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2 **Neuroprosthesis for retraining reaching and grasping**

3 **functions in severe hemiplegic patients**

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ABSTRACT

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4 During the course of rehabilitation hemiplegic patients who have Chedoke McMaster
5 Stages of Motor Recovery scores 4 and 5 measured three weeks after onset of stroke
6 often improve their arm and hand function to the point that they can later use it in the
7 activities of daily living (ADL).[1] These patients can be considered to have *mild arm*
8 *and hand paralysis* since they can grasp objects and manipulate them with minor
9 restrictions in the range of movement and force. On the other hand, hemiplegic patients
10 who have Chedoke McMaster Stages of Motor Recovery scores 1 and 2 measured three
11 weeks after onset of stroke, during the course of rehabilitation seldom improve their arm
12 and hand function, and when they do, the improvements are not sufficient to allow these
13 patients to use the arm and hand in ADL.[1] These patients can be also described as
14 patients who have *severe arm and hand paralysis*. Patients with severe arm and hand
15 paralysis cannot move their arm and hand voluntarily at all, or have very limited
16 voluntary movements that cannot be used to carry out ADL.

17 In recent years a variety of treatments such as constraint induced therapy,
18 functional electrical therapy, biofeedback therapy and robotics assisted therapies, were
19 proposed which main objective is to improve reaching and grasping functions in subjects
20 with unilateral arm paralysis. These therapies have shown encouraging results in patients
21 with mild arm and hand paralysis. However, the efficacy of these therapies was limited
22 when they were applied to patients with severe arm and hand paralysis. This article

Neuroprosthesis for retraining reaching and grasping functions in severe hemiplegic patients

Popovic M.R., Thrasher T.A., Zivanovic V., Takaki J, and Hajek V.

1 describes a new rehabilitation technique that can improve both reaching and grasping
2 functions in hemiplegic patients with severe unilateral arm paralysis.

3 A neuroprosthesis that applies surface electrical stimulation technology was used
4 to retrain hemiplegic patients who had severe arm and hand paralysis to reach and grasp.
5 The neuroprosthesis was applied both to acute and long-term hemiplegic patients.

6 Patients who were treated with the neuroprosthesis were compared to those patients who
7 were administered only standard physiotherapy and occupational therapy appropriate for
8 hemiplegic patients with unilateral upper extremity paralysis (controls). The treated and
9 control patients had approximately the same time allocated for arm and hand therapy.

10 After the treatment program was completed, the patients treated with the neuroprosthesis
11 significantly improved their reaching and grasping functions, and were able to use them
12 in ADL. However, the majority of the control patients did not improve their arm and
13 hand functions significantly, and were not able to use them in ADL.

14

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16 **Key Words:** Neuroprosthesis, functional electrical stimulation, functional electrical

17 therapy, stroke, hemiplegia, neuro-rehabilitation, arm and hand

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INTRODUCTION

3

4 According to the Heart and Stroke Foundation of Canada, there were between 1,300 and
5 1,600 strokes per million inhabitants in Canada in 2002. Stroke often leads to

6 hemiplegia, a unilateral arm and/or leg paralysis. Patients who start improving their arm
7 and leg functions immediately during the first three weeks after stroke may fully recover.

8 However, a significant number of hemiplegic patients with unilateral arm and leg

9 paralysis do not recover completely. Typically, patients improve their walking function

10 to the point that they can walk slowly on their own using a cane or a walker, while the

11 reaching and grasping functions frequently remain impaired. Comprehensive information

12 regarding stroke and its epidemiology can be found in [1-7].

13 Rand et al. reported in [1] that stroke survivors who participated in standard

14 physiotherapy and occupational therapy [2,3], which lasted approximately two months, at

15 the completion of the therapy were discharged with the following outcomes pertaining to

16 their arm and hand function:

17 • **55 % were classified as patients with nonfunctional arm and hand:** these

18 patients were unable to use their arm and hand at all in ADL

19 • **30 % were classified as patients with intermediate recovery:** these patients

20 have shown some improvement in arm and hand function, in particular range of

21 motion or strength, however, the improvement did not precipitate into substantial

22 or more frequent use of arm and hand in ADL

- 1 • **15 % were classified as patients with good recovery:** these patients were able
2 to use both arm and hand to carry out ADL

3

4 This statistics suggests that approximately 85 % of all stroke survivors who are
5 discharged home are unable to use their arm and hand in ADL.

