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ORIGINAL ARTICLE

Graded motor imagery for patients with stroke: a non-randomized controlled trial of a new approach

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ABSTRACT

BACKGROUND: Graded motor imagery (GMI) is a new approach that is thought to promote graded cortical brain activation and may promote motor recovery after stroke.
AIM: This non-randomized controlled trial investigated the feasibility and clinical effect of GMI in motor recovery after stroke.
DESIGN: Non-randomized controlled trial.
SETTING: Inpatient subjects of neurorehabilitation hospital.
POPULATION: Twenty-eight patients (*i.e.* 14 experimental and 14 control matched) with first-ever stroke.
METHODS: Patients were assessed before and after a 4-week intervention. Assessors were blinded to the protocol. The experimental group underwent 20 sessions (1-hour each) based on GMI principles; the control group received the same amount of conventional rehabilitation. Primary outcomes were Wolf Motor Function Test (WMFT) and the 66-points motor section of the Fugl-Meyer Assessment (FMA).
RESULTS: Groups were comparable under demographical and clinical features. Mean duration since stroke was 19 weeks. Patients were satisfied and adhered well to the protocol. Ten patients in the GMI group and four in the control group reached the minimal clinically important difference. Mean (SD) improvement in the GMI group was 0.72 (0.5) for WMFT, and 10.3 (8.9) points for FMA. The control group improved a mean (SD) of 0.21 (0.35) points at WMFT and 2.7 (0.35) points at FMA. Between-group analysis shows that GMI provided significantly greater improvements for both motor functions at WMFT (P=0.05) and in the pain section of FMA (P=0.006), respectively.
CONCLUSIONS: GMI is a feasible treatment for stroke patients with better outcomes than conventional therapy. A randomized controlled trial is warranted to minimise risk of selection bias.
CLINICAL REHABILITATION IMPACT: Clinicians should implement GMI treatment in their clinical practice, being a feasible, clinically relevant, costless, and easy-to-do treatment.

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Key words: Stroke - Rehabilitation - Physical therapy modalities.

Motor impairment is the most common impairment caused by stroke.[1] Important advances in stroke rehabilitation identified a number of clinical features that are able to predict motor recovery.[2, 3] Patients who show some residual motor function in shoulder abductors and wrist and finger extensors within four weeks from brain lesion have a greater probability of regaining functional movement in the upper limb. On the contrary, patients who show little or no upper limb function do not benefit from current therapies. One recent systematic review on the topic encouraged a high dose of repetitive, goal oriented practice, and suggested that

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unilateral arm training should be preferred to bilateral arm training.[4]

Motor imagery (or explicit motor imagery, EMI) and mirror therapy (MT) have also been shown to be effective treatments,[5, 6] and can be proposed to those people with little or no arm function, that are unable to perform active exercises. However, not all patients are able to perform EMI after stroke.[7] On the contrary, MT showed nice results in acute stroke patients with some preserved motor function,[8] but seems to have negligible effects when arm paresis following stroke is severe.[9]

Graded motor imagery (GMI) [10] can be introduced to overcome these problems. It consists of three specific elements delivered in levels of increasing complexity in terms of the time and difficulty, which is thought to reflect graded activation of cortical networks.[11] The first element is implicit motor imagery (IMI), which refers to a particular form of motor imagery, required in those task involving left/right judgments of pictured hands (or feet). It has been shown that left/right judgments involve preparing to manoeuvre one's own limb to match the posture shown in the picture.[12] A recent study, exploring IMI and EMI with electroencephalography, showed that both type of imageries have similar spatial and time-frequency activation in the somatosensory cortex.[7] When studied using positron emission tomography, IMI has showed to involve pre-motor activation but only sub-threshold priming of primary motor cortex cells.[12] Therefore, IMI is considered both a preliminary and complementary step of the more commonly used EMI.[7, 12] EMI is the second element of GMI and resembles mental practice. The patient is asked to actively imagine his/her own body part moving. The third element resembles mirror therapy. Functional MRI studies showed broad cortical activations during the task.[13] Mirror therapy can be employed by simply watching the unaffected limb reflected in the mirror and then progressing toward active and functional movements.

GMI has been extensively studied in chronic pain patients, especially chronic regional pain syndrome (CRPS).[14, 15] It was developed to grade cortical activation and to reduce cortical disinhibition in CRPS. [11,16] Cortical disinhibition is surely one of the patho-physiological consequence of stroke that contributes to motor impairment.[17] Stroke and CRPS have been compared on other grounds too.[18] GMI has been suggested as a treatment technique that should be utilised in addressing movement impairments following stroke.[18] To our knowledge, its application in this context has not yet been investigated. The purpose of this study was to evaluate the feasibility and potential value of GMI for reducing functional disability in the upper limb of patients with stroke. We hypothesised that GMI was a feasible, well-tolerable treatment, that could improve upper limb motor function in patients with stroke.

