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ELECTRICALLY ASSISTED MOVEMENT THERAPY IN CHRONIC STROKE PATIENTS WITH SEVERE UPPER LIMB PARESIS: A PILOT, SINGLE BLIND, RANDOMIZED CROSSOVER STUDY

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† Equal contributions

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Data presented are original and the material has never been published or presented before.

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ABSTRACT

Objective To evaluate the effects of a therapy where patients used self-modulated functional electrical stimulation to produce or assist task-specific upper limb movements, which enabled them to engage in intensive goal-oriented training. Functional electrical stimulation was modulated by a custom device controlled through the patient's unaffected hand. We defined our experimental intervention Electrically-Assisted Movement Therapy. Dose-matched goal-oriented standard care was used as a control intervention.

Design Randomized, crossover, assessor-blinded, 5-week trial with follow up at 18 weeks. This study is registered with ClinicalTrials.gov, number xxx.

Setting Rehabilitation University Hospital.

Participants A total of 11 chronic patients with severe stroke (mean age 47.9y), more than 6 months poststroke (mean time since event 46.3mo).

Interventions Each therapy consisted in 10 sessions of 90 minutes per day, five sessions per week, for two-weeks. After the first 10 sessions, group allocation was crossed-over, and patients received a one-week therapy break before receiving the new treatment.

Main Outcome Measures Fugl-Meyer Motor Assessment for the Upper Extremity, Wolf Motor Function Test, Spasticity, 28-Items Motor Activity Log.

Results 44 individuals were recruited, of whom 11 were eligible and participated. Five patients received the experimental treatment before standard care, and six received standard care before the experimental treatment. Electrically-Assisted Movement Therapy produced higher improvements in the Fugl-Meyer scale than standard care ($p<0.05$). Median improvements were 6.5 and 1 Fugl-Meyer points after the experimental treatment and standard care, respectively. The improvement was also significant in subjective reports of quality of movement and amount of use of the affected limb during activities of daily living ($p<0.05$).

Conclusions Electrically-Assisted Movement Therapy produces clinically important impairment reduction in stroke patients with chronic severe upper limb paresis.

Keywords: Electrical Stimulation Therapy, Cerebrovascular Accident, Hemiplegia, Motor Skills, Rehabilitation.

Abbreviations

EAMT: Electrically-Assisted Movement Therapy

SC: Standard Care

FES: Functional Electrical Stimulation

EMG: ElectromyographyFMA-UE: Fugl-Meyer Motor Assessment Upper Extremity

MAL: Motor Activity LogWMFT: Wolf Motor Function Test

REPAS: Resistance to passive movement

MRI: Magnetic Resonance Imaging

MCID: Minimal Clinically Important Difference

MDC: Minimum Detectable Change

CI: Confidence Interval

INTRODUCTION

Every year, 17 million people suffer a stroke worldwide, and approximately one third of them develop permanent upper limb paresis **(1)**. Among the available therapeutic approaches, functional electrical stimulation (FES) has been proposed as a viable intervention to increase range of motion **(2)** and to reduce upper limb impairment **(3)**, ultimately improving function and participation **(4)**. Many FES regimens and systems have been investigated **(5)**, but clear pathophysiological explications and protocols leading to improved efficacy are still lacking **(6)**.

FES regimens for the upper limb tested in clinical studies include cyclical FES, EMG-triggered FES, and neuroprosthetic FES. Cyclical stimulation produces repetitions of movements, without requiring patient's active participation **(2)**, and is often used in patients with severe impairments and absence of voluntary arm and hand activity. EMG-triggered FES is based on rewarding successful active attempts by the patient with a reinforcement signal in order to drive motor relearning and neuroplasticity **(7)**. To date, these two types of stimulation have not proven superior with respect to standard care **(2)** or other FES families **(7)**. Neuroprosthetic FES aims at promoting movement relearning by its ability to bypass lesions and restore function **(2)**. Neuroprostheses proposed in the past provided meaningful upper limb movements, and could produce pre-defined muscles activation sequences upon triggering by patients or therapists **(4, 8, 9)**. A special class of FES neuroprostheses enabled the control of FES at will by continuously detecting EMG activity, and promoted a significant reduction of impairment **(8).** Unfortunately, this type of self-modulated FES might be unfeasible in the severely impaired population due to abnormal or absent EMG patterns.

Providing a match between the intention to move the impaired limb and continuous FES assistance during the movement can be achieved without relying on paralyzed muscles activity by providing control means to the unaffected hand of the patient.

In this study, we introduce and test a therapy where patients with severe upper limb impairment self-modulate FES to produce or assist task-specific movements. A custom FES device enables them to engage in intensive goal-oriented training despite their impairment. We defined our experimental intervention "Electrically-Assisted Movement Therapy" (EAMT). During EAMT the use of the unaffected limb is limited by the need of operating the custom FES controller in order to self-modulate the delivery of electrical currents, and training is focused on the affected limb.

The purpose of this study is to determine whether EAMT produces higher improvements in upper limb motor impairment, skilled function, spasticity, and subjective perception of the ability to perform daily living tasks than dose-matched goal-oriented standard care (SC) in patients with severe upper limb paresis, more than six months after their stroke. This pilot study was designed in order to establish the presence of a clinically important effect on the selected population, and to estimate treatment effect sizes for further clinical testing **(10)**.

METHODS

Trial design

This study involved random allocation of patients and cross-over group assignment. This protocol was reviewed and approved by the xxx. This study is registered with ClinicalTrials.gov, number xxx.

Participants

Subjects of both genders, aged between 18 and 75, were eligible if they met the following inclusion criteria: diagnosis of one, first ever ischemic stroke verified by brain imaging (CT or MRI); chronic impairment after stroke (>6 months); no contraindications to neuromuscular electrical stimulation. Subjects were excluded if they showed unstable recovery stage, i.e. difference between two baseline examinations >1 point in the motor part of the Fugl-Meyer Assessment for the Upper Extremity scale (FMA-UE) **(11)**, mild-to-moderate impairment of the upper extremity (FMA-UE≥21), or excessive spasticity (median Ashworth Scale of the upper limb >2).