6 The first two categories of patients, nonfunctional and those with intermediate
7 recovery, can also be classified as *patients with severe arm paralysis*. These patients
8 cannot move their arm and hand voluntarily at all, or have very limited voluntary
9 movements that cannot be used to carry out ADL. If these patients are assessed with
10 Chedoke McMaster Stages of Motor Recovery (CMSMR) the scores they would typically
11 receive are either 1 or 2.[1,8] On the other hand the patients with good recovery (last
12 group of patients), can also be classified as *patients with mild arm and hand paralysis*.
13 These patients can grasp objects and manipulate them with difficulty, restricted range of
14 motion, and restricted grasping force. Patients with mild arm and hand paralysis
15 typically have CMSMR scores 4 and 5.[1] These findings, reported by Rand et al. in [1],
16 can be rephrased in the following way:

- 17 • 85 % of stroke survivors at discharge, after two months of standard occupational
18 therapy and physiotherapy, have CMSMR scores 1 and 2 and are unable to use
19 their arm and hand in ADL
- 20 • 15 % of stroke survivors at discharge, after two months of standard occupational
21 therapy and physiotherapy, have CMSMR scores 4 and 5 and are able to use their
22 arm and hand in ADL

23

1 In the last 10 to 15 years a number of therapies such as constraint induced therapy
2 [9,10], functional electrical therapy [11,12], biofeedback therapy [13-15], and robotic
3 assisted therapy [16] were proposed, which have shown potential to improve arm and
4 hand function in stroke survivors with unilateral arm paralysis. Although these therapies
5 have distinctive ways of engaging the patient and promoting the arm and hand recovery,
6 they have one thing in common. These therapies were only effective if they were applied
7 to hemiplegic subjects who had mild arm and hand paralysis, i.e. CMSMR scores 4 and
8 5. If they were applied to patients with severe arm and hand paralysis, i.e. CMSMR
9 scores 1 and 2, the efficacy of these therapies was difficult to prove.

10 In this article, a new intervention is presented which has resulted in improvements
11 in arm and hand functions in hemiplegic patients with severe arm and hand paralysis.

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OBJECTIVE

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16 The purpose of this study was to compare two types of therapies for upper extremity
17 hemi-paresis: conventional physiotherapy and occupational therapy [2,3] versus FES
18 therapy. These two therapies were applied to hemiplegic patients with severe arm and
19 hand paralysis (CMSMR scores 1 and 2) using a randomized treatment-versus-control
20 design.

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HYPOTHESIS

3

4 We hypothesized that the FES therapy would give rise to a greater improvement in arm
5 and hand function as measured by: 1) Parts of the Chedoke McMaster Stages of Motor
6 Recovery (CMSMR) test, pertaining to arm and hand functions of the hemiparetic arm
7 [8]; 2) Parts of the Fugl-Meyer Assessment (FMA) pertaining to shoulder, elbow,
8 forearm, wrist, and hand functions of the hemiparetic arm [17]; and 3) Rehabilitation
9 Engineering Laboratory Hand Function Test for Functional Electrical Stimulation
10 Assisted Grasping (REL Test) [18].

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METHODS

14

15 The study presented in this manuscript describes a randomized clinical trial with the
16 following main characteristics: 1) the method for analyzing data was specified in the
17 protocol before the study begun; 2) the study received ethics approvals from the
18 University of Toronto and the Toronto Rehabilitation Institute ethics boards; 3) the
19 patients were invited to participate in the study and they gave consent before the
20 inclusion/exclusion criteria were applied; and 4) after the patients were admitted to the
21 program they were randomly assigned to control or intervention group. The flow chart of

1 the recruitment, therapies and assessments that were applied to all participants, both
2 controls and those who participated in the FES therapy, is shown in Figure 1.