A phase II non-randomized controlled trial was set to assess feasibility and provide preliminary evidence on the clinical effect of GMI approach for stroke patients. Patients underwent GMI treatment for 4-weeks. Duration of treatment was set according to organizational issues within the hospital. Patients with stroke access IRCCS San Camillo Hospital Foundation according to Italian national guidelines on stroke rehabilitation and undergo inpatient and intensive rehabilitation treatments. All the patients included in the present study were provided with two hours of individually tailored motor rehabilitation program each day. One hour of their motor rehabilitation program was replaced by the experimental intervention (GMI), becoming the unique motor treatment for the upper limb provided to the participants for the study duration. A matched control group was enrolled to reduce biases due to natural recovery. Consecutive patients that fulfilled the same inclusion/exclusion criteria and that matched the treatment group for age, time since stroke, and motor ability assessed with Fugl-Meyer Assessment (FMA) were enrolled. The control group received two hours of motor rehabilitation each day, individually tailored on patient's motor and cognitive abilities and with one of them targeted specifically to upper limb function. We followed published recommendations for non-randomised controlled trial, following the TREND checklist.[19] Give the present work is the first one exploring GMI in stroke patients, we were not able to perform a proper sample size calculation. Due to organizational issues we were able to design this one-year treatment protocol. Our data allowed us to perform a proper sample size calculation, upon which we set up a RCT.

Materials and methods

Patients were referred to our laboratories by the physician in charge of the patient, anytime they fulfilled the eligibility criteria. Inclusion criteria were: 1) first ever

ischemic or hemorrhagic stroke within a year from the event; 2) age of participant between 18 and 75 years old; 3) absence of apraxia and global or severe aphasia assessed using the Aachener Aphasie Test;[20] 4) Mini-Mental State Examination score >23.[13] On the contrary, the presence of other neurological or orthopaedic disorders affecting upper extremity motor function, neglect, and significant spasticity defined as a score ≥24 points at the Tardieu Rating Scale (TRS),[21] were considered exclusion criteria. When patient's cognitive status could not be objectify using MMSE (*e.g.* due to dysarthria or aphasia), a pragmatic clinical opinion from the neuropsychologist was sought. The neuropsychologist was informed about the experiment, its inclusion and exclusion criteria, and the cognitive demand it requires. This additional assessment was made prior the enrolment and did not influence the group allocation. After this first evaluation, routinely made by a physician and a neuropsychologist and/or a speech therapist of our hospital, the patients underwent a second evaluation with a physical therapist. The therapist explained in detail the experiment and answered to patient's question. Signed informed consent to participate to the study was sought before the initial assessment, in accordance with the Declaration of Helsinki. Two therapists were in charge of all the assessments, before and after intervention, and were blinded to treatments. Both assessments and treatments were made in one of the quiet rooms of our hospital, designed for individual treatments.

Outcome measures

Initial and final clinical assessments were performed by two independent physical therapists — blinded to the treatment protocol. In order to reduce assessment biases, we made sure that the initial and final assessment of the same patient were made by the same therapist. Assessments included: Wolf Motor Function Test (WMFT), a global functionality assessment of the upper limb. We used only the functional section of the WMFT. WMFT includes 16 items, each items score from 0 to 5. Data are reported as the average for the 16 items.[22] Fugl-Meyer Assessment for Upper Limb (FMA). We used the 66-points motor section of the scale, which specifically explores motor functions including synergies, coordination, active movements and hand grips;[23] WMFT and FMA were considered as the primary outcomes.

Secondary outcome measures were, Tardieu Rating Scale for spasticity (TRS).[14] The muscles chosen for assessing spasticity were: pectoralis major, biceps brachii, wrist extensor, deep and superficial finger flexors. TRS was preferred to the most common Asworth Scale because of its higher validity and inter-rater reliability.[18] Pain was assessed using a 10 cm Visual Analogic Scale for pain intensity together with the pain section of the FMA.[20] Patients were asked to refer their pain intensity at rest and during the most painful passive movement. Functional Independence Measure (FIM) assessed physical and cognitive abilities and disabilities in patient's everyday life. Satisfaction questionnaire (SQ),[24] we used an already published questionnaire to assess patient's subjective evaluation and satisfaction of the treatment provided. The questionnaire includes 12 items investigating satisfaction toward the therapist, satisfaction toward the treatment, satisfaction toward general organization and time scheduling. Each item ranges from 0 (completely unsatisfied) to 5 (completely satisfied). Scores range from 0 to 60.

We also noted adverse effects and the number of treatments missed during the treatment protocol as an indicator for treatment safety.

GMI intervention

Participants underwent GMI treatment for 20 sessions of 1 hour over a 4-week period, Monday to Friday. GMI included three consecutive steps: implicit motor imagery (IMI), explicit motor imagery (EMI) and mirror therapy (MT). IMI training was delivered until the patient achieved accuracy and reaction time values considered normal on both sides according to Moseley *et al.* (2012) [10] (*i.e.* accuracy ≥80%; reaction time =2.0±0.5 seconds). If the patient did not reach these values within six sessions, he maintained IMI training for two further sessions. In order to progress treatment, EMI was gradually introduced from the 6th session regardless of the respective IMI scores. Patients underwent a minimum of six and a maximum of 8 EMI and MT sessions. As patients progressed through treatment programme different modalities might overlap for 2 sessions maximum, when stepping from previous to following stage. A complete description of the experimental intervention can be found in Table I.

