2019年9月3日

文部科学省　研究振興局振興企画課競争的資金調整室　御中

# 慶應大学リハビリテーション医学教室の里宇明元医師による BMI-HANDS療法論文における効果捏造・改竄行為の告発状

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2016 年 9 月に出版された慶應大学リハビリ医学教室里宇明元医師による，貴省事業の論文 “Kawakami M, Fujiwara T, Ushiba J, Nishimoto A, Abe K, Honaga K, Nishimura A, Mizuno K, Kodama M, Masakado Y, and Liu M. A new therapeutic application of brain-machine interface (BMI) training followed by hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy for patients with severe hemiparetic stroke: A proof of concept study. Restor Neurol Neurosci. 2016 Sep 21;34(5):789-97.” （以下，本論文：資料 1）において，

1) 本研究期間中に，被験者の手指屈筋群に対し，A 型ボツリヌス毒素製剤（以下，ボトックス）による治療を施すことにより BMI 療法の効果を捏造・改竄し，さらに，これを論文に記載せず隠蔽して査読者や読者などを欺いた疑い
2) 本研究の HANDS 療法用電気刺激装置 MUROsolution（以下，MURO）が本論文に記載されている動作と一致せず，電気刺激の強度が筋電量に比例していないという誤動作が生じていた事実と，それにもかかわらず，BMI-HANDS 療法により治療効果が認められたとする結論が導かれていることから，データを捏造あるいは改竄した疑い
3) 被験者として参加した殆どの者は，慢性期脳卒中片麻痺患者の身体障害者で，生活困窮者であった．参加者は非侵襲 BMI 治療器（以下，BMI 治療器：図 1）による麻痺回復の効果がボトックスの効果による捏造であったと知れば，その倫理的，道義的問題は計り知れない問題

の 3 点の疑惑や問題が存在しています．

以上，里宇明元医師の研究活動の不正行為につき，文部科学省に告発する次第です．具体的内容は以下の通りです．

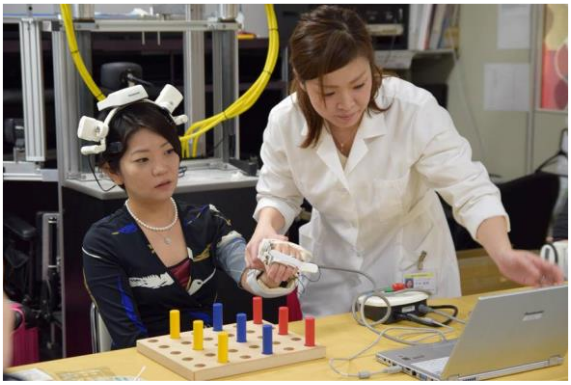


図 1　非侵襲 BMI 治療器

1. 被験者へのボトックス治療について

私どもは，里宇明元医師が進める，慢性期重度片麻痺患者の手指伸展筋を回復させる BMI 治療器の臨床試験研究に専門的観点などから興味を持ち，その研究成果には，臨床経験的かつ生体計測工学的に多くの疑問を抱きつつ，本研究に関わる論文や報告書などに注目してきました．昨年，偶然里宇明元医師らの BMI 治療器研究に関して本論文に先行する Kasashima-S Y et al（以下，Kasashima 論文）の BMI 治療器研究において，「ボトックスが注入されていた」

事実を知り，一連の BMI 治療器研究に対して研究活動の不正が存在すると考え，文部科学省等へ告発文（以下，資料 2）を提出致しました．

里宇明元医師らは，慶應理工学部牛場潤一博士により開発された「頭部に脳波用電極内蔵のヘッドギアを取り付け，手指伸展のイメージをすると，頭皮上から指伸展に対応した部位の活動をヘッドギアが感知し，手関節部の電動装具の手指伸展をトリガーする BMI 治療器」を毎日約 45 分間使用することで，指伸展の筋電が全く見られない患者でも，10 日間で指伸展ができるようになると報告してきました．しかしながら，治療器が完成したと報じられた 2008 年以降，10 年以上にわたり，臨床試験を続けて来たにもかかわらず，BMI 治療器の効果を確認した者は，里宇明元医師の研究グループ以外誰一人いません．ところが，このような状況に不審を抱いていたところ，ボトックスを当時慶應大学病院リハビリ科で論文責任著者であった藤原俊之医師が，BMI 治療器の臨床試験中に被験者に注入していた事実を被験者の一人が Blog に詳細に記述していたことを発見し，BMI 治療器の効果が，抗痙縮薬剤のボトックスによるものであったことに納得いたしました．

さらに， Kasashima 論文には，ボトックス使用に関する記述は一切無いどころか，「臨床試験前 1 ヶ月から臨床試験後 3 ヶ月間は，運動機能に影響を与える抗痙縮薬をはじめとする薬物治療などは行なっていない」と明記しており，ボトックス注入の事実を積極的に隠蔽していました．

屈筋群へのボトックス注入により伸筋群が促通されることは，ボトックス使用前に義務付けられている講習会でも必ず説明があり，BMI 治療器の効果判定には，他のいかなる抗痙縮薬や主動筋を促通する薬物投与など施してはならないことは，リハビリ科医師にとって初歩的かつ常識中の常識です．つまり，里宇明元医師らは，BMI 治療器の効果を，ボトックスの効果で偽装していたと言わざるを得ません．更には，偽装した研究成果により業績を積み上げ，虚偽かつ誇張された申請を以て助成先を選定する審査員や BMI 治療器に期待する国民を欺き，本研究に関連して公的資金を不正に受給しており，公的研究費詐欺と言っても過言ではありません．