3

4

Figure 1 should be placed here

5

6

7 **Participants**

8

9 The study was conducted with stroke patients with severe unilateral upper extremity
10 paralysis (CMSMR scores 1 or 2). When they joined the program, the participants either
11 could not generate the following movements voluntarily at all, or were able to generate a
12 twitch or a very weak contraction in some of the muscles responsible for the following
13 movements: 1) flex, extend, abduct, adduct and rotate the shoulder; 2) flex and extend
14 the elbow; 3) pronate and supinate the forearm; 4) flex, extend, abduct and adduct the
15 wrist; and 5) move fingers. Acute patients were recruited to the study at the
16 rehabilitation unit at the Toronto Rehabilitation Institute at least three weeks after the
17 onset of stroke (see Figure 1). Long-term patients were recruited to the study through an
18 outpatient follow-up clinic at the Toronto Rehabilitation Institute at least 12 months after
19 the onset of stroke. From our experience, patients who do not show any signs of
20 spontaneous recovery during the first three weeks after stroke typically do not have
21 significant spontaneous recovery of the arm and hand in the following months and years.
22 That is why the participants for our study were recruited only after the third week

1 following stroke and only if they did not show any signs of spontaneous recovery. A
2 medical doctor, or another member of the patients' core care team, identified potential
3 candidates. The same team member approached the candidates, and made the initial
4 contact. The patients' names were then passed on to our research team.

5

6 The inclusion criteria for this study were:

- 7 • Patient was eligible to provide informed consent as determined by a social
8 worker.
- 9 • Patient had hemiplegia and the level of hemiplegia was confirmed by an attending
10 physiatrist.
- 11 • Stroke was confirmed with a Computed Tomography or Magnetic Resonance
12 Imaging scan in an acute care facility.

13

14 The exclusion criteria were:

- 15 • Patient had global aphasia or had significant language barrier as determined by an
16 attending speech language pathologist.
- 17 • Patient who had skin rash, allergy or wounds at the locations where stimulation
18 electrodes were expected to be placed.
- 19 • Patient who had seizure episodes
- 20 • Patient who had edema in the paralyzed arm or had Shoulder Hand Syndrome.
- 21 • Patient who had early signs of spontaneous recovery of the hemiplegic arm and
22 hand functions (within first three weeks post-onset of stroke) and had a score of

1 motor recovery greater than 2 according to the Chedoke McMaster Stages of
2 Motor Recovery.[8]

3

4 After they were admitted to the program the subjects were *randomly assigned* to two
5 groups: **Group A** - *the control group* who were administered only standard
6 physiotherapy and occupational therapy; and **Group B** – *the treatment group* who were
7 trained with the neuroprosthesis in addition to standard physiotherapy and occupational
8 therapy (this training will be referred to further in the text as the *neuroprosthesis*
9 *treatment or FES group*). The treated and control patients had approximately the same
10 time allocated for arm and hand therapy, as discussed later in this section.

11

12

13 **Randomization**

14

15 Participants were randomized using two sets of sealed envelopes. An unmarked set of 40
16 envelopes were presented to a patient to select one. The unmarked envelopes contained a
17 single sheet of paper with a printed number in the range from 1 to 40. In the second set
18 of envelopes, which were marked with numbers from 1 to 40, control and intervention
19 sheets were sealed. 20 randomly selected numbers in the range from 1 to 40 were
20 assigned to control group and the remaining 20 numbers were assigned to intervention
21 group. Randomization was done using *randperm.m* function seeded with an arbitrary
22 clock value in Matlab (The MathWorks, Inc.). This ensured that the relationship between

1 numbers 1 to 40, and control and intervention options were properly randomized. Since
2 the subjects chose a random envelop from the unmarked set, and since the relationship
3 between the unmarked and the marked sets of envelopes was randomized, the participants
4 were randomly assigned to control and intervention groups. This was later confirmed in
5 our statistical analysis presented in section Results. Once an unmarked envelope was
6 drawn, the unmarked enveloped and its matching marked partner were destroyed. This
7 ensured that the randomization process could not be contaminated.

8

9

10 **Outcome Measures**

11

12 The following tests were administered both before and after the intervention to measure
13 change in motor functions following the neuroprosthetic and conventional interventions.
14 The tests also served to characterize the intervention and control participants. All but one
15 of the following tests were standard clinical tests with previously demonstrated reliability
16 and validity. The Rehabilitation Engineering Laboratory Hand Function Test (REL test)
17 was the only nonstandard test applied in this study. It was designed by our team to assess
18 a gross motor function of grasping. In the scientific literature, a test that can properly
19 perform such assessment does not exist yet.[18] Since FES therapy primarily promotes
20 improvement in gross motor function of grasping, a test that can provide increased
21 sensitivity to the presence of subtle changes in gross motor function of the grasp as well
22 as to provide enhanced ecological validity, was needed. That is why our team had to

1 develop the REL test, to which preliminary validity and reliability data are provided in
2 [18].

