group sizes among small samples. We excluded subjects who had undergone brain surgery or who were at risk for seizures from the tDCS-BCI group, while including them in the BCI group. There was no sham stimulation in the BCI group. The clinical features in the 2 groups, such as the gender, size of stroke, lesion side and motor function, were not significantly different except for finger spasticity. These discriminations, however, may have introduced a further variable. Secondly, anodal tDCS was applied for only 10 min immediately before the BCI training. The effect of 10 min of anodal tDCS with an intensity of 1 mA on TMS-evoked MEPs was shown to be maintained for less than 40 min in a previous study (35). In this study, the BCI training was performed for 45 min. The effect of the tDCS may have been lost by the end of the training. Thirdly, the position of M1 of the affected hemisphere was determined by using the symmetrical opposite side as a marker, that is, M1 of the unaffected hemisphere. This is not the exact position as identified by MEP of the affected EDC through directly stimulating the affected hemisphere. Finally, there is a possibility that some participants did not imagine well, which is very difficult to assess. The development of more effective BCI systems for stroke patients in terms of feedback accuracy, delay and modality is needed.

Conclusion

Anodal tDCS can be used as a conditioning tool for BCI training to increase ERD for the trigger of BCI. However, further randomized controlled trials are needed to ascertain the real effect of BCI training and the adjunctive effect of anodal tDCS for BCI training in more homogenous stroke populations.

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