資料 3 は，去る 2018 年 8 月 11 日に「慶應大学リハビリテーション医学教室における薬剤使用による BMI 療法効果捏造行為の告発状」（資料 2）に対して，慶應大学により行われた本調査の結果です．本調査では，Kasashima 論文以外の BMI 治療器論文についても，調査が行われ，その中で，臨床試験 (UMIN000002121) に基づく論文は，2009 年 8 月から 2011 年 3 月に実施された Kasashima 論文 (資料 3 の添付資料 3-5, 2015) ，2011 から 2013 年に実施された Nishimoto 論文 (同 3-7, 2018) ，2012 年 1 月から 2013 年 2 月に実施された本論文 (同 3-6, 2016) の 3 論文であり，この期間の症例数は 52 例とのことでした. Nishimoto 論文の被験者は, 実施期間が Kasashima 論文と, 本論文に跨り，かつ取込み基準も実施内容も同一であることから，両論文の被験者から抜粋した同一被験者と考えられます．したがって，52 例から Kasashima 論文の 24 例を除いた 28 症例は，本論文の被験者と考えられます．2009-2013 年の期間に合計 6 名の被験者にボトックスを施注したとされています．その内，Kasashima 論文において被験者 3 名にボトックスを刺注していることから，本論文の被験者においてはボトックスを施注した患者は 3 名いることになります．このことから，この 3 名においては，手指屈筋群へのボトックス注入により手指伸筋群を促通することで，BMI 治療器の効果を偽装（捏造・改竄）した疑いがあります．尚，本論文の研究実施時期は，ボトックスが国内で使用できるようになった 2010 年 10 月から 1 年以上経過しており，それに先立

ち行われたボトックスの治験に参加し，その効果を2010年10月以前から熟知していた慶應リハビリ医学教室のグループに限らず，既にボトックスの効果が広く知られるようになっていたことを申し添えておきます．

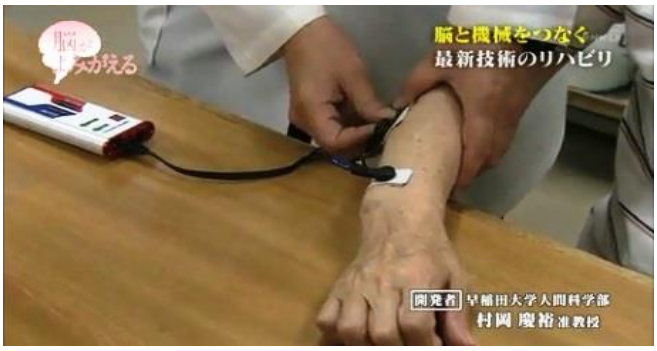



図 2　MURO 開発者（村岡慶裕）紹介テロップ
(2011.9.4 放送 NHK スペシャルより)

2. 電気刺激治療器：MURO の誤動作について

図 2, 3 は，2011 年 9 月 4 日（日）21 時より NHK 総合テレビで放映された NHK スペシャル「脳がよみがえる～脳卒中リハビリ革命～」 (https://www.dailymotion.com/video/xueqx0#.UccE9IKCiM8) の映像です．本番組の 27 分 25 秒から，慶應所有の MURO が登場します．図 2 に示す通り，MURO は申立者の一人である村岡慶裕により開発されました．MURO は，本論文中 792 頁 “This NMES continually changes its stimulation intensity in direct proportion to the amplitude of the voluntary EMG.”の通り，随意筋電量に比例した強度の電気刺激を出力する装置です．

一方，資料 4 は，現・東京湾岸リハビリテーション病院部長の新藤恵一郎医師から，MURO の開発者である村岡宛に 2013 年 1 月 7 日に送られてきた，MURO の誤動作に関するメールです．そこには，「治療器が説明書通りに電気刺激を出力していない」旨が述べられていました．添付データを確認したところ，メーカーが製造時にアルゴリズムを間違えてプログラミングし，筋電に比例して出力されていないことが判明しました．したがって，少なくとも 2013 年 1 月以前は，MURO は誤動作していたことになります．

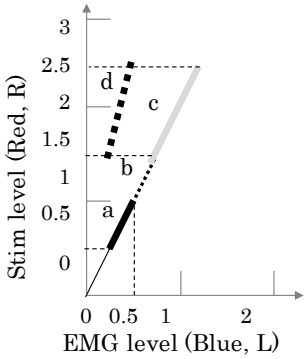
前述の NHK の番組において，患者に MURO を装着後，27 分 48 秒から筋電レベル（左：青）と刺激レベル（右：赤）が LED の点灯により表示されています．この LED が，左右 LED で正常動作（筋電に比例した刺激レベル）では生じ得ない点灯パターンが存在しており，正常動作していないことが確認できます．正常動作では，刺激レベルは筋電レベルに比例しており，図 3 において，筋電レベルが増加するにつれ(a) → (b) → (c) の順序で遷移するはずです．ところが，慶應 MURO は，(d) の如く，筋電レベル（左：青）がゼ

(a) EMG<0.5, 0.5≦Stim.<1.5

(b) 0.5 ≦EMG< 1.5, 0.5≦Stim.<1.5

(c) 0.5≦EMG<1.5, 1.5≦Stim.<2.5

(d) EMG<0.5, 1.5≦Stim.<2.5
＜malfunction＞



(e) Relationship of EMG level – Stimulation level

図 3　筋電レベルのランプと刺激レベルのランプの関係
状態 d で誤動作確認可 (2011.9.4 放送 NHK スペシャルより)