3 The following tests were administered to all participants in the study (both
4 Group A and Group B).

5 **A. Neurological test:** Canadian Neurological Scale [19] was used to assess
6 neurological profile of the subjects.

7 **B. Functional tests:**

8 a. Functional Independence Measure (FIM) – total score [20]

9 b. Barthel Index (BI)¹ – total score [21]

10 c. Chedoke McMaster Stages of Motor Recovery (CMSMR) – only a part of
11 the total score pertaining to arm and hand functions of the hemiparetic arm
12 [8]

13 d. Fugl-Meyer Assessment (FMA) – complete upper limb section score, i.e.
14 only a part of the total score pertaining to shoulder, elbow, forearm, wrist,
15 and hand functions of the hemiparetic arm [17]

16 e. Rehabilitation Engineering Laboratory Hand Function Test (REL test) of
17 the hemiparetic arm – total score [18] (see the following subsection for
18 details)

19

20 The FIM and BI tests were used to determine the level of disability with respect to ADL.

21 The CMSMR test was used to assess the functional state of the hemiplegic upper

22 extremity since this test can capture the neuromuscular recovery of the patient's

¹ FIM and BI are routinely collected with all stroke patients at the Toronto Rehabilitation Institute.

1 arm/hand. The FMA was used to assess development of the upper limb motor function
2 in post stroke patients. The REL test was used to assess a patient's unilateral hand
3 function and its improvements.

4 After signing a letter of consent, participants were administered the FIM, BI,
5 CMSMR, FMA, and REL tests. Following the tests, the final admissibility of the subject
6 to the program was approved and the subject was randomly assigned to one of the two
7 groups (see Figure 1). The FIM, BI, CMSMR, FMA, and REL test results were used as a
8 base line against which patients' subsequent test scores were compared. After the
9 treatment was completed, the same functional tests were performed again to measure the
10 level of improvement as a result of the neuroprosthesis treatment, compared to subjects
11 who received standard physiotherapy and occupational therapy alone. The tests were
12 always performed in the same, chronologic order: 1) FIM, 2) BI, 3) CMSMR, 4) FMA,
13 and 5) REL. The measured scores for all five tests were scaled with respect to the
14 maximum score and were presented as percentages of the maximum score. The scaling
15 of the scores into percentages allowed us to present different tests in a uniform manner,
16 which was later found useful when the data was statistically analyzed and presented.

17 Due to the nature of the treatment used in the study, it was impossible to blind the
18 therapists and participants from the knowledge of which of the two groups individual
19 participants were assigned to. **An attempt was made to blind the assessor from** the
20 knowledge of which of the two groups individual patients were assigned to. However,
21 substantial difference in the final outcomes in patients in Group B compared to Group A
22 was clear indication to the assessor to which of the two groups the participant was

1 assigned to. After we realized our failure to blind the assessor, a statistician who was not
2 a member of the core research team was asked to process the data.

3

4

5 ***Rehabilitation Engineering Laboratory Hand Function Test for Functional Electrical***
6 ***Stimulation Assisted Grasping***

7

8 The REL test was developed to evaluate improvement of the gross motor function of the
9 unilateral grasp due to neuroprosthesis for reaching and grasping treatment. Hand
10 functions that were tested with the REL test were: *lateral or pulp pinch*, and *palmar*
11 *grasps*. The REL test consisted of three tests. The first test evaluated the palmar grasp, the
12 second evaluated the pulp or lateral pinch grasp, and the third evaluated the strength of
13 both plamar and pulp/lateral pinch grasps. To test the palmar grasp, the subject was
14 presented with the following five items: *mug*, *book*, *pop can*, *isosceles triangular sponge*
15 and *mobile phone* (Figure 2 items 1,3,5,7 and 9, respectively). To test lateral or pulp
16 pinch grasp, the subject was presented with the following five items: *paper sheet*, *zip-*
17 *lock-bag filed with five golf balls*, *die*, *credit card* and *pencil* (Figure 2 items 4,6,8 and
18 10). To test the strength of the grasps, the subject was presented with the following items:
19 *nine rectangular blocks*, *instrumented cylinder*, *credit card attached to a dynamometer*
20 and *wooden bar* (Figure 2 items 11,12,13 and 14).