Interventions

Electrically-assisted movement therapy (EAMT) was achieved by using a custom FES device allowing patients to control and modulate the electrical stimulation using the unaffected hand in order to produce task-specific movements of the affected limb. The system allowed therapists to choose and reproduce movements of the whole paralyzed upper limb, re-engaging patients into goal-oriented exercises.

Whenever the patient had difficulties in simultaneously controlling the device and performing exercises, the therapist provided help and ensured the use of the affected limb. During each

session three types of exercises were possibly performed: mobilization, games, and training for activities of daily living (ADL). Therapy was provided in 10 sessions of 90 minutes per day over two consecutive weeks.

SC consisted in goal-oriented occupational therapy delivered as mobilization, games, and training for ADL. Therapy was provided in 10 sessions of 90 minutes per day over two consecutive weeks, to match the amount of EAMT. Standard care (SC) always excluded FES, CIMT, and Robotic training.

Progressive exercise shaping, behavioral training towards transfer of exercises to ADL, and daily administration of the Motor Activity Log (MAL) **(12)** were applied to both interventions, as formerly proposed in other effective treatments **(13, 14)**.

There were two investigation groups: EAMT-SC, where EAMT preceded SC, and SC-EAMT, where SC preceded EAMT.

Outcomes

The primary outcome measure was the change in FMA-UE. The threshold for assessing a minimal clinically important difference (MCID) between groups was set to 5.25 points **(15)**, and the minimum detectable change (MDC) between groups was 5.2 points (with no differentiation by severity of impairment) **(16, 17)**.

Secondary outcome measures were: Wolf Motor Function Test (WMFT) **(18)**; Resistance to Passive Movement (REPAS) to test hand and arm spasticity **(19)**; MAL **(12)**. Stroke type was classified using the Bamford classification **(21)**.

For each patient, brain lesions were delimited and measured (size) using the Medical Imaging Interaction Toolkit software from structural MRI acquired before trial start. Therapy was delivered at the xxxx of the xxx in xxx, xxx.

Clinical outcomes of patients assigned to EAMT-SC and SC-EAMT groups were collected at T0 (baseline), at T1 (week 3), T2 (week 6), and T3 (follow-up, week 18). One week before T0, the primary outcome measure was collected for all patients to ensure they were in a stable plateau of recovery. Patients were excluded if the difference between the two baseline examinations was >1.

Sample size

Sample size was determined through two-samples testing by estimating effect sizes for the two groups, assuming a statistical power of 80% and a significance level of 5%. Average treatment effects were estimated in 3.1 FMA-UE points for SC **(22)** and 8.35 FMA-UE points for EA. The choice of 8.35 points for EAMT is justified by the fact that, in order to be an effective treatment and yield an effect on the selected population, the therapy should be able to produce a MCID in the primary outcome. Standard deviations for both therapies were set to 3 FMA-UE points **(15)**, and accounted for the inactivity of patients that was ruled out after training.

Randomization

The allocation sequence was generated from a normally distributed pseudorandom number sequence of 12 elements in MATLAB®. Patients were allocated to therapy groups upon collection of the signed consent form. Random allocation sequence was sent to one representative of xxx and one of xxx, before trial start. Representatives had no contact with the assessor nor with patients during the whole study duration. Random allocation sequence was generated at xxx, and patients were enrolled and assigned to interventions by the clinical staff at xxx.

Blinding

The outcome assessor was a trained physician with more than 15 years of experience in neurological rehabilitation. The assessor was blinded to interventions after assignment, and had no access to the room where the therapy was delivered, preventing unwanted therapy unmasking.

Statistical analyses

The difference between treatment effects (EAMT vs SC) and negligible carry-over effects on primary and secondary outcomes were tested with an unpaired, two-tailed Mann-Whitney U-test **(23)**. Within-subjects differences of the relative improvements at T1 and at T2 were tested to detect a significant effect of the therapy type, and within-subjects sums of the relative improvements at T1 and T2 were tested to confirm negligible carry-over effects. Asymptotic p-values are reported in order to account for ties in the ranking procedure.

Difference between treatment effects

Null Hypothesis: $[(R1\text{-}R2)_{EAMT\text{-}SC}]$ and $[(R1\text{-}R2)_{SC\text{-}EAMT}]$ have equal medians, rejected if $p<0.05$

Negligible carry-over effects

Null Hypothesis: $[(R1+R2)_{EAMT\text{-}SC}]$ and $[(R1+R2)_{SC\text{-}EAMT}]$ have equal medians, rejected if $p<0.05$

One of the patients in the SC-EAMT group dropped out from the study for unrelated medical reasons, and her evaluation at T2 was missed. For this reason, only the 10 patients that received therapy in both periods were considered to test the difference between treatment effects. All available data was used in order to estimate effect sizes (intent-to-treat).

Two patients assigned to the EAMT-SC group took a longer washout period than the other patients in the group, namely eight and six weeks instead of one: evaluations were repeated before starting the second therapy period in order to check for carry-over effects (evaluation T1*). We estimated the effect of EAMT by using T0 and T1 evaluations and the effect of SC by using T1* and T2 evaluations for the two patients who received longer washout, i.e. leaving uncontrolled recovery outside analyses. Carry-over effects were checked by conservatively including uncontrolled recovery into the second therapy period, i.e. by checking for statistical differences in T1-T0 against T2-T1, for all patients.

Post-hoc tests of between-groups differences of the relative improvement in primary and secondary outcome measures were tested with an unpaired, two-tailed Mann-Whitney U-test.

Within-groups differences of the relative improvement in primary and secondary outcome values were tested with paired, two-tailed Wilcoxon signed-rank test. In both cases, significance levels were Bonferroni corrected to account for multiple comparisons.

Differences in the occurrence of large recoveries of at least 5 FMA-UE points after either treatment were tested by means of two-tailed Chi-square test. Odds ratio of large recoveries was calculated by computing the geometrical average of the U-statistic: $r=Z/\sqrt{N}$.

All calculations and statistical analyses were computed with IBM SPSS Statistics 20®.