ロであるにも関わらず，刺激レベル（右：赤）が 2 目盛まで上がっています．これは MURO が誤動作している証拠となります．

さらに筋電に比例して出力されていない同様の現象が，メーカーが MURO 設定の説明用として健常者を対象に設定デモを行っている動画（https://www.youtube.com/watch?v=fY1NbfzOAaE, 2012/07/19 公開）の 9 分 3 秒以降の治療モードにおいても確認できます．

このように，「本研究実施当時，MURO 全個体が誤動作していた」と言えます．

また，このような誤動作の電気刺激を脳卒中患者の麻痺した筋肉へ与えることによって，患者に誤学習を促し，症状を悪化させる危険性もあり，MURO による HANDS 療法は，麻痺を回復させる効果など期待される筈がないばかりか，逆に，運動機能を増悪させる危険性もあった筈です．しかしながら，本論文において，HANDS 療法の有効性を認めたと結論付けられていることから，データの改竄や捏造が疑われます．

3. 本論文の研究対象者（被験者）の殆どの方は，慢性期脳卒中片麻痺患者で身体障害者です．そして，同じ苦しみを持つ人達のために，麻痺した手指伸筋が回復する新しい医療機器の実用化を夢見て，本研究に自らの心身を捧げたことと思います．麻痺した手指伸筋の回復が，手指屈筋群へのボトックス注入による，手指屈筋群相反性抑制からの脱抑制効果によるもの，つまり，不正研究と知っていたなら，本研究に協力することもなかったに違いありません．

ボトックス治療は，地域の病院，クリニックの外来診療で，「ボトックス」使用のための講習会・実技セミナーを受講した医師によって治療されています．つまり，近所の医療機関での日帰り受診で事足りたはずです．しかしながら，本研究に協力した被験者は，BMI 療法という餌に釣られて，わざわざ東京まで足を運び，2 週間も慶應病院に拘束された挙句に，慶應以外でも受けられるボトックスを含めた他の通常治療を施され，その治療代の金額を事前に知らされること無く，退院時に数十万円もの大金を騙し取られていました．つまり，長期 2 週間の入院による休職と身体拘束，更に精神的負担，BMI 療法以外の治療費や減給などの実質的損害が発生しています．

本研究により，被験者の患者さんが被った，倫理的，道義的，経済的，法的（詐欺容疑）問題などには計り知れないものと言えます．

資料１：Kawakami M, Fujiwara T, Ushiba J, Nishimoto A, Abe K, Honaga K, Nishimura A, Mizuno K, Kodama M, Masakado Y, and Liu M. A new therapeutic application of brain-machine interface (BMI) training followed by hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy for patients with severe hemiparetic stroke: A proof of concept study. Restor Neurol Neurosci. 2016 Sep 21;34(5):789-97.
https://www.ncbi.nlm.nih.gov/pubmed/27589505

資料２：慶應大学リハビリテーション医学教室における薬剤使用による BMI 治療効果捏造行為の告発状 **（＝告発3の資料1）**

資料３：慶應義塾大学研究コンプライアンス委員会の調査報告書**（＝告発3の資料2）**

資料４：2013 年 1 月 7 日付新藤恵一郎医師から連名申立者村岡慶裕宛の MURO ソリューションの欠陥に関するメール

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# A new therapeutic application of brain-machine interface (BMI) training followed by hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy for patients with severe hemiparetic stroke: A proof of concept study

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**Abstract.**

**Background:** Hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy improved paretic upper extremity motor function in patients with severe to moderate hemiparesis. We hypothesized that brain machine interface (BMI) training would be able to increase paretic finger muscle activity enough to apply HANDS therapy in patients with severe hemiparesis, whose finger extensor was absent.

**Objective**: The aim of this study was to assess the efficacy of BMI training followed by HANDS therapy in patients with severe hemiparesis.

**Methods**: Twenty-nine patients with chronic stroke who could not extend their paretic fingers were participated this study. We applied BMI training for 10 days at 40 min per day. The BMI detected the patients' motor imagery of paretic finger extension with event-related desynchronization (ERD) over the affected primary sensorimotor cortex, recorded with electroencephalography. Patients wore a motor-driven orthosis, which extended their paretic fingers and was triggered with ERD. When muscle activity in their paretic fingers was detected with surface electrodes after 10 days of BMI training, we applied HANDS therapy for the following 3 weeks. In HANDS therapy, participants received closed-loop, electromyogram-controlled, neuromuscular electrical stimulation (NMES) combined with a wrist-hand splint for 3 weeks at 8 hours a day. Before BMI training, after BMI training, after HANDS therapy and 3month after HANDS therapy, we assessed Fugl-Meyer Assessment upper extremity motor score (FMA) and the Motor Activity Log14-Amount of Use (MAL-AOU) score.

**Results**: After 10 days of BMI training, finger extensor activity had appeared in 21 patients. Eighteen of 21 patients then participated in 3 weeks of HANDS therapy. We found a statistically significant improvement in the FMA and the MAL-AOU scores after the BMI training, and further improvement was seen after the HANDS therapy.

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**Conclusion**: Combining BMI training with HANDS therapy could be an effective therapeutic strategy for severe UE paralysis after stroke.

Keywords: Brain-machine interface, rehabilitation, upper extremity, stroke

## 1. Introduction

Stroke is one of the most prevalent neurological conditions worldwide, especially among the elderly. Recovery of function in the hemiparetic upper extremity (UE) is noted in less than 15% of patients after stroke in the case of initial paralysis (Hendricks et al., 2002). It has been reported that the major portion of recovery of UE motor impairment occurs over the first few months (Kwakkel et al., 2006). However, recent newly developed approaches for rehabilitation have also improved UE motor function in patients with chronic stroke (Wolf et al., 2006; Stinear et al., 2008; Fujiwara et al., 2009).

Hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy is a newly developed therapeutic approach that has shown promise in improving UE function in patients with chronic stroke (Fujiwara et al., 2009, 2015; Shindo et al., 2011a). In HANDS therapy, closed-loop, electromyogram-controlled neuromuscular electrical stimulation (NMES) is applied to the paretic finger extensors, combined with the use of a wrist-hand splint, 8 hours a day for 3 weeks. This closed-loop electrical stimulator continually changes its stimulation intensity in direct proportion to the voluntary electromyographic (EMG) amplitude of the paretic finger extensors, and it becomes easier for participants to extend their paretic fingers and perform pinch and release. Participants can therefore use this stimulator at will in their daily lives for as long as 8 hours a day. A randomized control study showed that HANDS therapy in addition to standard rehabilitation produced a significantly greater improvement of paretic UE motor function in patients with severe to moderate hemiparesis, compared with a control group of patients with stroke (Shindo et al., 2011a). However, detection of EMG activity is necessary in order to apply HANDS therapy on paretic finger extensor muscles (e.g., the extensor digitorum communis (EDC) or the extensor pollicis longus (EPL).

Brain-machine interface (BMI) can directly translate brain signals into commands to control an external device. BMI training for stroke enhances the volitional recruitment of surviving motor pathways and facilitates paretic muscle activity. Shindo et al. reported that after BMI training, finger extensor EMG activity appeared in 50% of patients (Shindo et al., 2011b). Therefore, we hypothesized that this training would be able to increase paretic finger muscle activity enough to apply HANDS therapy in patients with severe hemiparesis. BMI training might also increase the potential for application of HANDS therapy. Moreover, HANDS therapy following BMI training might improve UE motor function more than BMI training alone.

To confirm these hypotheses, we studied the effect of BMI training in patients with severe hemiparesis who could not extend their paretic fingers and who showed no EMG activity in the paretic finger extensors. We conducted tests to determine whether BMI training increases EMG activity in the paretic finger extensors enough to apply HANDS therapy. We also studied whether BMI training followed by HANDS therapy actually improved UE motor function more than BMI training alone.

## 2. Materials and methods

### 2.1. 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 during the month before the intervention. We excluded the patients with visuospatial neglect

Table 1
Patient characteristics and clinical evaluations

| | |
|---|---|
| Age, y | 50.6 ± 10.9 |
| Gender | 21 males, 8 females |
| Type of stroke | 23 putaminal hemorrhage,<br>1 thalmic hemorrhage,<br>2 MCA area infarction,<br>3 corona radiata infarction |
| Time since stroke, Month | 48.0 ± 41.4 |
| Hemiparetic side | 13 Rt, 16 Lt |
| Dominant hand affected | 13 |
| FMA-total | 19.2 ± 6.4 |
| FMA-A | 16.0 ± 5.1 |
| FMA-B | 0.3 ± 0.8 |
| FMA-C | 2.6 ± 2.0 |
| FMA-D | 0.3 ± 1.1 |
| MAL-AOU | 2.1 ± 2.7 |
| MAS of elbow | 2 (1–4) |
| MAS of wrist | 1 (1–3) |
| MAS of fingers | 1.5 (1–4) |

Values are given as mean ± standard deviation or median with range. FMA Fugl-Meyer test upper extremity motor score, MAL-AOU; Motor activity log amount of use score, MAS; modified Ashworth scale.

according to tape bisection test. The patients with apraxia were also excluded with the assessment of gesture production.

From January 2012 to February 2013, 41 patients were seen in the outpatient clinic to be evaluated for this study. Twelve patients were excluded because they did not meet the inclusion criteria, and 29 patients were enrolled in the study. The study purpose and procedures were explained to the participants, and written informed consent was obtained from each. This study was approved by the Institutional Ethics Review Board and was registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN 000002121 and 000001986).

The study sample mean age was 50.6 years (SD 10.9), and the median time from stroke onset was 30.5 months (range, 9 to 180 months). Clinical details of the participants are shown in Table 1.

### 2.2. *Brain-machine interface*

#### 2.2.1. *Electroencephalography recording*

Electroencephalography (EEG) was recorded 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 bipolar manner. The signals were digitized at 256 Hz using a biosignal amplifier (g.Mobilab+, g.tec medical engineering GmbH, Austria).

#### 2.2.2. *Event-related desynchronization (ERD) quantification*

As a feature representing the participant's motor imagery, the mu ERD, which is a diminution of the alpha band (8–13 Hz) of the mu rhythm amplitude, was used to control the BMI [9]. 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 the equation (1): $ERD(f, t) = \{(R(f) - A(f, t)) / R(f)\} \times 100\ (\%)$; (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 start of the imagery task, and R(f) is the power spectrum at the same frequency f [Hz] as that of the baseline period (Kasashima-Shindo et al., 2015).

#### 2.2.3. *BMI training*

Motor imagery-based BMI 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 of daily living (ADLs). Details of the training protocol are described elsewhere (Shindo et al., 2011b); a brief overview is given here. The participants were seated in comfortable chairs, with their arms supported and relaxed on the armrest in pronation, and they faced a 39.1 cm computer monitor which was placed approximately 60 cm in front of them. A motor-driven orthosis with a servomotor was attached to the affected hand to achieve finger extension–flexion movement at the metacarpophalangeal joints.

