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

4

5

6 **ABSTRACT**

7

8

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

15

16 **Design** Randomized, crossover, assessor-blinded, 5-week trial with follow up at 18 weeks.

17 This study is registered with ClinicalTrials.gov, number xxx.

18

19 **Setting** Rehabilitation University Hospital.

20

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

23

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

27

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

30

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

39

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

42

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

45

46 **Abbreviations**

47 EAMT: Electrically-Assisted Movement Therapy

48 SC: Standard Care

49 FES: Functional Electrical Stimulation

50 EMG: Electromyography FMA-UE: Fugl-Meyer Motor Assessment Upper Extremity

51 MAL: Motor Activity Log WMFT: Wolf Motor Function Test

52 REPAS: Resistance to passive movement

53 MRI: Magnetic Resonance Imaging

54 MCID: Minimal Clinically Important Difference

55 MDC: Minimum Detectable Change

56 CI: Confidence Interval

57

58 INTRODUCTION

59

60

61 Every year, 17 million people suffer a stroke worldwide, and approximately one third of them
62 develop permanent upper limb paresis **(1)**. Among the available therapeutic approaches,
63 functional electrical stimulation (FES) has been proposed as a viable intervention to increase
64 range of motion **(2)** and to reduce upper limb impairment **(3)**, ultimately improving function
65 and participation **(4)**. Many FES regimens and systems have been investigated **(5)**, but clear
66 pathophysiological explications and protocols leading to improved efficacy are still lacking
67 **(6)**.

68 FES regimens for the upper limb tested in clinical studies include cyclical FES, EMG-
69 triggered FES, and neuroprosthetic FES. Cyclical stimulation produces repetitions of
70 movements, without requiring patient's active participation **(2)**, and is often used in patients
71 with severe impairments and absence of voluntary arm and hand activity. EMG-triggered FES
72 is based on rewarding successful active attempts by the patient with a reinforcement signal in
73 order to drive motor relearning and neuroplasticity **(7)**. To date, these two types of stimulation
74 have not proven superior with respect to standard care **(2)** or other FES families **(7)**.

75 Neuroprosthetic FES aims at promoting movement relearning by its ability to bypass lesions
76 and restore function **(2)**. Neuroprostheses proposed in the past provided meaningful upper
77 limb movements, and could produce pre-defined muscles activation sequences upon
78 triggering by patients or therapists **(4, 8, 9)**. A special class of FES neuroprostheses enabled
79 the control of FES at will by continuously detecting EMG activity, and promoted a significant
80 reduction of impairment **(8)**. Unfortunately, this type of self-modulated FES might be
81 unfeasible in the severely impaired population due to abnormal or absent EMG patterns.

82

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

86

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

94

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

101

102 **METHODS**

103

104

105 *Trial design*

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

109

110 *Participants*

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

119 *Interventions*

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

125

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

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

131

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

136

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

140

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

143

144 *Outcomes*

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

149

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

153

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

157

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

163

164 *Sample size*

165 Sample size was determined through two-samples testing by estimating effect sizes for the
166 two groups, assuming a statistical power of 80% and a significance level of 5%. Average
167 treatment effects were estimated in 3.1 FMA-UE points for SC (**22**) and 8.35 FMA-UE points
168 for EA. The choice of 8.35 points for EAMT is justified by the fact that, in order to be an
169 effective treatment and yield an effect on the selected population, the therapy should be able
170 to produce a MCID in the primary outcome. Standard deviations for both therapies were set to
171 3 FMA-UE points (**15**), and accounted for the inactivity of patients that was ruled out after
172 training.

173

174 *Randomization*

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

182

183 *Blinding*

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

188

189 *Statistical analyses*

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

196 Difference between treatment effects

197 Null Hypothesis: $[(R1-R2)_{EAMT-SC}]$ and $[(R1-R2)_{SC-EAMT}]$ have equal medians, rejected if
198 $p < 0.05$

199 Negligible carry-over effects

200 Null Hypothesis: $[(R1+R2)_{EAMT-SC}]$ and $[(R1+R2)_{SC-EAMT}]$ have equal medians, rejected if
201 $p < 0.05$

202

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

207

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

216

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

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

222

223

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

227

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

229

230 **RESULTS**

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

233

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

237

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

241

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

245

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

247

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

249 *Primary outcome*

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

256

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

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

263 recovery between groups at T2 with respect to T0 determines a negligible carry-over effect in
264 the primary outcome measure (4). In addition, relative recovery at T2 with respect to T1 was
265 not significantly different between groups (0.8 ± 1.7 FMA-UE points for EAMT-SC and
266 4.8 ± 4.8 for SC-EAMT). Median improvements disregarding when therapies were provided
267 were 6.5 and 1 FMA-UE points after EAMT and SC, respectively. The difference in recovery
268 between therapies is greater than the MDC and MCID.