RESULTS

Between September 28, 2015 and January 11, 2016, 44 individuals were tested for eligibility, of whom 11 were eligible and agreed to participate.

Five patients were assigned to the EAMT-SC group and six were assigned to the SC-EAMT group. Their data was included and analyzed for the primary and secondary outcome measures.

Patients' demographics and clinical characteristics at baseline are reported in **Table 1**, while detailed single-patient data are shown in **Supplementary Table 1**. There were no statistically significant differences between groups at baseline.

Relative improvements with respect to previous evaluation in primary and secondary outcome measures are reported in **Table 2**, along with the corresponding p-values for the main cross-over and carry-over effects.

Absolute changes in primary and secondary outcome measures are reported in **Table 3**.

---------- *please insert Table 1, 2, and 3 approximately here* ----------

Primary outcome

Improvements after the first and the second period, i.e. differences between scores at T1-T0 and scores at T2-T1, scored higher in the EAMT-SC group (median=16; mean rank=3.00) than in the SC-EAMT group (median=-4; mean rank=3.00), as shown in **Figure 1**. Mann-Whitney U-value was found to be statistically significant U=3.00 (Z=-1.984), $p<0.05$, as reported in **Table 2**. The difference between recoveries was large (r=-.88), and no significant carry-over effects were found (p=0.075).

---------- *please insert Figure 1 approximately here* ----------

Relative improvements with respect to baseline were not significantly different between groups at T1, although the average recovery was larger in the EAMT-SC group (12.2±6.7 FMA-UE points for EAMT-SC and 4.3±4.4 for SC-EAMT), nor at T2 (16.4±5.8 FMA-UE points for EAMT-SC and 8.6±4.5 for SC-EAMT). Changes in absolute FMA-UE scores are reported in **Table 3** and **Supplementary Figure 1**. The absence of a significant difference in

recovery between groups at T2 with respect to T0 determines a negligible carry-over effect in the primary outcome measure **(4)**. In addition, relative recovery at T2 with respect to T1 was not significantly different between groups (0.8±1.7 FMA-UE points for EAMT-SC and 4.8±4.8 for SC-EAMT). Median improvements disregarding when therapies were provided were 6.5 and 1 FMA-UE points after EAMT and SC, respectively. The difference in recovery between therapies is greater than the MDC and MCID.

Follow-up evaluations revealed that six of the ten patients that were assessed still reported a large recovery with respect to T0 (baseline), and three of these six patients showed a further improvement >5 FMA-UE points with respect to T2. Detailed single-patient primary outcome data are shown in **Supplementary Figure 2**. At the follow up evaluation, the improvement with respect to T0 was 12.4±7.8 and 12.2±10.6 FMA-UE points for the EAMT-SC and SC-EAMT groups, respectively.

Cumulating the effects of the two consecutive therapies, 10/11 patients achieved a large recovery. Large recoveries were more frequent after two weeks of EAMT (70% of the patients) than after two weeks of SC (27% of the patients, Chi-square=3.834, p=0.05). After EAMT, they occurred at T1 (4/5 patients) and at T2 (3/5 patients), while after SC they occurred only at T1 (3/6 patients). The odds of achieving a large recovery after receiving EAMT were 6.22 times higher than after SC (95% CI:0.9-41.3).

Secondary outcomes

Significantly higher improvements after EAMT than after SC were found for self-reported

MAL amount of use ($p<0.05$) and MAL quality of movement ($p<0.05$), as shown in **Figure 1**. No significant carry-over effects were found in these two measures, as reported in **Table 2**. Recovery in FMA-UE scores was moderately correlated to recovery in MAL quality of movement scores ($r=0.57$, $p<0.01$) and MAL amount of use score ($r=0.51$, $p<0.05$). Although their change was not significant, WMFT time scores were improved at T1 and T2 with respect to T0 (EAMT-SC was 6.4±9.6 s faster at T1 and further 6.4±7.0 s faster at T2; SC-EAMT was 1.3±3.3 s slower at T1 but 4.4±5.9 s faster at T2). REPAS did not change significantly during the study.

Lesion volumes, reported in **Supplementary Table 1**, were not correlated with any relative or absolute measure of the primary outcome.

DISCUSSION

We have shown that self-modulated FES and intensive goal-oriented training of the affected limb result in clinically relevant reduction of impairment in chronic stroke patients with severe paresis. One and a half hours of EAMT five times a week for two weeks had 6.22 times higher odds of large recovery in the primary outcome measure than dose-matched SC. Although our results in primary and secondary outcomes indicate early evidence of superiority of EAMT with respect to SC, superiority should be properly investigated in later stage clinical trials with higher statistical power. To this aim, effect sizes estimates for EAMT and SC were found to be 6.5 and 1 FMA-UE points, respectively. The difference between

these treatment effects was above the MDC and the MCID. Follow-up evaluations showed retention or further improvement of function in patients that were able to achieve substantial gains already at T2, i.e. at the end of the interventional period.

This is the first time to the best of our knowledge that a therapy regimen involving self-modulated FES of the affected limb results in clinically relevant improvement in patients with severe impairment. The idea of using contralateral hand to control FES is not novel **(24)**, although former studies focused the treatment on the hand only **(24, 25)**. As already observed in the past, the timeliness and regimens of FES produce substantially different outcomes in stroke patients **(6)**. FES is a powerful ally of other effective treatments in neurorehabilitation for its capacity to provide limb actuation, rich afferent stimulation in sensation and proprioception, and increase cortical excitability in the short time scale **(26)**. Our results show that combining coarse and imprecise movements generated via FES to volitional attempts and residual capability in order to complete tasks of progressive complexity can improve movement relearning and perceived functionality of the affected limb. We cannot exclude, as pointed out from recent studies **(27)**, that some effect may arise directly from sensory stimulation coupled with goal-oriented training. Another recent study **(28)** has shown that EMG-triggered FES is not better than conventional care in absence of fingers extension, relating this finding to a potential involvement of corticospinal integrity **(29)**. In our study, only one of the patients presented partial fingers extension at baseline, but nonetheless we observed large recoveries, motivating further research in self-modulated stimulation assisting training of daily living tasks.