TABLE I.—*Detailed description of the experimental treatment. Adapted from the TIDIeR checklist (http://www.equator-network.org/reporting-guidelines/tidier/).*

Brief name	Graded Motor Imagery (GMI)
Why (Rationale)	GMI has been suggested as a treatment technique that should be utilised in addressing movement impairments following stroke. It was developed to grade cortical activation and to reduce cortical disinhibition.
What (Materials)	GMI included three consecutive steps: Implicit Motor Imagery (IMI), Explicit Motor Imagery (EMI) and Mirror Therapy (MT). The IMI training used the Left/Right Hand Judgment Task included the random presentation of 60 images of right (N.=30) or left (N.=30) hands oriented in various positions and degrees of rotation. Images were projected on a 15" screen. EMI was assessed using the short form of the Kinaesthetic and Visual Imagery Questionnaire (KVIQ) was used for assessing the quality of the imagination.[25] The therapist described the movements the patient had to imagine, alternatively, a video showing one movement, repeated twice, was used for practising EMI, as described by Beaumont and co-workers (2011).[26] In MT section of GMI visual feedbacks are provided placing a mirror in front of the subject, on his/her midline, so that when the patient looks into the mirror can see his/her unaffected limb reflected.
What (Procedures)	Participants underwent GMI treatment for 20 sessions of 1 hour over a 4-week period, Monday to Friday. IMI training was delivered until the patient achieved accuracy and reaction time values considered normal on both sides according to Moseley and co-workers (2012) [10] (*i.e.* accuracy ≥80%; reaction time =2.0±0.5 seconds). If the patient did not reach these values within six sessions, he maintained IMI training for two further sessions. In order to progress treatment, EMI was gradually introduced from the 6th session regardless of the respective IMI scores. Patients underwent a minimum of six and a maximum of eight EMI and MT sessions. As patients progressed through treatment programme different modalities might overlap for 2 sessions maximum, when stepping from previous to following stage – mirror therapy.
Who (Profession, expertise, background, specific training)	Two physiotherapists with more than 5 years of experience in neurological rehabilitation were chosen as blinded assessors. Two other physiotherapists – a young and an experienced one – were in charge of the treatment. Both physiotherapists had no experience with GMI principles and undergo a short specific training about it. The training lasted 8 hours and was distributed in three sessions in three different days.
How (Modes of delivery)	One to one individual treatment.
Where (Infrastructure and relevant features)	In one of the quiet rooms of our hospital.
When and how much (Number of session, intensity or dose)	Participants underwent GMI treatment for 20 sessions of 1 hour over a 4-week period, Monday to Friday.
Tailoring (Personalization)	In order to deliver a standardized treatment, no personalization was allowed. Some variability was allowed in the protocol, as detailed in the procedure section.
Modifications (From existing or initial protocol)	No modification of the protocol occurred.
How well – planned (Adherence and procedure to maintain it)	No particular procedure for adherence were delivered. Patient were informed about the rational of the treatment protocol before the start of the treatment.
How well – actual	The standardized protocol was followed in its details. For reasons unrelated to GMI, two patients missed one treatment and another one missed three treatment sessions.

IMI

The IMI training used the Left/Right Hand Judgment Task included the random presentation of 60 images of right (N.=30) or left (N.=30) hands oriented in various positions and degrees of rotation. Images were projected on a 15" screen. For each image, the patients were required to choose whether the images seen were a right or left hand by clicking the respective right or left button on a computer mouse as quickly as possible. Given the novelty of the task, a first familiarisation session, using 20 images of different body parts and with no time limits, was performed. Patients needed to demonstrate they clearly understood the task mirroring with their own body part the picture shown on the screen and then clicking the correct button on the mouse. Familiarisation was also used to confirm that the cognitive abilities of the subject were enough to fully understand and follow the treatment. After this familiarisation session, the actual IMI task could start. Accuracy and reaction times of responses were recorded by a dedicated software (E-Prime®, Psychology Software Tools, Sharpsburg, MD,

USA). To perform the task, patients used their non-affected hand. The affected hand was placed next to the unaffected hand, in front of the subject. Patients were asked to complete the task as quickly as possible. Actual movement of the hands was not permitted as the task is meant to rely only on mental capacity. Each session, the patients had to complete the IMI task for at least four times within the hour of treatment.

EMI

EMI was introduced during the sixth IMI session and gradually complexity of motor skills to be imagined was increased. The short form of the Kinaesthetic and Visual Imagery Questionnaire (KVIQ) was used for assessing the quality of the imagination.[25] The KVIQ consists of five movements that have to be imagined by the subject: shoulder flexion, fingers tapping, trunk flexion, hip abduction and foot dorsal flexion. The subject first rates the clarity of the image (visual EMI; VEMI) on a five-point scale (where 1="I can see no image"; and 5="Imagine is as clear as seeing"). The quality of the sensation during imagination (kinaesthetic EMI; KEMI) was then rated on the same 5 point-point scale. Details for the assessment can be found elsewhere.[25] EMI training was performed in a quiet room, the therapist described the movements the patient had to imagine, alternatively, a video showing one movement, repeated twice, was used for practising EMI, as described by Beaumont *et al.* (2011).[26] Patients, sitting in a relaxed position, were asked to close their eyes and imagine themselves sitting in a familiar place. They were asked to execute the movement as if it was real in all its aspects, including the timing taken to move. Patients executed two series of 20 repetitions for every imagined movement in each session. They performed 6 to 8 different movements in each session.