269

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

276

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

283

284 *Secondary outcomes*

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

286 MAL amount of use ($p<0.05$) and MAL quality of movement ($p<0.05$), as shown in **Figure 1**.
287 No significant carry-over effects were found in these two measures, as reported in **Table 2**.
288 Recovery in FMA-UE scores was moderately correlated to recovery in MAL quality of
289 movement scores ($r=0.57$, $p<0.01$) and MAL amount of use score ($r=0.51$, $p<0.05$). Although
290 their change was not significant, WMFT time scores were improved at T1 and T2 with respect
291 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
292 1.3 ± 3.3 s slower at T1 but 4.4 ± 5.9 s faster at T2). REPAS did not change significantly during
293 the study.

294

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

297

298 **DISCUSSION**

299

300

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

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

312

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

331

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

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

337

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

345

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

354

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439

440 **SUPPLIERS**

441

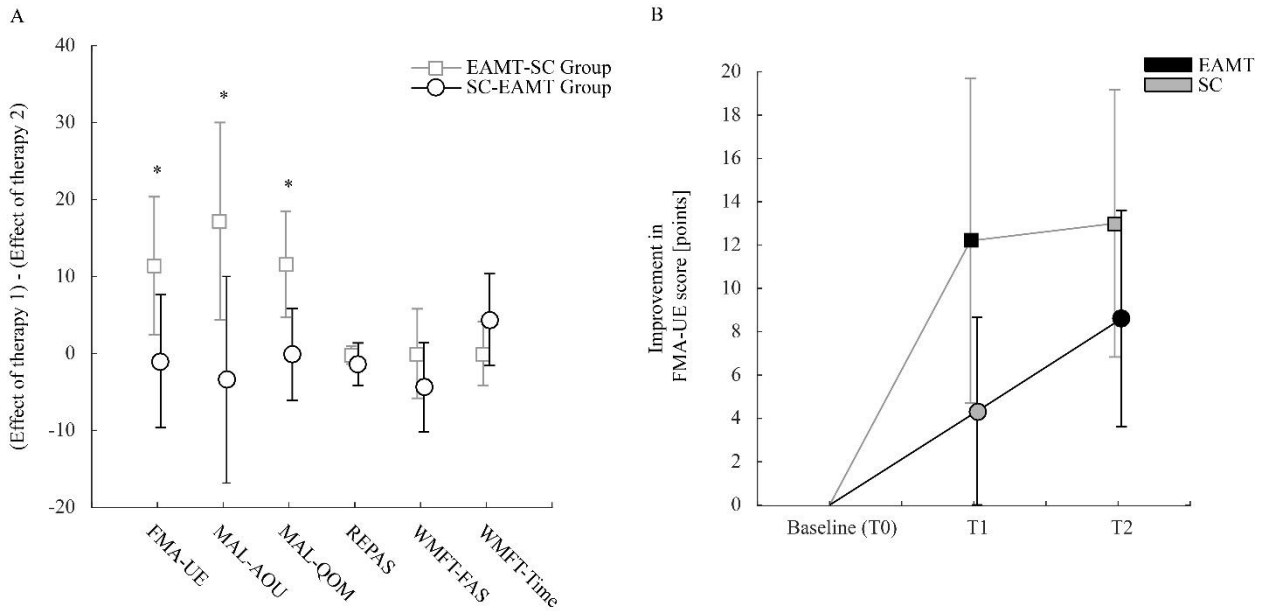
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447