This pilot study was limited by the small sample size, and results should be replicated on a

larger population of patients. Assessor blinding and trial design ensured the absence of confirmatory bias at T1 towards one of the groups. Nevertheless, effect sizes of both groups might have been inflated by the fact that the assessor knew that patients received some form of therapy before T1 and before T2, so effect sizes should be taken cautiously.

Two patients that received EAMT as first therapy took a longer washout period than scheduled, reporting consistent increases during this uncontrolled time. The statistical analyses did not include this uncontrolled recovery except for the carry-over effects. Although these effects were negligible in the context of this study, further studies should be designed to account for this potential source of bias, i.e. avoiding the cross-over design. The recovery during uncontrolled time after EAMT could be explained by the fact that both patients reported attempting to use their affected limb more often at home.

In addition, the current study design did not allow us to provide an explanation regarding the difference in recovery between groups achieved in the first period of treatment with respect to the second. We speculate that this may be due to: i) allocation specific difference in motivation in patients who may see more rapid progress in one of the groups; ii) a neurophysiologic phenomenon favoring improvements within the scale of two weeks and penalizing later improvements that occur later in time; iii) small sample size, although known cofactors were balanced between groups (age, time since event, lesion type, baseline FMA-UE score).

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133(4):e38-360.
2. Alon G, Levitt AF, McCarthy PA. Functional electrical stimulation (FES) may modify the poor prognosis of stroke survivors with severe motor loss of the upper extremity: a preliminary study. Am J Phys Med Rehabil. 2008;87(8):627-36.
3. Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist extensors in poststroke hemiplegia. Stroke. 1999;30(7):1384-9.
4. Thrasher TA, Zivanovic V, McIlroy W, Popovic MR. Rehabilitation of reaching and grasping function in severe hemiplegic patients using functional electrical stimulation therapy. Neurorehabil Neural Repair. 2008;22(6):706-14.
5. Peckham PH, Knutson JS. Functional electrical stimulation for neuromuscular applications. Annu Rev Biomed Eng. 2005;7:327-60.
6. Pomeroy VM, King L, Pollock A, Baily-Hallam A, Langhorne P. Electrostimulation for promoting recovery of movement or functional ability after stroke. Cochrane Database Syst Rev. 2006(2):CD003241.
7. Wilson RD, Page SJ, Delahanty M, Knutson JS, Gunzler DD, Sheffler LR, et al. Upper-Limb Recovery After Stroke: A Randomized Controlled Trial Comparing EMG-Triggered, Cyclic, and Sensory Electrical Stimulation. Neurorehabil Neural Repair. 2016;30(10):978-87.
8. Hu XL, Tong RK, Ho NS, Xue JJ, Rong W, Li LS. Wrist Rehabilitation Assisted by an Electromyography-Driven Neuromuscular Electrical Stimulation Robot After Stroke. Neurorehabil Neural Repair. 2015;29(8):767-76.

9. Popovic DB, Popovic MB, Sinkjaer T, Stefanovic A, Schwirtlich L. Therapy of paretic arm in hemiplegic subjects augmented with a neural prosthesis: a cross-over study. Can J Physiol Pharmacol. 2004;82(8-9):749-56.

10. Dobkin BH. Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor Interventions. Neurorehabil Neural Repair. 2009;23(3):197-206.

11. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. Phys Ther. 1993;73(7):447-54.

12. Uswatte G, Taub E, Morris D, Light K, Thompson PA. The Motor Activity Log-28: assessing daily use of the hemiparetic arm after stroke. Neurology. 2006;67(7):1189-94.

13. Morris DM, Taub E, Mark VW. Constraint-induced movement therapy: characterizing the intervention protocol. Eura Medicophys. 2006;42(3):257-68.

14. Taub E, Uswatte G, Mark VW, Morris DM, Barman J, Bowman MH, et al. Method for enhancing real-world use of a more affected arm in chronic stroke: transfer package of constraint-induced movement therapy. Stroke. 2013;44(5):1383-8.

15. Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. Phys Ther. 2012;92(6):791-8.

16. Lin JH, Hsu MJ, Sheu CF, Wu TS, Lin RT, Chen CH, et al. Psychometric comparisons of 4 measures for assessing upper-extremity function in people with stroke. Phys Ther. 2009;89(8):840-50.

17. Wagner JM, Rhodes JA, Patten C. Reproducibility and minimal detectable change of three-dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke. Phys Ther. 2008;88(5):652-63.

18. Morris DM, Uswatte G, Crago JE, Cook EW, 3rd, Taub E. The reliability of the wolf motor function test for assessing upper extremity function after stroke. Arch Phys Med Rehabil. 2001;82(6):750-5.

19. Platz T, Vuadens P, Eickhof C, Arnold P, Van Kaick S, Heise K. REPAS, a summary rating scale for resistance to passive movement: item selection, reliability and validity. Disabil Rehabil. 2008;30(1):44-53.

20. Hantson L, De Weerdt W, De Keyser J, Diener HC, Franke C, Palm R, et al. The European Stroke Scale. Stroke. 1994;25(11):2215-9.

21. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337(8756):1521-6.

22. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2):159-66.

23. Díaz-Uriarte R. Incorrect analysis of crossover trials in animal behaviour research. . Anim Behav. 2002;63(4):815-22.

24. Knutson JS, Harley MY, Hisel TZ, Chae J. Improving hand function in stroke survivors: a pilot study of contralaterally controlled functional electric stimulation in chronic hemiplegia. Arch Phys Med Rehabil. 2007;88(4):513-20.

25. Knutson JS, Gunzler DD, Wilson RD, Chae J. Contralaterally Controlled Functional Electrical Stimulation Improves Hand Dexterity in Chronic Hemiparesis: A Randomized Trial. Stroke. 2016;47(10):2596-602.

26. Barsi GI, Popovic DB, Tarkka IM, Sinkjaer T, Grey MJ. Cortical excitability changes following grasping exercise augmented with electrical stimulation. Exp Brain Res. 2008;191(1):57-66.