MT

In MT section of GMI visual feedbacks are provided placing a mirror in front of the subject, on his/her midline, so that when the patient looks into the mirror can see his/her unaffected limb reflected. The patient is told to move the unaffected arm while looking in the mirror. This gives the illusion that a "new" strong arm has replaced the affected one. Mirror exercises began with simply watching the reflection of the unaffected hand in the mirror and then progressed from static to active and functional movements. When possible, gentle and synchronous movements of the affected hand were encouraged behind the mirror. Three series of 12-15 minutes were performed in each session, with 5 minutes between sessions to allow for resting and relaxing the arm (Table I).

Control treatment for upper limb

The control treatment program was based on current standard practice protocols and aimed at restoring upper limb motor functions, tailored to each patient's residual ability. Treatment included a variety of passive and active movements and when possible functional exercises. Activities during the treatment increased in task difficulty along with patient improvement. The therapist in charge of the control treatment decided time and dose of the proposed activities.

Statistical analysis

The Kolmogorov-Smirnov Test was used to study the skewness of distribution for all the variables. Correlation matrices were employed, in order to avoid biases due to strong correlations between variables. A two-way ANOVA for repeated measures with time as within factor and treatment (*i.e.* GMI or control) as between factor was used for WMFT and FMA. Age, weeks from stroke onset and severity (*i.e.* Bamford classification) were considered as covariates. Wilcoxon signed rank test was used *post-hoc* to compare outcome measures differences after treatment, within groups. Mann-Whitney test for independent samples was used post-hoc for comparing differences at baseline and after treatments between experimental and control groups. Published data for minimum clinically important difference (MCID) were used to classify the changes seen in our patients as clinically meaningful or not. The MCID after a given treatment was calculated as 0.4 points at WMFT (on average for each item) in patients 6 months after stroke,[27] and as 9 points at FMA for sub-acute stroke patients (mean time after stroke: 8.4 weeks).[28] We then calculated the Number Needed to Treat (NNT) as an indicator of effectiveness of GMI for stroke patients. NNT is a powerful and easy-to-use measure of effectiveness of a given

treatment, which allows clinicians and researcher to calculate the absolute power of a treatment when compared to a control group. NNT calculation was based on a change of at least the MCID. Data were analysed with IBM SPSS 20.0 software. Using data resulting from the present study we can run a sample size calculation, that will in turn allow us to set a proper randomised control trial.

Results

Between February and December 2014 we screened thirty-nine consecutive patients with first ever stroke. Seventeen patients fulfilled eligibility criteria; fourteen accepted to participate and were enrolled for the study. Other thirty patients were assessed and fourteen of them enrolled as matched controls (see supplementary material for the flowchart). No patients were lost during the protocol and all the 28 subjects enrolled completed the assigned treatment. Mean (SD) age was 56.6 (12.5) years for the treatment group and 58.8 (13.3) for the control group. Mean (SD) time since stroke was 17.2 (12.1) weeks for the treatment group and 19.5 (10.2) for the control group. We used Bamford's classification for stroke severity. None of the patients had Total anterior circulation infarct (TACI) or Posterior circulation infarct (POCI). Five patients and seven controls had mild or moderate aphasia. Further descriptive data of demographics and baseline scores are reported in Table 2. The groups were comparable for all the clinical variables at baseline. In both groups 10 out of fourteen patients had severe motor impairment (FMA<20 points).

Patients adhered well to the protocol and reported no side effects during the treatment protocol. No differences were found at the satisfaction questionnaire between groups, and all patients reported to be between "Satisfied" to "Completely Satisfied" at all items. For reasons unrelated to GMI, two patients missed one treatment and another one missed three treatment sessions. Three patients missed respectively one, two and three treatments in the control group (Table II).

Table III reports the results from the IMI tasks and EMI assessment. No significant correlations were found between IMI and EMI. Accuracy scores in both the GMI (71.4% +/- 26.2) and control group (70.7% +/- 18.7) were below the scores considered normal.[10] On the contrary, reaction times were similar to the ones considered normal.[10] No differences between groups were found at the task.

Ten patients out of fourteen in the treatment group showed a change equal to or greater than the minimum clinically important difference (MCID) in either the WMFT or FMA scores (Table IV). Nine patients reached the MCID in both the WMFT and FMA. Analysis of variance revealed that the severity of stroke (*i.e.* Bamford Classification) was a significant covariate only for the F-M UE (F=4.560, P=0.044). Conversely, none of the other covariates like age, weeks since stroke and aphasia were significant factors for both FMA and WOLF. Moreover, the type of treatment received was a significant factor between groups for both FMA (F=4.810, P=0.039) and WOLF (F=7.168, P=0.014). *Post-hoc* tests showed that both primary outcomes had a significant improvement after treatment (Table V). The GMI group improved on average 0.72 points for

TABLE II.—*Preintervention demographics and primary outcome scores.*

	Control group (N.=14)	GMI group (N.=14)	P value
Sex (M/F)	11/3	10/4	0.663[α]
Age (years)	58.75 (13.3)	56.6 (12.4)	0.541[U]
Affected side (R/L)	11/3	9/5	0.403[α]
Aetiology (I/H)	12/2	12/2	1.000[α]
Weeks since stroke	19.54 (10.2)	17.23 (12.1)	0.454[U]
Stroke severity (PACI/LACI)	12/2	9/5	0.190[α]
Aphasia	7/14	5/14	0.445[α]
WMFT	0.74 (0.87)	1.09 (1.08)	0.329[U]
FMA	15.2 (14.2)	16.35 (15.6)	0.734[U]