A star-shaped cursor began to move at a fixed rate from left to right across the monitor over a 10 s period. The participants were instructed to rest for 6 s and then either to imagine extending their affected fingers or to 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 cursor moved down on the screen as a visual

feedback. Then the motor-driven orthosis extended their affected fingers for 5 s, and neuromuscular electrical stimulation was simultaneously applied to the paretic EDC muscle at the stimulus intensity of the motor threshold with surface electrodes. Each trial was performed at 30 s intervals. The training session consisted of 10 trials of motor imagery and 10 trials of relaxation, presented in a random order. Daily BMI training consisted of 3 training sessions. Before each training session, calibration was performed to adjust the EEG classification parameters, as described elsewhere (Guger et al., 2003). In a random 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.

### 2.3. *Hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy*

The participants received closed-loop, EMG-controlled NMES (MURO solutions, Pacific Supply Co., Osaka, Japan) combined with a wrist-hand splint (Wrist Support, Pacific Supply Co.) for 8 hours a day over 3 weeks (HANDS therapy) (Fujiwara et al., 2009, 2015; Shindo et al., 2011a). The stimulus intensity and duration were controlled by EMG of the paretic EDC muscles (Muraoka, 2002). This NMES continually changes its stimulation intensity in direct proportion to the amplitude of the voluntary EMG. The surface electrodes pick up EMG signals at the target muscle and simultaneously stimulate it in direct proportion to the detected EMG signal, with the exception of the section of 25 ms after delivering each stimulation pulse, in which stimulation artifacts and M waves are observed. The details of the stimulator are described elsewhere (Fujiwara et al., 2009 Shindo et al., 2011a).

The rationale for combining the stimulation system with a wrist-hand splint was derived from the work of Fujiwara et al. (Fujiwara et al., 2004), who reported that a wrist-hand splint could reduce spasticity in the finger, wrist, and elbow flexors, and could facilitate finger extensor muscle activity. In our study, the HANDS system was active for 8 hours, and patients were instructed to use their paretic hand as much as possible while wearing it. Their non-paretic UE was not restrained. The patients were also instructed to practice bimanual ADLs.

The length of the intervention was 21 days, during which time all participants were admitted to hospital. They also received 90 minutes per day of occupational therapy, 5 days a week. Each session consisted of gentle stretching exercises of the paretic UE, active muscle re-education exercise, and instructions by occupational therapists on the use of their paretic hands in ADLs with the HANDS system. The therapists were directed to focus on the participants' goals and their particular impairments and disabilities; thus, the specific therapy varied according to the needs of each patient.

### 2.4. *Assessment*

#### 2.4.1. *Assessment of paretic fine extensor muscle activity*

The muscle activity of the paretic EDC, EPL, and flexor digitorum superficialis (FDS) was recorded with Ag-AgCl surface electrodes with diameters of 9 mm (Nihon Koden, Tokyo, Japan). The electrodes were applied with center-to-center spacing of 20 mm and were placed parallel to the muscle fibers and distal from the motor points of individual muscles. Before the electrodes were attached, the skin areas were rubbed with alcohol, and the skin resistance was kept below 5 kΩ. A Neuropack 8 EMG machine (Nihon Kohden, Tokyo, Japan) was used to record and analyze the EMG data. The bandpass filter was set at 30 Hz to 2 kHz. To ensure that the position of the EMG electrodes was identical at every recording session and to avoid variation of electrode placement, the exact position of the electrodes (contour) was redrawn daily with a permanent marker. The patients were placed in a comfortable chair with their arms on an armrest, and the angle of their elbows was kept at 70–90 degrees. They were instructed to rest for 4 s and then to extend their affected fingers for the next 4 s. After trying to extend their affected fingers, they were instructed to rest for 4 s. The EMG data from 4.5 s to 7.5 s were designated as the finger extension task phase. We used the EMG data from 0 s to 3.5 s and from 8.5 s to 12 s for the rest phase.

We took into account the influence of the crosstalk from the FDS to the extensor muscle when interpreting the EMG amplitude of the EDC and the EPL. *Mogk* has reported that less than 2% of the common signal was present between the flexor and extensor electrode pairs during both the pinch and the grasp tasks (Mogk and Keir, 2003).

Patients underwent HANDS therapy if they had met the following criteria after BMI training: (i) The value of the maximum EMG amplitude evaluations for the EDC or EPL muscles minus 5% of the amplitude for the FDS at the same time during the extension task phase was over 100 μV; (ii) the average EMG

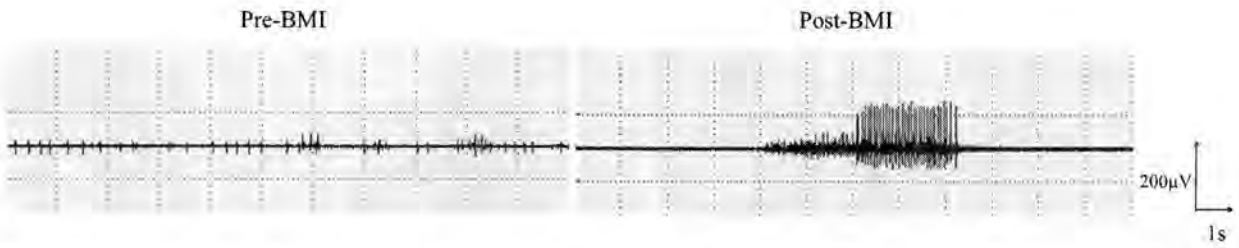


Fig. 1. EMG activity of the affected extensor digitorum communis muscle (EDC) before BMI training (pre-BMI) and after BMI training (post-BMI). Electrodes were placed on the affected EDC. Patients were asked to extend their paretic fingers repeatedly for 4 seconds.

amplitude evaluations for the EDC or EPL muscles in the rest phase were less than 20 μV.