27. Carrico C, Chelette KC, 2nd, Westgate PM, Powell E, Nichols L, Fleischer A, et al. Nerve Stimulation Enhances Task-Oriented Training in Chronic, Severe Motor Deficit After Stroke: A Randomized Trial. Stroke. 2016;47(7):1879-84.

28. Kwakkel G, Winters C, van Wegen EE, Nijland RH, van Kuijk AA, Visser-Meily A, et al. Effects of Unilateral Upper Limb Training in Two Distinct Prognostic Groups Early After Stroke: The EXPLICIT-Stroke Randomized Clinical Trial. Neurorehabil Neural Repair. 2016;30(9):804-16.

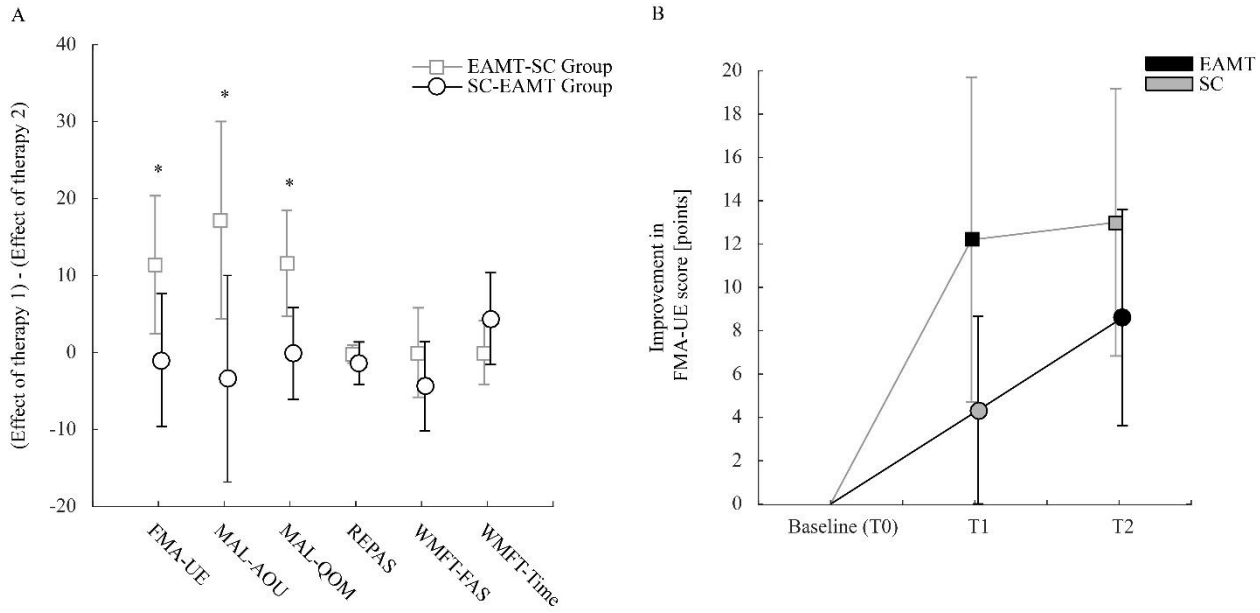
29. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012;135(Pt 8):2527-35.

SUPPLIERS

a. Matlab2014a, The MathWorks, Inc., Natick, Massachusetts, United States
b. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.
c. Medical Imaging Interaction Toolkit (MITK), available on http://mitk.org/wiki/MITK