Mean (with Standard Deviation, SD) of data are reported. GMI: Graded Motor Imagery; M/F=male/female; R: right side affected; L: left side affected; I: ischemic; H: hemorrhagic. Weeks: time since stroke in weeks; Stroke severity is based on Bamford classification,[34] PACI: partial anterior circulation infarct; LACI: lacunar infarct. WFMT: Wolf's Motor Function Test.; FMA: 66-points motor section of Fugl-Meyer Assessment. [α]Chi-Squared test for dichotomous measures; [U]non-parametric Mann-Whitney Test for comparing between groups sample distribution.

TABLE III.—*Implicit and explicit motor imagery.*

	Control group	GMI	U
Accuracy (%)	70.7 (18.7)	71.4 (26.2)	0.93
Reaction Time (s)	2.34 (0.7)	2.55 (0.5)	0.37
Visual EMI (KVIQ)	13.3 (6.7)	13.2 (6.0)	0.97
Kinaesthetic EMI (KVIQ)	13.1 (6.11)	14.6 (5.75)	0.53

Accuracy rate (in percentage, %) and Reaction Times (in seconds, s) at the Left/Right Hand Judgment Task. Visual EMI (KVIQ): visual section of the kinesthetic and visual motor imagery for the assessment of Explicit Motor Imagery. Kinesthetic EMI: kinesthetic explicit motor imagery. Data are reported as Mean (Standard Deviation, SD) for all patients included in the study. U: non-parametric Mann-Whitney Test for comparison between groups.

TABLE IV.—*Primary outcome results. Effect of treatment on primary outcomes for both groups; proportion of patients who showed a reliable change and proportion of patients who reached or exceeded Minimally Clinically Important Difference (MCID) for both outcomes.*

	Control group (N.=14)			GMI group (N.=14)		
	Pre	Post	MCID	Pre	Post	MCID
WMFT	0.74 (0.86)	0.95 (1)	4/14	1.09 (1.08)	1.81 (1.5)** #	10/14
FMA	15.2 (14.2)	17.9 (16)	4/14	16.4 (15.6)	26.7 (19.6)**	10/14

MCID for WMFT is 0.4 points; MCID for FMA is 9 points. WFMT: Wolf's Motor Function Test (functional section). WMFT is showed as the average for the 15 items. FMA: 66-points Motor Section of Fugl-Meyer Assessment.
*Statistical significance at the Wilcoxon signed rank test for within group analysis with P value below 0.05 level of significance; **statistical significance at the Wilcoxon signed rank test for within group analysis with P value below 0.005 level of significance; #statistical significance at Mann-Whitney Test for between groups analysis (GMI *vs.* Control) with P value below 0.05 level of significance.

TABLE V.—*Effect of treatments on secondary outcomes.*

	Control group (N.=14)		GMI group (N.=14)	
	Pre	Post	Pre	Post
Pain-FMA	19.4 (2.4)	18.4 (4.5)	19.6 (3.5)	21.9 (1.9) * #
VAS	4.3 (2.7)	5.2 (2.1)	3.74 (2.9)	3.7 (2.3)
TRS	7.1 (7.4)	7.2 (7.6)	8.4 (7.3)	7.8 (6.5)
FIM	75.3 (21.4)	73.7 (26.7)	87.8 (24.6)	94.1 (23.1) ** #
SQ	-	53.07 (4.1)	-	52.1 (5.2)
Adverse symptoms	-	N/A	-	N/A
Missed treatments	-	6 / 280	-	6 / 280

Mean (with Standard Deviation, SD) pre- and postintervention scores for secondary outcomes. Pain-FMA: Pain section at Fugl-Meyer Assessment; VAS: Visual Analogic Scale for Pain Intensity assessment; TRS: Tardieu Rating Scale for Spasticity assessment; FIM: Functional Independence Measure; SQ: Satisfaction questionnaire; Missed treatment refers to the total of the treatments missed for all patients.
*Statistical significance at the Wilcoxon signed rank test for within group analysis with P value below 0.05 level of significance; **statistical significance at the Wilcoxon signed rank test for within group analysis with P value below 0.005 level of significance; #statistical significance at Mann-Whitney Test for between groups analysis (GMI *vs.* control) with P value below 0.05 level of significance.

each item at WMFT (P=0.001). FMA also showed an improvement, 10.3 points on average, which was statistically significant (P=0.003). Within the secondary outcomes (Table V), spasticity (TRS) and pain at VAS showed no change. However, scores from FMA Pain Section improved significantly after treatment (P=0.04).

In the control group, four out of fourteen patients showed a change that reached the MCID. After treatment, the control group improved a mean (SD) of 2.7 (0.3) at FMA and a mean (SD) of 0.21 (0.34) at WMFT. Within group analysis of the control group showed no significant changes in primary and secondary outcomes.

Between group analysis showed that the improvement at both the primary outcomes was significantly greater in the GMI group than in the control group (P=0.002 for WMFT; P=0.006 for FMA). In addition, Pain Section of FMA, WMFT and FIM significantly improved after treatment (respectively P=0.006; P=0.05; P=0.05). The NNT to get yield a MCID for the GMI intervention, when compared to current best practice, was 4.7.