1 **Figures**

2 **Figure 1 – Clinical effects.**

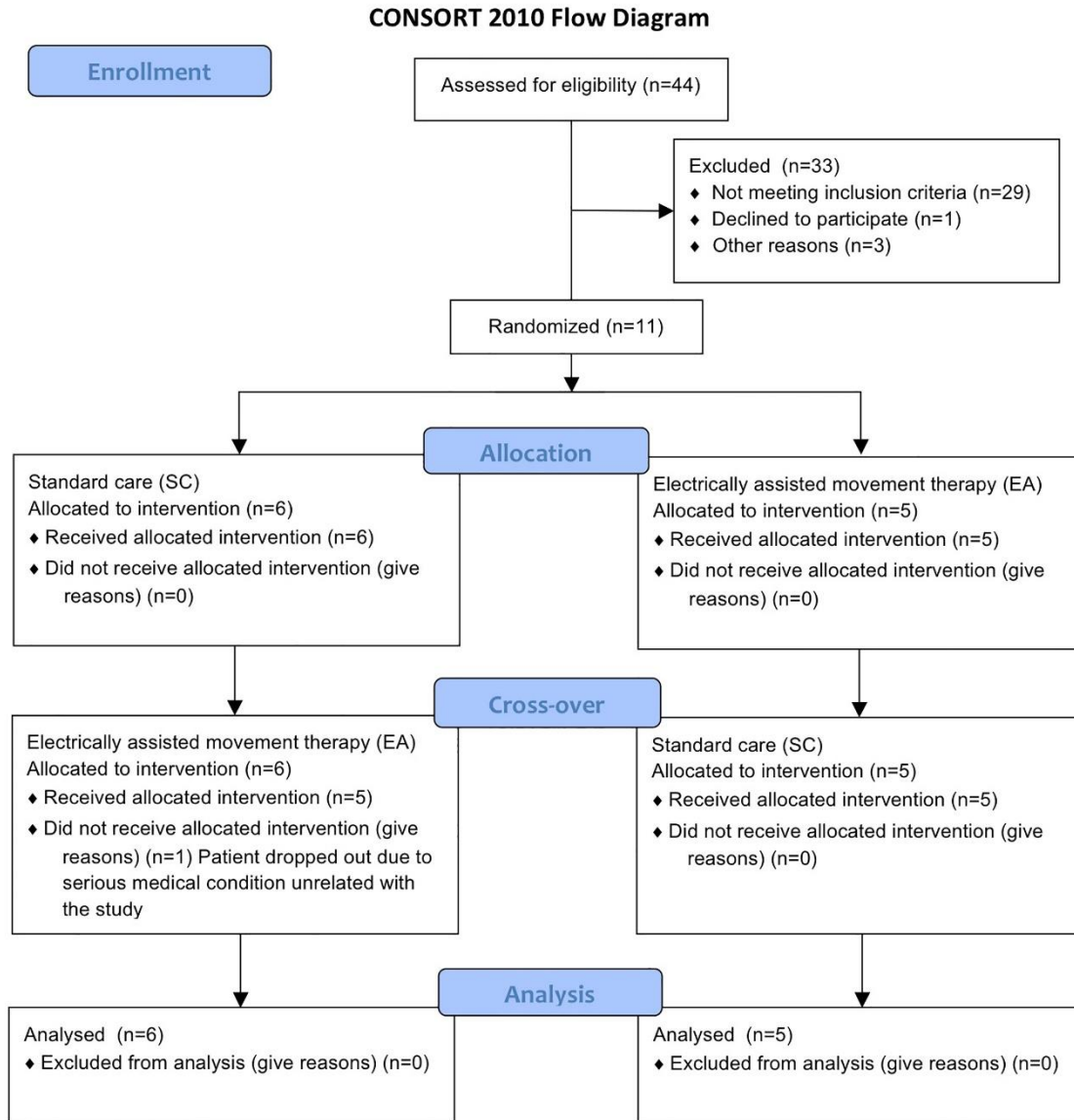


3

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

14

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



17 **Tables**

18 **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‡

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

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

24

25 **Table 2 – Primary and secondary outcomes, relative improvement with respect to previous**
 26 **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		

27 ‡ Independent Samples Mann-Whitney U-test

28 Hp: statistical hypothesis that was tested; EAMT-SC≠SC-EAMT: main cross-over effect, i.e. the
 29 difference of first and second therapy effects is significantly different between groups;

30 EAMT+SC≠SC+EAMT: carry-over effect, i.e. the sum of first and second therapy effects is
 31 significantly different between groups; statistically significant p-values are reported in bold.