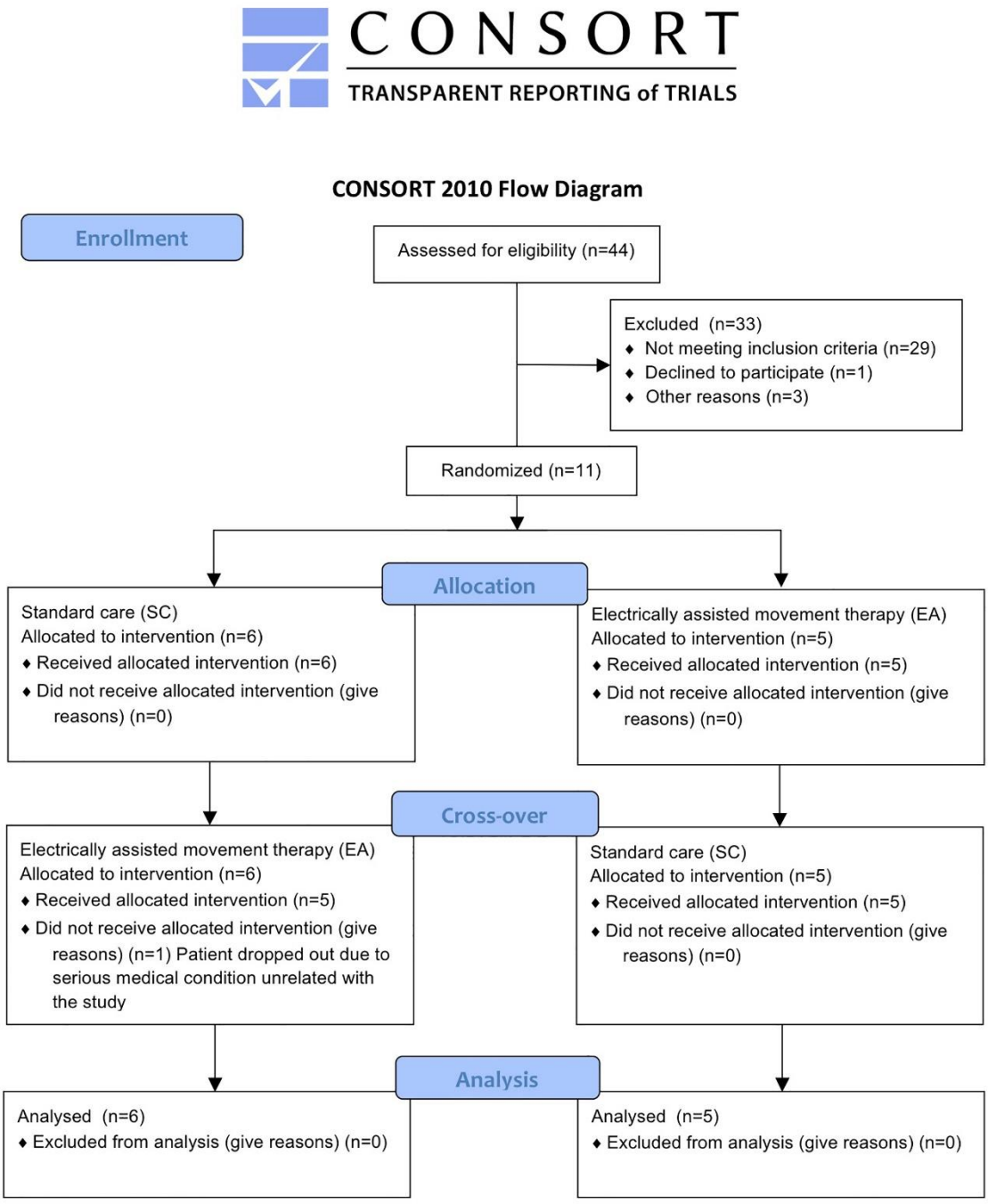
Figures

Figure 1 – Clinical effects.



A) Main cross-over effect in primary and secondary outcomes. The main cross-over effect is assessed by comparing the difference between the two responses to therapy between groups. In other words, each patient provides a single value indicating how much the first therapy provided a larger response than the second therapy; for the EAMT-SC group, the vector indicates how larger the improvement following EAMT was with respect to the improvement due to SC, and viceversa for the SC-EAMT group. B) Relative improvement in FMA-UE, the primary outcome measure of this study, with respect to the baseline evaluation at T0. Patients of the EAMT-SC group received EAMT between T0 and T1, and further received SC between T1 and T2. On the contrary, patients of the SC-EAMT group received SC between T0 and T1, and further received EAMT between T1 and T2.

15 **Figure 2– CONSORT flow diagram.**



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Tables

Table 1 – **Baseline demographics and clinical characteristics.**

	EAMT-SC (N = 5)	SC-EAMT (N = 6)	p-value
Gender			
Male, n (%)	4 (80)	3 (50)	0.54†
Age [y]			
Mean ± SD	45.6 ± 14.5	49.8 ± 13.3	0.66‡
Age group (%)			
18 - 30, n (%)	1 (20)	0 (0)	
31 - 45, n (%)	1 (20)	3(50)	
45 - 65, n (%)	3 (60)	3 (50)	
>65, n (%)	0 (0)	0 (0)	
Time Since Event [mo]			
Mean ± SD	52 ± 50.5	41.5 ± 31.7	1‡
Lesion side			
Right hemisphere, n (%)	2 (40)	4 (66)	0.57†
Stroke type			
TACI, n (%)	4 (80)	4 (66)	1†
FMA-UE at T0			
Mean ± SD	11 ± 6	13.2 ± 5.4	0.54‡

† Fisher's Exact Test (two-tailed) ; ‡ Independent Samples Mann-Whitney U-test

EAMT-SC: this group of patients received electrically-assisted movement therapy before standard care; SC- EAMT: this group of patients received standard care before electrically-assisted movement therapy. TACI: Total Anterior Circulation Infarct. FMA-UE: Fugl-Meyer Assessment for the Upper Extremity.

Table 2 – **Primary and secondary outcomes, relative improvement with respect to previous evaluation.**

	Evaluation		p-value cross-over (Hp: EAMT-SC ≠ SC-EAMT) ‡	p-value carry-over (Hp: EAMT+SC ≠ SC+EAMT) ‡
	T1-T0	**T2-T1**		
FMA-UE			**0.047**	0.075
EAMT-SC	12.2 ± 6.7	0.8 ± 1.7		
SC-EAMT	4.3 ± 4.4	4.8 ± 4.8		
WMFT time			0.147	0.459
EAMT-SC	-6.4 ± 9.6	-6.4 ± 7.0		
SC-EAMT	1.3 ± 3.3	-4.4 ± 5.9		
WMFT-FAS			0.341	0.169
EAMT-SC	3.2 ± 3.7	3.2 ± 3.3		
SC-EAMT	0.0 ± 0.0	4.4 ± 5.9		
REPAS			0.527	0.167
EAMT-SC	1.0 ± 1.7	1.2 ± 2.3		
SC-EAMT	-0.7 ± 1.5	0.5 ± 2.4		
MAL-AOU			**0.036**	0.207
EAMT-SC	14.4 ± 10.7	-2.8 ± 5.0		
SC-EAMT	3.7 ± 12.4	3.8 ± 5.2		
MAL-QOM			**0.028**	0.059
EAMT-SC	13.6 ± 8.0	0.8 ± 5.0		
SC-EAMT	4.0 ± 8.5	0.9 ± 3.7		

‡ Independent Samples Mann-Whitney U-test

Hp: statistical hypothesis that was tested; EAMT-SC≠SC-EAMT: main cross-over effect, i.e. the difference of first and second therapy effects is significantly different between groups; EAMT+SC≠SC+EAMT: carry-over effect, i.e. the sum of first and second therapy effects is significantly different between groups; statistically significant p-values are reported in bold. FMA-UE: Fugl-Meyer Assessment for the Upper Extremity; WMFT time: Wolf Motor Function Test timing (in seconds); WMFT-FAS: Wolf Motor Function Test Functional Activity Scale; REPAS: Resistance to Passive Movement Scale; MAL-AOU: Motor Activity Log Amount Of Use; MAL-QOM: Motor Activity Log Quality Of Movement. Improvements are reported as

mean ± standard deviation of the individual change within each group. EAMT-SC: this group of patients received electrically-assisted movement therapy before standard care; SC- EAMT: this group of patients received standard care before electrically-assisted movement therapy.