Based on these results we calculated the sample size needed for a setting an adequate RCT. We used means and standard deviations data of our first primary outcome, WMFT. We set Alpha error at 0.05 and Beta error at 0.1, in order to have a statistical power of 90% and we used the formula as described by Rosner (2011).[29] Based on this calculation, we need to set up a RCT with a total of 56 patients (28 in each group).

Discussion

The challenge for neuro-rehabilitation is to find the treatment that best stimulate recovery in order to guarantee functional movements. Here, we proposed a new approach for improving upper limb function in patients with stroke - GMI. GMI is feasible, inexpensive and easy to teach and learn for physiotherapists, as well as easy to deliver to patients. The treatment load was tolerable for patients and all patients were highly satisfied.

GMI was superior to the same amount of control therapy, inducing significant clinical improvements. Ten out of fourteen of our cohort reached or exceeded published MCID [27, 28] with a short GMI programme. We then calculated the NNT using the published MCID as

cut-off above which the treatment was considered effective. NNT for the GMI in stroke patients was 4.7. Considering our data in light of published work using similar cohorts, GMI is at least comparable with various experimental treatments - which have demonstrated their clinical efficacy.[30-33]

We used a matched control group to reduce biases due to natural recovery. We acknowledge patients in the GMI group were younger, but age differences were not statistically significant. In addition, our groups were comparable under all those demographical and clinical features that might influence functional recovery like stroke severity, time since stroke, aphasia, and motor function.[2, 3, 34] When taking all the variables into account, only stroke severity seemed to play a role in predicting functional recovery. This is not surprising and confirms other works on this topic.[34-36] Importantly however, the treatment effect remained significant despite the effect of the severity of stroke.

The IMI task revealed interesting outcomes. All patients demonstrated accuracy below the values considered normal for the left/right judgment task,[10] although reaction times were normal. This suggests that the IMI ability of these patients is impaired. Similarly, EMI scores were not high. However, to our knowledge, there is not a cut-off or a proposed score for KVIQ or other questionnaires used for the assessment of explicit motor imagery, which indicates when a subject has sufficient imaginative skills.

Whether good imaginative skills are a mandatory requirement for delivering motor imagery treatments or, on the contrary, motor imagery can be trained using a combination of EMI and IMI, and can be proposed also to those patients with poor imagery skills, is still unknown. We believe that would be an interesting clinical question but it was beyond the aim of this study. Here, we did not exclude patients because of poor imaginative skills. However, we made sure that patients' cognitive abilities were enough to understand each task and the overall treatment. We used the MMSE as an exclusion criteria and, where MMSE could not be used (*e.g.* because of poor language skills) we excluded patients with severe and global aphasia, given the strong association between cognitive function and language.[37] In addition, an expert neuropsychologist always confirmed that comprehension abilities were preserved on the basis of clinical judgment, before final enrolment.

Despite IMI and EMI explore the same cognitive skill (*i.e.* the ability to imagine a movement) our correlation analysis showed no correlation between the two, confirming a previous work.[38] This result suggests that implicit and explicit motor imagery are complementary and can be used in combination to train patient's imagery abilities. There are a number of studies exploring effectiveness of EMI for stroke rehabilitation.[5] There are conflicting results when EMI is provided as single treatment. However, when provided in addition to more conventional motor rehabilitation programmes EMI improves motor function.[39, 40]

On the contrary, IMI has not been studied in patients after stroke. IMI training using real photographs of hands and feet is a conceptually simple cognitive task, thus easy to comprehend as evidenced by robust data from children as young as five. [41] IMI has been widely studied in healthy adults,[42] people with chronic pain [15] or dizziness [43] and our data suggest this as an area worthy of further exploration. IMI can be used to train motor imagery abilities in people with stroke in combination with EMI training.

It is notable that GMI incorporates implicit motor imagery, EMI and MT. MT is increasingly gaining attention in the rehabilitation of patients with stroke, being a simple, low cost treatment that is thought to induce cortical activation and reorganization through mirror-induced visual illusions.[13, 44] MT shows some effectiveness for improving upper limb function, at least when added to conventional rehabilitation programmes.[45, 46] Not surprisingly, when arm paresis following stroke is severe, MT seems to have negligible effects.[9] Here, of the ten patients we enrolled in the GMI group with baseline FMA scores of less than 20, six exceeded the published MCID. On the contrary, no one showed a clinically important change in the control group. NNT for GMI in patients with severe arm paresis would be 3.3. Our data raise the exciting possibility that GMI may have a particular application in this group.

The theoretical underpinnings of GMI offer a feasible mechanism to explain our results. In pathological pain, the order of components of GMI seems critical to gain a positive significant effect.[11] Whereas explicit motor imagery can exacerbate the pain and motor impairment of CRPS,[47] implicit motor imagery does not. Moreover, with regard to explicit motor imagery is no longer problematic if it is undertaken after a period of implicit mo-

tor imagery. This finding corroborates the notion that IMI involves sub-threshold priming of primary motor cortex cells[12] and promotes cortical reorganisation to a less extent than EMI. Mirror therapy induces broader cortical activities [13, 46] and it is therefore the last step of GMI. Grading the exercises might be a key factor for patients with severe arm paresis.