*2.4.2. Clinical assessment*

UE motor function was assessed with the Fugl-Meyer Assessment UE motor score (FMA) (Fugl-Meyer et al., 1975). The FMA consists of four categories: A) shoulder/elbow/forearm; B) wrist; C) hand; D) coordination; maximum score: 66. It is a commonly used measure with excellent inter-rater reliability and construct validity (Platz et al., 2005).

The Motor Activity Log (MAL) is a structured interview used to measure UE disability in ADLs. The MAL-14 includes 14 items, scored on an 11-point amount of use (AOU) score (range 0–5) to rate how much the arm is used (Uswatte et al., 2005). High construct validity and reliability of the MAL have been demonstrated in patients with chronic stroke (Van der Lee et al., 2004; Uswatte et al., 2005). We calculated the sum of each items as the MAL-AOU. Spasticity of the fingers, wrist, and elbow was measured with the Modified Ashworth Scale (MAS) (Bohannon and Smith, 1987). These three clinical measures were scored by a blinded examiner, who did not know which patients were recruited for this study. This examiner assessed all the patients with stroke, who were admitted to our department during the study period, including patients not recruited for this study. These clinical assessments were performed before BMI training (pre-BMI), after BMI training (post-BMI), after HANDS therapy (post-HANDS), and 3 months after HANDS therapy (3m-HANDS).

*2.5. Statistical analyses*

After the normality of data distribution was examined with the Kolmogorov-Sminov test, repeated measure analysis of variance (ANOVA) was used in the analysis of the total FMA score (FMA-total), the score of FMA category A (FMA-A), the score of FMA category B (FMA-B), the score of FMA category C (FMA-C), the score of FMA category D (FMA-D), and the MAL-AOU with a main effect of Time (pre-BMI, post-BMI, post-HANDS, and 3m-HANDS). The paired *t*-test was used in the *post hoc* analysis. The MAS of the elbow, wrist, and fingers was examined with the Friedman test. The Wilcoxon signed-rank test was used in the *post hoc* analysis because the MAS data were not normalized.

In the MAS score, score 1+ was transformed to 2, and scores 2 and 3 were transformed to 3 and 4. The effects were considered significant if $P < 0.05$. All statistical analyses were performed with SPSS, version 23.

## 3. Results

*3.1. Paretic fine extensor muscle activity*

After BMI training, 21 of 29 patients fulfilled the criteria of EMG activity for HANDS therapy. Figure 1 shows the typical changes of EMG activity of the affected EDC from before to after 10 days of BMI training in one patient.

*3.2. Overall time effects*

Eighteen of 21 patients participated in the HANDS therapy (Fig. 2). Three of 21 subjects did not participate in this therapy because they could not afford to remain in hospital for a further 3 weeks. The mean interval from the end of BMI therapy to the beginning of HANDS therapy was $8.6 \pm 6.8$ months. Repeated measure ANOVA showed a significant main effect of Time (pre-BMI, post-BMI, post-HANDS, and 3m-HANDS) in the FMA-total, the FMA-A, the FMA-B, the FMA-C, and the MAL-AOU in 18 patients (Table 2). The Friedman test showed a significant main effect of Time (pre-BMI, post-BMI, post-HANDS, and 3m-HANDS) in the MAS of the elbow, the wrist and the fingers (Table 2).

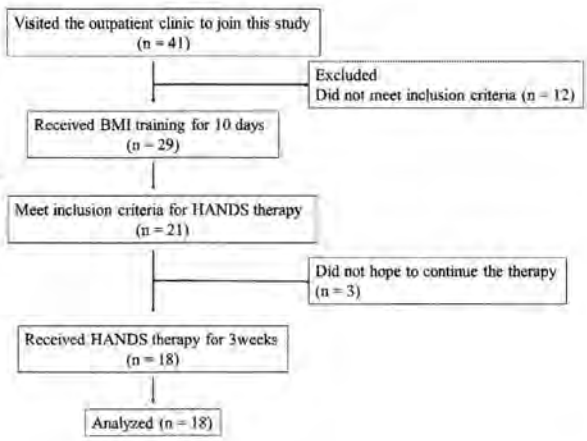


Fig. 2. Flow diagram for subject assignments in the study.

We did not find any negative change of face, trunk and leg function.

### 3.3. Post-hoc time effects

#### 3.3.1. The effect of BMI training

The *post hoc* paired t-test showed significant improvement of the FMA-total, the FMA-A, the FMA-C, and the MAL-AOU between the pre-BMI and the post-BMI, but no significant change in the FMA-B (Table 2).

The *post hoc* Wilcoxon signed-rank test showed significant improvement in the MAS of the elbow and the fingers between the pre-BMI and the post-BMI, but no significant change in the MAS of the wrist (Table 2).

#### 3.3.2. The effect of HANDS therapy after BMI training

The *post hoc* paired t-test showed significant improvement of the FMA-total, the FMA-A, the FMA-B, the FMA-C, and the MAL-AOU between the post-BMI and the post-HANDS (Table 2).

The *post hoc* Wilcoxon signed-rank test showed significant improvement in the MAS of the elbow and the fingers between the post-BMI and the post-HANDS (Table 2).