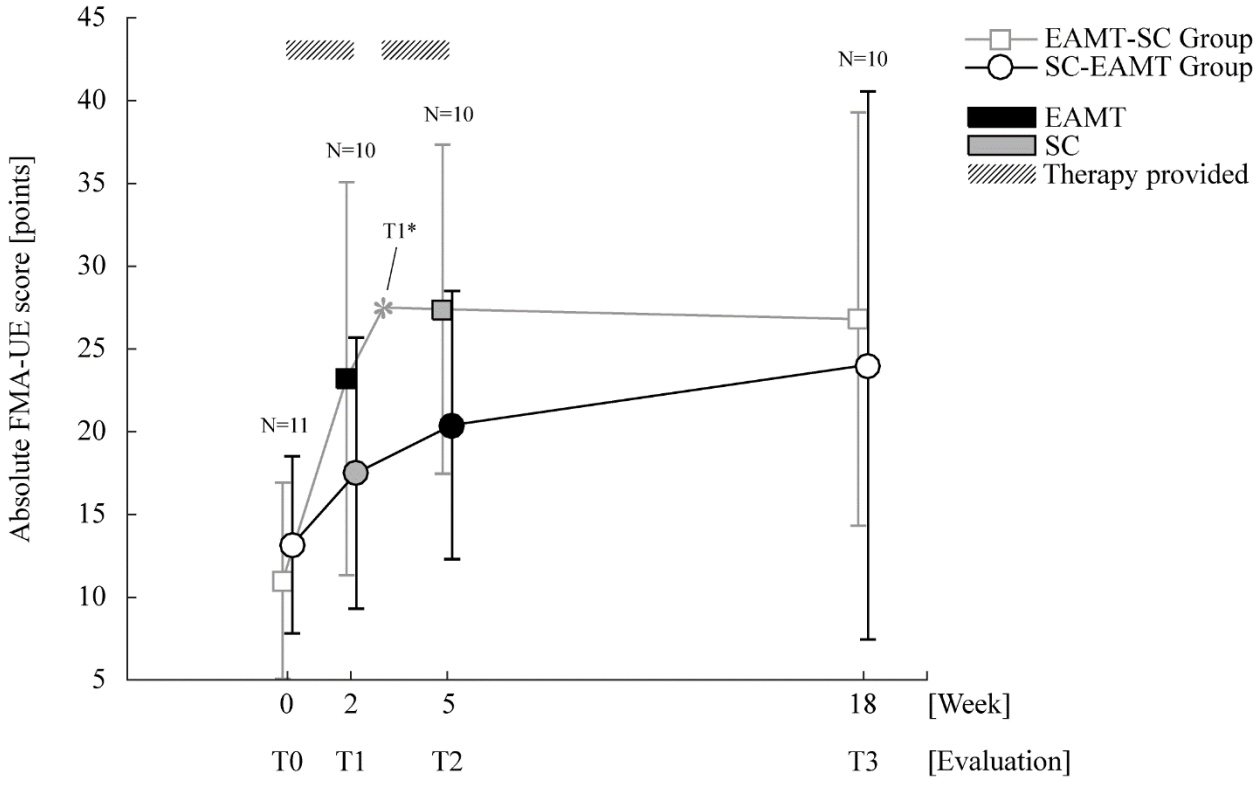
Table 3 – Primary and secondary outcomes, absolute group scores across the study.

	T0	T1	T1*	T2	T3
FMA-UE					
EAMT-SC	11±5.4	23.2±10.7	26.6±9.6	27.4±9	26.8±11.2
SC-EAMT	13.2±4.9	17.5±7.5		20.4±7.3	24±14.9
WMFT time					
EAMT-SC	99.8±20.3	93.4±18.5	89±17.7	82.6±19.6	85±21.6
SC-EAMT	86.2±31.3	87.5±30		88.4±32.4	87.2±31.7
WMFT-FAS					
EAMT-SC	12.6±10.8	15.8±13.5	19.6±11.7	22.8±11.8	23±12.8
SC-EAMT	14.8±11.3	14.8±11.3		16.4±14.1	20.6±18.8
REPAS					
EAMT-SC	9.2±5.2	10.2±6.4	8.8±4.3	10±5.3	10.4±7
SC-EAMT	8.8±3.7	8.2±3		9.4±1.5	10.6±1.5
MAL-AOU					
EAMT-SC	4.2±7	18.6±11.1	17.2±12.5	18.6±10.2	22.4±16.2
SC-EAMT	7±10.7	10.7±7.4		12.6±8.3	21.1±27.3
MAL-QOM					
EAMT-SC	4±7	17.6±10.4	18.6±10.4	19.4±11	20.8±13.9
SC-EAMT	5.7±8	9.7±7.7	0±0	8.5±9.5	18±29.1

FMA-UE: Fugl-Meyer Assessment for the Upper Extremity; WMFT time: Wolf Motor Function Test Timing (in seconds); WMFT-FAS: Wolf Motor Function Test Functional Activity Scale; REPAS: Resistance To Passive Movement; MAL-AOU: Motor Activity Log Amount Of Use; MAL-QOM: Motor Activity Log Quality Of Movement. Scores changes are reported as mean ± standard deviation of the absolute scores within each group. EAMT-SC: electrically-assisted movement therapy before standard care; SC- EAMT: standard care before electrically-assisted movement therapy. T1* group mean and standard deviation was calculated by including T1* evaluations instead of T1 evaluations for the two patients who took a longer washout period.