32 FMA-UE: Fugl-Meyer Assessment for the Upper Extremity; WMFT time: Wolf Motor Function

33 Test timing (in seconds); WMFT-FAS: Wolf Motor Function Test Functional Activity Scale;

34 REPAS: Resistance to Passive Movement Scale; MAL-AOU: Motor Activity Log Amount Of

35 Use; MAL-QOM: Motor Activity Log Quality Of Movement. Improvements are reported as

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

39 **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

40

41 FMA-UE: Fugl-Meyer Assessment for the Upper Extremity; WMFT time: Wolf Motor Function

42 Test Timing (in seconds); WMFT-FAS: Wolf Motor Function Test Functional Activity Scale;

43 REPAS: Resistance To Passive Movement; MAL-AOU: Motor Activity Log Amount Of Use;

44 MAL-QOM: Motor Activity Log Quality Of Movement. Scores changes are reported as mean ±

45 standard deviation of the absolute scores within each group. EAMT-SC: electrically-assisted

46 movement therapy before standard care; SC- EAMT: standard care before electrically-assisted

47 movement therapy. T1* group mean and standard deviation was calculated by including T1*

48 evaluations instead of T1 evaluations for the two patients who took a longer washout period.

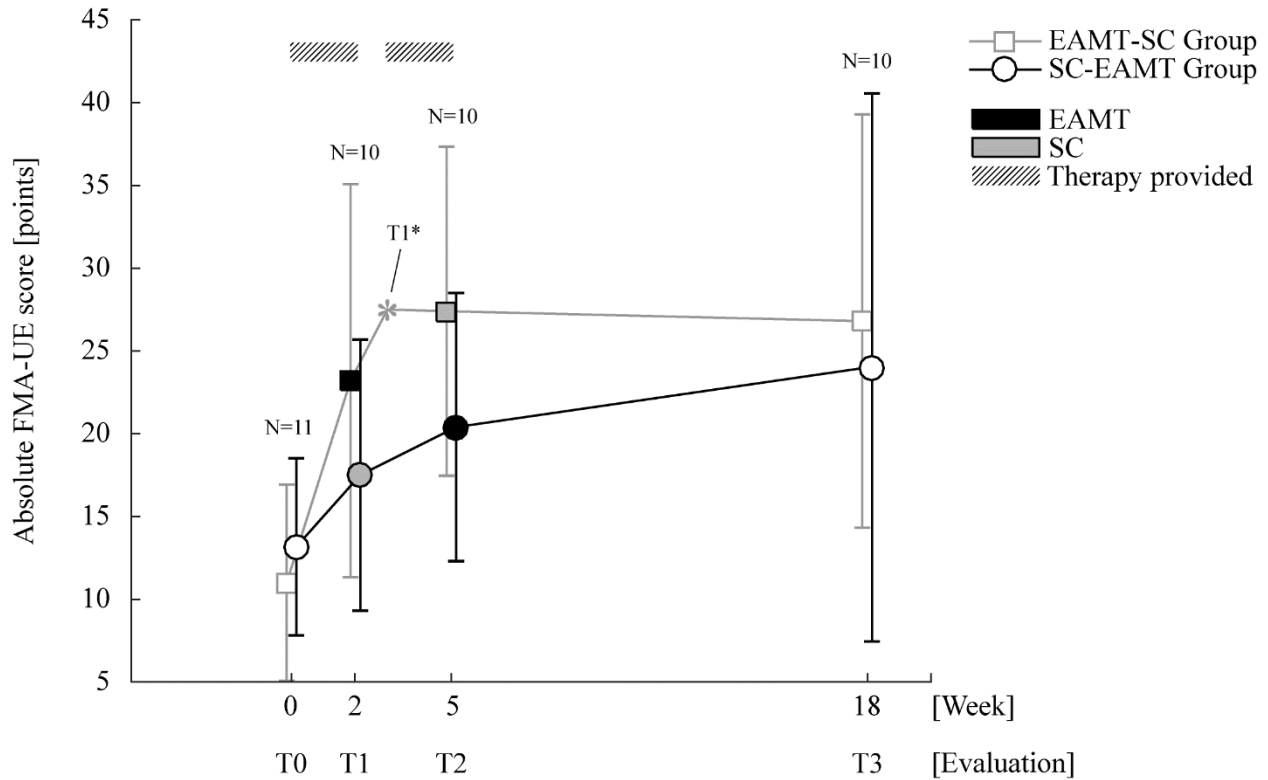
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51 **Supplementary material**