#### 3.3.3. Three-month follow-up

The *post hoc* paired t-test showed significant improvement of the FMA-total, the FMA-A and the FMA-C between the post-HANDS and 3m- HANDS (Table 2).

The *post hoc* Wilcoxon signed-rank test showed significant improvement in the MAS of the wrist between the pre-BMI, the post-BMI and 3m-HANDS (Table 2).

## 4. Discussion

To our knowledge, this is one of the first study to demonstrate the efficacy of BMI training followed by HANDS therapy. This sequential rehabilitation program improved UE motor function in patients with severe hemiparesis, for whom there are few other effective therapies.

BMI has been shown to be an effective therapy for patients with severe hemiparesis who cannot move their paretic fingers (Shindo et al., 2011b; Ramos-Murguialday et al., 2013). HANDS therapy combined

Table 2
Changes of clinical assessments

| | | Pre BMI training | Post BMI training | Post HANDS therapy | 3m-HANDS | F value | *P* value |
|---|---|---|---|---|---|---|---|
| FMA-U | total | 19.8 (5.9) | 23.1 (6.9)* | 29.0 (8.1)*,† | 34.4 (9.0)*,†,‡ | 52.4 | <0.001 |
| | A | 16.2 (4.6) | 18.2 (5.3)* | 20.9 (5.1)*,† | 23.1 (5.7)*,†,‡ | 21.0 | <0.001 |
| | B | 0.3 (0.8) | 0.7 (1.0) | 1.3 (1.4)*,† | 2.0 (1.8)*,† | 8.0 | <0.001 |
| | C | 3.2 (2.2) | 4.1 (2.6)* | 6.3 (2.1)*,† | 8.6 (2.7)*,†,‡ | 25.9 | <0.001 |
| | D | 0.1 (0.5) | 0.2 (0.6) | 0.6 (1.1) | 0.7 (1.4) | 2.9 | 0.11 |
| MAL AOU | | 2.5 (2.8) | 5.3 (4.0)* | 11.1 (4.7)*,† | 12.8 (6.5)*,† | 23.3 | <0.001 |
| MAS | Elbow | 2.2 (0.8) | 1.8 (0.9)§ | 1.4 (0.7)§,‖ | 1.3 (0.9)§,‖ | | <0.001 |
| | Wrist | 1.5 (0.8) | 1.5 (0.8) | 1.3 (0.5) | 0.9 (0.9)§,‖ | | <0.01 |
| | Finger | 1.8 (1.0) | 1.4 (0.6)§ | 1.2 (0.6)§,‖ | 1.1 (0.9)§,‖ | | <0.01 |

Values are mean value (SD). FMA-U; Fugl-Meyer test upper extremity motor score, MAL AOU; Motor activity log amount of use score, MAS; modified Ashworth scale. *Post hoc* paired *t* test showed significant difference with pre BMI training value*($p<0.05$), post BMI training value†($p<0.05$) and post HANDS therapy‡($p<0.05$). *Post hoc* wilcoxon signed-rank test showed significant difference with pre BMI training value§($p<0.05$) and post BMI training value‖($p<0.05$). F value and *P* values were calculated with repeated measure ANOVA and Friedman test.

with BMI training improved the FMA score, with a mean gain of 9.2. This gain represents a clinically important difference for treatment-induced gains in the setting of chronic stroke (4.25 points on the FMA) (Page et al., 2012). In our study, BMI training alone improved the FMA with a mean gain of 3.3. A previous study showed a mean gain of the FMA with BMI training of 3.4 in patients with chronic severe hemiparesis (Ramos-Murguialday et al., 2013).

In a previous report, the mean gain of the FMA with HANDS therapy in patients with severe hemiparesis was 7.7 (Fujiwara et al., 2015), while our study showed the mean gain of HANDS therapy to be 5.9. The difference in the gain may be explained by the difference in the score before HANDS therapy. The mean FMA score before HANDS therapy in our study was 23.1, but it was 33.3 in a previous study (Fujiwara et al., 2015).

We found further improvement in the MAL-AOU with BMI followed by HANDS therapy than with BMI training alone. HANDS therapy may induce dose-dependent functional recovery and task-specific improvement because patients use their paretic hand in their ADLs. These results confirmed our hypothesis that BMI followed by HANDS therapy resulted in more functional recovery than with BMI training alone.

Shindo et al. reported that new voluntary finger extensor EMG activity developed in 4 of 8 patients (50%), although they had shown little or no finger extensor EMG activity before BMI training (Shindo et al., 2011b). In our study, 21 of 29 participants showed new voluntary finger extensor EMG activity, which fulfilled the criteria for HANDS therapy. The success rate for transfer from BMI to HANDS therapy was 72.4%, which we believe justifies the clinical use of BMI to induce paretic finger extensor activity.

### 4.1. *Mechanism for BMI to increase paretic muscle activity*

Our BMI system was triggered with ERD at the affected motor cortex during motor imagery, which is a reflection of motor cortex activity. Takemi et al. showed that the magnitude of ERD during motor imagery represents the motor cortex excitability, which was measured as the motor evoked potential (MEP) and the downregulation of intracortical inhibitory interneurons (Takemi et al., 2013). BMI training, repetitive motor imagery, and sensory motor stimulation with passive movement and electrical stimulation all increased motor cortex excitability in the affected hemisphere (Shindo et al., 2011b). It is hypothesized that increased motor cortex excitability may increase the descending volley to the target muscle. It is also possible that the neural link between brain activity and paretic limb movements influences the specific neural network activity of the visuomotor loop involved in a motor task. This neural link may strengthen the associative connection between a movement attempt and an actual finger movement, which is an example of Hebbian plasticity (Jackson et al., 2012). Increased corticospinal excitability and strengthening of the specific neural network involved in finger extension can induce actual finger extensor muscle activity (Ramos-Murguialday et al., 2013).