Conclusions

Our aim was to establish the feasibility and potential of GMI for upper limb rehabilitation. Clinical features at baseline were variable within the current samples, which reflects our *a priori* decision to undertake a pragmatic study with consecutive patients, who would have variable time since stroke and different clinical presentations. Nonetheless, a more robust approach would be to include a randomised sampling, which, due to procedural issues, we were not in a position to do. We suggest that a randomised controlled trial is clearly warranted and we are currently recruiting patients; the study protocol has been registered on www.clinicaltrials.gov (Clinical Trials Identifier: NCT01993563).

References

1. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet 2011;377:1693-702.
2. Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery after stroke: a systematic review and meta-analysis. Clin Rehabil 2012;26:291-313.
3. Smania N, Paolucci S, Tinazzi M, et al. Active finger extension: A simple movement predicting recovery of arm function in patients with acute stroke. Stroke 2007;38:1088-90.
4. McInnes K, Friesen C, Boe S. Specific brain lesions impair explicit motor imagery ability: a systematic review of the evidence. Arch Phys Med Rehabil 2016;97:478-89.
5. Braun S, Kleynen M, van Heel T, Kruithof N, Wade D, Beurskens A. The effects of mental practice in neurological rehabilitation; a systematic review and meta-analysis. Front Hum Neurosci 2013;7:390.
6. Dohle C, Püllen J, Nakaten A, Küst J, Rietz C, Karbe H. Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. Neurorehabil Neural Repair 2008;23:209-17.
7. Osuagwu BA, Vuckovic A. Similarities between explicit and implicit motor imagery in mental rotation of hands: an EEG study. Neuropsychologia 2014;65:197-210.
8. Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Mirror therapy for improving motor function after stroke. Stroke 2013;44.
9. Thieme H, Bayn M, Wurg M, Zange C, Pohl M, Behrens J. Mirror therapy for patients with severe arm paresis after stroke--a randomized controlled trial. Clin Rehabil 2013;27:314-24.
10. Moseley GL. The graded motor imagery handbook. Noigroup publications; 2012.
11. Moseley GL. Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial. Pain 2005;114:54-61.
12. Parsons LM, Fox PT, Downs JH, Glass T, Hirsch TB, Martin CC, *et al.* Use of implicit motor imagery for visual shape discrimination as revealed by PET. Nature 1995;375:54-8.
13. Hamzei F, Lappchen CH, Glauche V, Mader I, Rijntjes M, Weiller C. Functional plasticity induced by mirror training: the mirror as the element connecting both hands to one hemisphere. Neurorehabil Neural Repair 2012;26:484-96.
14. Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: A randomised controlled trial. Pain 2004;108:192-8.
15. Bowering KJ, O'Connell NE, Tabor A, Catley MJ, Leake HB, Moseley GL, *et al.* The effects of graded motor imagery and its components on chronic pain: a systematic review and meta-analysis. J Pain 2013;14:3-13.
16. Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, *et al.* Primary motor cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain 2013;14:1270-88.
17. Manganotti P, Acler M, Zanette GP, Smania N, Fiaschi A. Motor cortical disinhibition during early and late recovery after stroke. Neurorehabil Neural Repair 2008;22:396-403.
18. Acerra NE, Souvlis T, Moseley GL. Stroke, complex regional pain syndrome and phantom limb pain: can commonalities direct future management? J Rehabil Med 2007;39:109-14.
19. Des Jarlais DC, Lyles C, Crepaz N. Improving the Reporting Quality of Nonrandomized Evaluations of Behavioral and Public Health Interventions: The TREND Statement. Am J Public Health 2004;94:361-6.
20. Luzzatti C, Willmes K, De Bleser R. New normative data for the Italian version of the Aachen Aphasia Test (A.A.T.). [Nuovi dati normativi per la versione italiana dell'Aachener Aphasie Test (A.A.T.)]. Arch di Psicol Neurol e Psichiatr 1994;55:1086-31.
21. Mehrholz J, Wagner K, Meissner D, Grundmann K, Zange C, Koch R, *et al.* Reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in adult patients with severe brain injury: a comparison study. Clin Rehabil 2005;19:751-9.
22. Wolf SL, Thompson PA, Morris DM, Rose DK, Winstein CJ, Taub E, *et al.* The EXCITE trial: attributes of the Wolf Motor Function Test in patients with subacute stroke. Neurorehabil Neural Repair 2005;19:194-205.
23. Platz T, Pinkowski C, van Wijck F, Kim I-H, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. Clin Rehabil 2005;19:404-11.
24. Piron L, Turolla A, Tonin P, Piccione F, Lain L, Dam M. Satisfaction with care in post-stroke patients undergoing a telerehabilitation programme at home. J Telemed Telecare 2008;14:257-60.
25. Malouin F, Richards CL, Durand A, Doyon J. Clinical assessment of motor imagery after stroke. Neurorehabil Neural Repair 2008;22:330-40.
26. Beaumont G, Mercier C, Michon PE, Malouin F, Jackson PL. Decreasing Phantom Limb Pain Through Observation of Action and Imagery: A Case Series. Pain Med 2011;12:289-99.
27. Lin K, Hsieh Y, Wu C, Chen C, Jang Y, Liu J. Minimal detectable change and clinically important difference of the Wolf Motor Function Test in stroke patients. Neurorehabil Neural Repair 2009;23:429-34.
28. Arya KN, Verma R, Garg RK. Estimating the minimal clinically important difference of an upper extremity recovery measure in subacute stroke patients. Top Stroke Rehabil 2011;18)(Suppl 1):599-610.
29. Rosner B. Fundamentals of biostatistics. Seventh Edition. Boston: MA Brooks/Cole, Cengage Learn; 2011.
30. Piron L, Turolla A, Agostini M, Zucconi CS, Ventura L, Tonin P, *et al.* Motor learning principles for rehabilitation: a pilot randomized controlled study in poststroke patients. Neurorehabil Neural Repair 2010;24:501-8.
31. Turolla A, Dam M, Ventura L, Tonin P, Agostini M, Zucconi C, *et al.* Virtual reality for the rehabilitation of the upper limb motor func-