Supplementary material

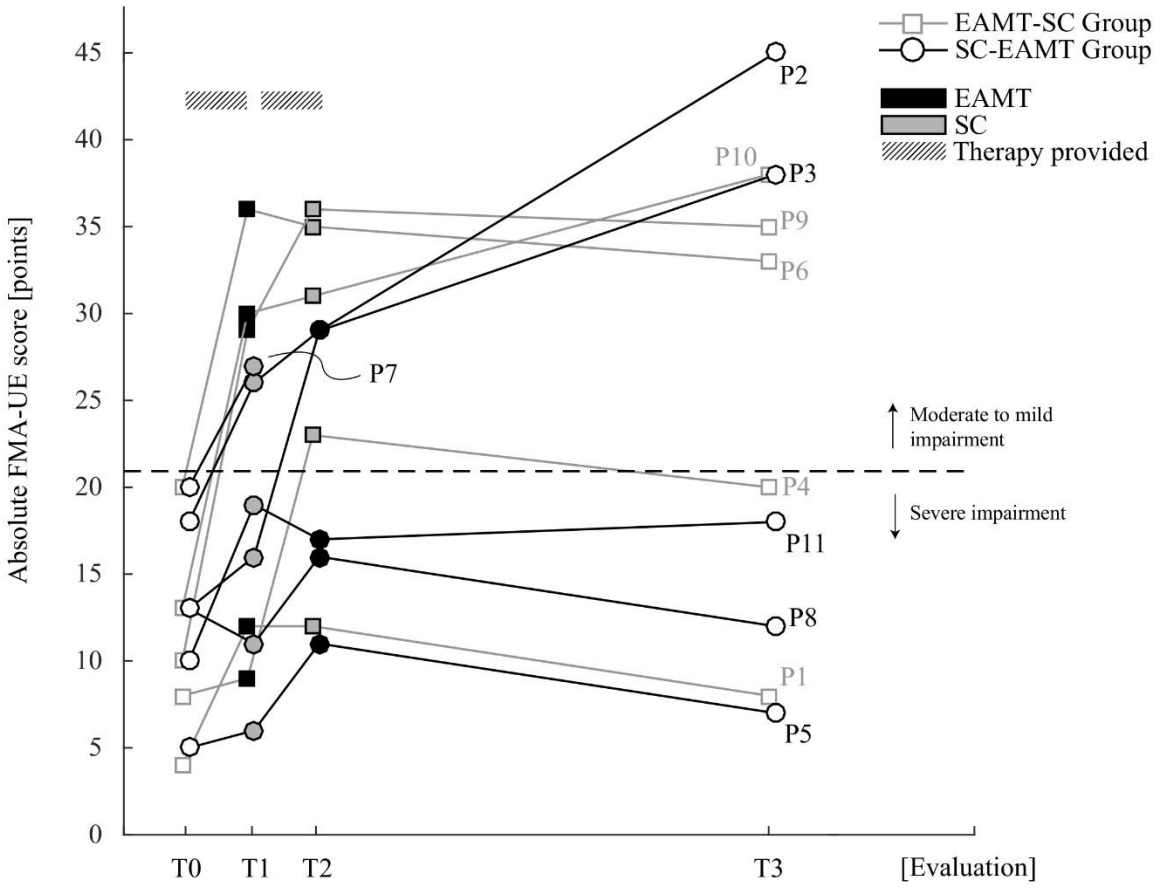
Supplementary Figure 1 – Change in primary outcome metric including the follow-up assessment.



Absolute change in FMA-UE at all evaluations, displayed by group. Therapy was only provided between T0 and T1 and between T1 and T2. T1 was collected of the beginning of the washout week between the two therapies. T1* group average was calculated by including T1* evaluations instead of T1 evaluations for the two patients who took a longer washout period.

Supplementary Figure 2 – Single-patient primary outcome data.

A



B

Patient	Allocation	Absolute FMA-UE Scores					Relative FMA-UE Improvements			
		T0	T1	T1*	T2	T3	T1-T0	T2-T1	T2-T0	T3-T0
P1	EAMT-SC	4	12		12	8	8	0	8	4
P2	SC-EAMT	18	26		29	45	8	3	11	27
P3	SC-EAMT	13	16		29	38	3	13	16	25
P4	EAMT-SC	8	9	19	23	20	1	4	15	12
P5	SC-EAMT	5	6		11	7	1	5	6	2
P6	EAMT-SC	20	36		35	33	16	-1	15	13
P7	SC-EAMT	20	27				7			
P8	SC-EAMT	13	11		16	12	-2	5	3	-1
P9	EAMT-SC	10	29	36	36	35	19	0	26	25
P10	EAMT-SC	13	30		31	38	17	1	18	25
P11	SC-EAMT	10	19		17	18	9	-2	7	8

A) Graphical representation of the change of FMA-UE scores for each patient. Each trajectory represents the evolution of FMA-UE score of a patient. B) Individual FMA-UE scores at T0, T1, T2, and T3 evaluations. Patients 4 and 9 took a longer washout time than the others, and were screened at T1* before starting the second therapy. Relative improvements for those two patients were calculated as T1-T0 and T2-T1*. Patient 7 dropped out after receiving SC for medical reasons unrelated to this study. We also report the change of FMA-UE score after both therapies with respect to baseline (i.e. T2-T0) and the overall change 18 weeks after therapy start with respect to baseline (i.e. T3-T0).

Supplementary Table 1 – Single-patient demographics and lesions characteristics.

Patient	Allocation	Age [y]	TSE [mo]	Side	Type	Volume [mm3]	Location
P1	EAMT-SC	62	133	R	TACI	347,638†	Fronto-Parieto-Temporal Cortex.
P2	SC-EAMT	33	9	R	PACI	5,372	Internal Capsule (Basal Ganglia).
P3	SC-EAMT	34	9	L	TACI	169,016	Temporo-Parieto-Prefrontal Cortex.
P4	EAMT-SC	44	16	L	PACI	49,821	Insula and Basal Ganglia.
P5	SC-EAMT	63	98	R	TACI	n/a	White Matter and Basal Ganglia‡.
P6	EAMT-SC	19	13	L	TACI	653,506	Fronto-Parieto-Temporo-Occipital Cortex, Insula, and Basal Ganglia.
P7	SC-EAMT	62	63	R	PACI	36,204	Fronto-Insular Cortex.
P8	SC-EAMT	63	26	L	TACI	101,853	Temporo-Parietal Cortex and Insula.
P9	EAMT-SC	52	90	L	TACI	55,934†	White Matter-Fronto-Patietal.
P10	EAMT-SC	51	8	R	TACI	221,575	Fronto-Parietal Cortex and Insula.
P11	SC-EAMT	44	44	R	TACI	222,839	Temporo-Parieto-Frontal Cortex.

TSE: time since event. TACI: total anterior circulation infarct. PACI: partial anterior circulation infarct. Lesion side referred to R: right hemisphere, and L: left hemisphere. All patients presented an ischemic lesion. Lesion volumes and lesion locations were assessed by means of magnetic resonance imaging performed before trial start, except for the marked cases where data were †: images were retrieved from former MRI scan and ‡: images were retrieved from former CT scan.