BMI improved FMA-A and C but not B and D. Our BMI system trained to extend the paretic fingers. Therefore we found task specific finger function improvement after BMI. It is supposed that BMI training increased the awareness of paretic arm and use of the paretic UE in their ADL. That may explain the improvement of proximal arm function. BMI reduced muscle spasticity in elbow. Reducing spasticity in elbow may reduce the synergy pattern and improve the FMA-A score. The items of FMA-D are difficult task for severe hemiparetic patients. Mean FMA-D value before FMA-D was 0.1. That means most of participants in this study could not touch their nose with their paretic hand. It is difficult to change the FMA-D items in severe hemiparetic patients. Patients, who cannot extend their paretic fingers, extend the finger using tenodesis-like action. When they want to extend their paretic fingers they flex their wrist. In their ADL, they use this tenodesis-like action. It may explain one of the reason why BMI did not improve the elbow spasticity and FMA-C.

### 4.2. *Mechanism for HANDS therapy to improve UE motor function*

HANDS therapy following BMI training further improved UE motor function and increased use of the paretic hand. A previous study has reported that electrical stimulation combined with voluntary contraction of the target muscle with closed-loop, EMG-triggered NMES, induced downregulation of intracortical inhibitory interneurons, with subsequent facilitation of corticospinal activity in the intended movement (Fujiwara et al., 2015). HANDS therapy provides day-to-day assistance whenever patients attempt to extend their paretic fingers. Co-activation of the brain and the spinal cord may strengthen the

surviving connections between the two sites due to Hebbian mechanisms (Jackson et al., 2012).

With HANDS therapy, the patients learned how to use their paretic UE in their ADLs. Therefore, daily use of the paretic hand after HANDS therapy may result in use-dependent recovery, which might explain the further improvement of the MAL-AOU after this therapy.

In general, the process of stroke rehabilitation should be state-dependent and goal-oriented. Treatments might target several different problems, from relieving very specific impairments, to improving activity and participation (Langhorne et al., 2011).

Actual participation by the patients in use of their paretic UE after BMI training was limited. The mean sum of the MAL-AOU score of 5.3 signified that patients did not use their paretic UE for most of the MAL-AOU items. Consequently, we believe that the goal of BMI should be facilitation of paretic finger muscle activity, and that the goal of HANDS therapy should be improved participation of patients in use of their paretic UE in their daily lives. We were able to improve use of the paretic UE with HANDS therapy. The mean sum of MAL-AOU became 11.1 after HANDS therapy, which means that patients used their paretic UE in most items of the MAL-AOU.

There are, however, several limitations to this study. The number of patients treated in this study was small and follow up data was limited in post HANDS therapy. Participants of this study are limited in patients with subcortical lesion and 24 out of 29 participants are hemorrhagic stroke patients. We should consider the influence of the type of stroke on the effect of BMI since ischemic stroke patients frequently have cortical lesions. There was no age-matched control or sham treatment group. Despite these limitations, however, we believe that the present findings provide important information for the treatment of chronic stroke patients with severe UE hemiparesis. The pilot data presented in this study provide the basis for designing and conducting a larger-scale trial with a more rigorous study design, including masking and randomization, to test the hypothesis that this training program is more effective and less labor intensive than other strategies in the management of the chronically paretic UE.

## 5. Conclusions

In conclusion, functional recovery from stroke has been induced with BMI training followed by HANDS therapy, even in patients with chronic and moderate-to-severe hemiparesis. This new therapeutic strategy may open a new door in stroke neurorehabilitation.

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新藤です。
御無沙汰しております。
現在、デンマークで研究留学をしております。

運動学習の研究で、IVES（MUROsolution）を使うことを考えています。

Pilot study をしたところ、筋電検出と刺激出力について、一定のルールを見いだせず、パシフィックサプライに問い合わせをしましたが、私には理解しにくいところがあるため、村岡先生にお伺いできれば、と思います。

具体的な設定は、下記のようです。
Minimum: 0
Maximum: 8
Threshold: 20
Assist: 5

右第一背側骨間筋に、MURO の電極を設置し、右示指の外転⇒内転をすばやく行う課題を行っています。同時に、表面筋電図も記録したかったので、MURO の記録電極 2 つを挟むようにして、別の電極を設置しました。

exp 1-4 の図の、横軸は時間（単位：秒）、グラフは一番上が表面筋電図、下の 3 つは加速度計の x, y, z 軸方向の成分です。電気刺激が 16Hz で起こっているのが確認できます。

この図で疑問であるのは、小さな筋電図しか記録されていないのに、電気刺激が起こったり（exp2)、相対的に大きな筋電図が出ているにもかかわらず、電気刺激が起こらないこと(exp1, 3,4)があります。

パシフィックサプライから、「刺激出力の算出」と「刺激出力算出のタイミング」についての説明を頂い

たのですが、まだ、理解できない部分が残ります。

たとえば、
１）筋電検知から出力まで、検出のタイミングによっては、最大 0.125sec（8Hz)かかることがあるのでしょうか？

２）「前回」と「今回」の差分値が、仮に同じ値だった場合は、刺激が出力されない（あるいは刺激が変わらない？）のでしょうか？

村岡先生にご意見を伺えたら助かります。
お忙しいところ誠に申し訳ありませんが、宜しくお願い申し上げます。

PS [redacted] よろしくお伝えください。
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