tion after stroke: a prospective controlled trial. J Neuroeng Rehabil 2013;10:85.
32. Shimodozono M, Noma T, Nomoto Y, Hisamatsu N, Kamada K, Miyata R, *et al.* Benefits of a repetitive facilitative exercise program for the upper paretic extremity after subacute stroke: a randomized controlled trial. Neurorehabil Neural Repair 2013;27:296-305.
33. Platz T, van Kaick S, Mehrholz J, Leidner O, Eickhof C, Pohl M. Best conventional therapy versus modular impairment-oriented training for arm paresis after stroke: a single-blind, multicenter randomized controlled trial. Neurorehabil Neural Repair 2009;23:706-16.
34. Bamford J, Sandercock P, Dennis M, Warlow C, Burn J. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337:1521-6.
35. Kwakkel G, Kollen BJ, Van der Grond JV, Prevo AJH. Probability of regaining dexterity in the flaccid upper limb: Impact of severity of paresis and time since onset in acute stroke. Stroke 2003;34:2181-6.
36. Winters C, van Wegen EEH, Daffertshofer A, Kwakkel G. Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. Neurorehabil Neural Repair 2015;29:614-22.
37. Kang EK, Jeong HS, Moon ER, Lee JY, Lee KJ. Cognitive and language function in aphasic patients assessed with the Korean version of mini-mental status examination. Ann Rehabil Med 2016;40:152-61.
38. de Vries S, Tepper M, Feenstra W, Oosterveld H, Boonstra AM, Otten B. Motor imagery ability in stroke patients: the relationship between implicit and explicit motor imagery measures. Front Hum Neurosci 2013;7:790.
39. Page SJ, Levine P, Sisto S, Johnston MV. A randomized efficacy and feasibility study of imagery in acute stroke. Clin Rehabil 2001;15.
40. Timmermans AAA, Verbunt JA, van Woerden R, Moennekens M, Pernot DH, Seelen HAM. Effect of Mental Practice on the Improvement of Function and Daily Activity Performance of the Upper Extremity in Patients With Subacute Stroke: A Randomized Clinical Trial. J Am Med Dir Assoc 2013;14:204-12.
41. Dey a., Barnsley N, Mohan R, McCormick M, McAuley JH, Moseley GL. Are children who play a sport or a musical instrument better at motor imagery than children who do not? Br J Sports Med 2012;46:923-6.
42. Coslett HB, Medina J, Kliot D, Burkey AR. Mental motor imagery indexes pain: The hand laterality task. Eur J Pain 2010;14:1007-13.
43. Wallwork SB, Butler DS, Moseley GL. Dizzy people perform no worse at a motor imagery task requiring whole body mental rotation; a case-control comparison. Front Hum Neurosci 2013;7:258.
44. Ramachandran VS, Altschuler EL. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain 2009;132:1693-710.
45. Selles RW, Michielsen ME, Bussmann JBJ, Stam HJ, Hurkmans HL, Heijnen I, *et al.* Effects of a mirror-induced visual illusion on a reaching task in stroke patients: implications for mirror therapy training. Neurorehabil Neural Repair 2014;28:652-9.
46. Michielsen ME, Selles RW, van der Geest JN, Eckhardt M, Yavuzer G, Stam HJ, *et al.* Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. Neurorehabil Neural Repair 2011;25:223-33.
47. Moseley GL, Zalucki N, Birklein F, Marinus J, van Hilten JJ, Luomajoki H. Thinking about movement hurts: the effect of motor imagery on pain and swelling in people with chronic arm pain. Arthritis Rheum 2008;59:623-31.

Authors' contributions.—Andrea Polli had the scientific and intellectual responsibility of the study. He contributed to the scientific design of the study, recruitment and treatment of patients and both statistical and writing process. G. Lorimer Moseley contributed to the concept behind the study, design, statistical analysis, and had a major role in reviewing the entire manuscript. Elisabetta Gioia gave a substantial contribution to the conceptualization of the study and had a role in recruiting and treating patients. Tim Beames had an intellectual role in designing the treatment protocol and in the writing process. Alfonc Baba gave a substantial contribution to the conceptualization of the study and was in charge of patients' clinical assessment. Michela Agostini gave a substantial contribution with the study design and conceptualization. Paolo Tonin gave a substantial contribution with the study design and conceptualization. Andrea Turolla gave a substantial contribution to the statistical analysis and in study supervision.

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