52 **Supplementary Figure 1 – Change in primary outcome metric including the follow-up**

53 **assessment.**

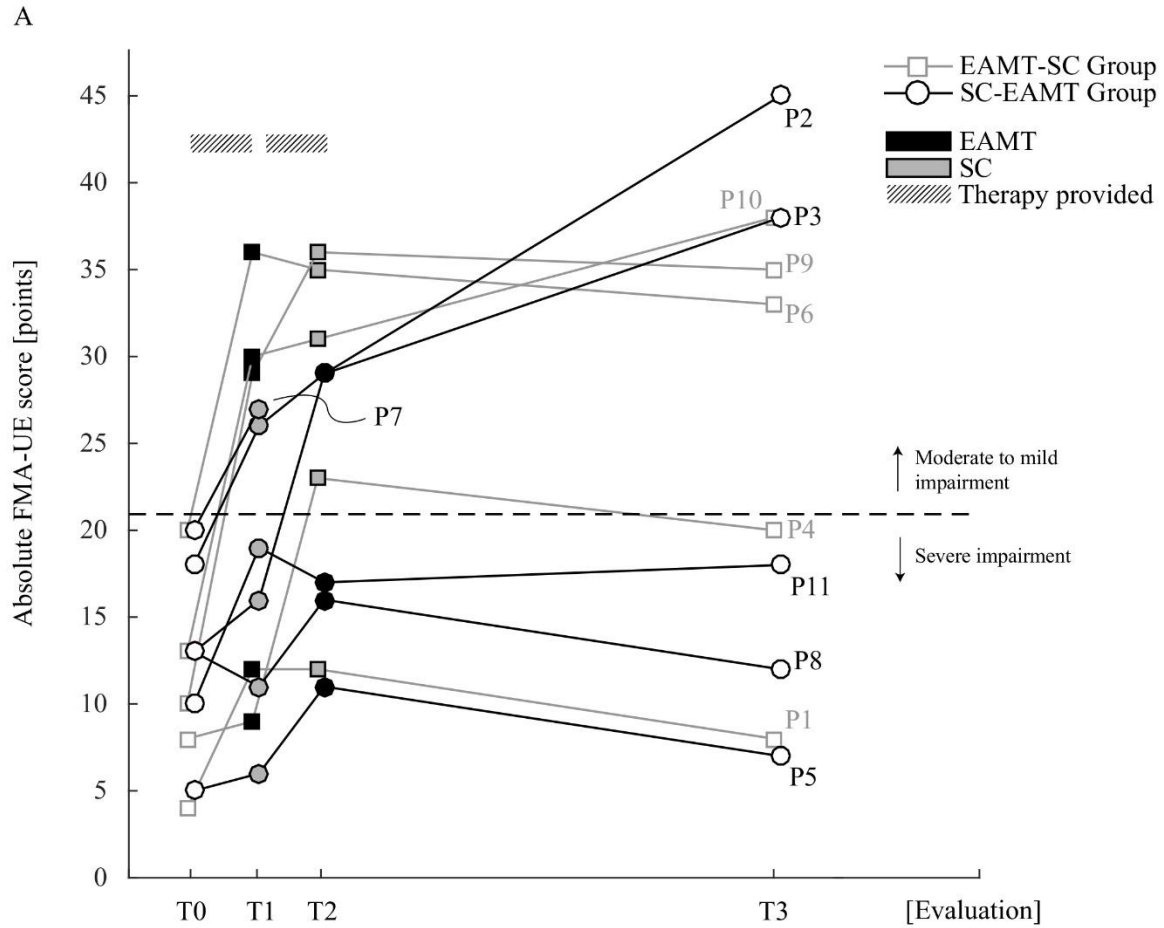


54
55 Absolute change in FMA-UE at all evaluations, displayed by group. Therapy was only provided
56 between T0 and T1 and between T1 and T2. T1 was collected of the beginning of the washout
57 week between the two therapies. T1* group average was calculated by including T1* evaluations
58 instead of T1 evaluations for the two patients who took a longer washout period.

59

60

61 **Supplementary Figure 2 – Single-patient primary outcome data.**



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

62

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

71

72

73

74

75 **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-Parietal.
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.

76

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