21 **Scoring:** With exception to the *instrumented cylinder*, *credit card attached to a*
22 *dynamometer* and *wooden bar*, all test objects in Figure 2 were placed on a desk 20 to

1 30 cm in front of the subject, one after another. The subject was expected to pick up the
2 objects, lift them in front of his/her chest and move the objects from supination, to neutral
3 and then to pronation position. In each position, the subject was expected to hold the
4 object for 20 to 30 s. If in any of these three positions, the subject was unable to hold the
5 object, he/she received 0 points for that position. If the subject could hold the object for a
6 short period of time (2 to 10 s) and eventually dropped the object, the subject was
7 awarded 1 point. Finally, if the subject was able to hold the object for 20 to 30 s, he/she
8 received 2 points for that hand position. Since holding the mug and the zip-lock-bag in
9 supination position has no practical value, the subject was not asked to perform these two
10 tasks.

11 The *instrumented cylinder*, *credit card attached to a dynamometer* and *wooden*
12 *bar* were used to measure torque generated by the palmar grasp, force produced by the
13 pinch grasp, and exocentric load that the palmar grasp can sustain, respectively. For
14 more details about the REL test, please consult [18].

15

16 ***Figure 2 should be placed here***

17

18 For the purpose of this study, scores for the *mug*, *book*, *pop can*, *isosceles*
19 *triangular sponge*, *mobile phone*, *paper sheet*, *zip-lock-bag filled with five golf balls*, *die*,
20 *credit card*, and *pencil*, were all summed together to produce the *REL Test - object*
21 *manipulation* score. Scores from the *nine rectangular blocks* tests were summed together
22 to produce the *REL Test - wooden blocks* score. Scores for the *instrumented cylinder*
23 were presented as *REL Test – torques* score and scores obtained with the *credit card*

1 *attached to a dynamometer* produced the *REL Test – forces* score. Scores for the *wooden*
2 *bar* tests were presented as the *REL Test – eccentric load* score. The rationale for
3 arranging the scores in this way was to group them according to the skills that were tested
4 and the type of measures applied to obtain the score. Please note that the maximum
5 scores for the REL Tests *object manipulation, wooden blocks, forces, torques, and*
6 *eccentric load score* were 56, 18, 5 Nm, 50 N, and 60 cm, respectively.

7

8

9 **Conventional Physiotherapy and Occupational Therapy**

10

11 Conventional physiotherapy and occupational therapy included: muscle facilitation
12 exercises emphasizing the neurodevelopmental treatment approach; task-specific,
13 repetitive functional training; strengthening and motor control training using resistance to
14 available arm motion to increase strength; stretching exercises; electrical stimulation
15 applied primarily for muscle strengthening (this is not FES therapy); activities of daily
16 living including self-care where the upper limb was used as an assist if appropriate; and
17 caregiver training.[4] Therapy dose was: 45 minutes daily, 3 to 5 days per week, 12 to 16
18 weeks.

19

1

2 **FES Therapy**

3

4 **Neuroprosthesis Hardware**

5

6 The Compex Motion electric stimulator was used as a hardware platform for the
7 neuroprosthesis for reaching and grasping.[22] This is a fully programmable FES system
8 with standard self-adhesive surface stimulation electrodes that can be used to develop
9 sophisticated, custom-made neuroprostheses. During the course of the treatments, the
10 patients' arm functions improved in different ways requiring individualized stimulation
11 protocols and custom-made neuroprostheses "fine-tuned" to meet particular patients'
12 needs. Individualized and evolving stimulation protocols allowed us to maximize the
13 training results with respect to the patients' disabilities and latest impairment
14 status/condition.

15

16

17 **FES Protocols Used in the Study**

18

19 The neuroprosthesis treatment consisted of a functional training program carried out in
20 the following way. The subject was asked to execute a task with the impaired arm (e.g.
21 reaching and grasping a pen) unassisted. The subject would then try to execute the task

1 unassisted. The components/sequences of the task the subject was unable to carry out
2 him/her self were assisted with the neuroprosthesis (see Figure 3). During the treatment,
3 a therapist controlled/triggered the reaching and grasping functions using a pushbutton.
4 In the early stages of the treatment, the arm/hand tasks were performed by the
5 neuroprosthesis alone. As the patient improved, the neuroprosthesis assistance was
6 reduced to the necessary minimum and eventually was removed from the treatment
7 protocol. Typically, the stimulation protocols were adjusted weekly or biweekly. The
8 participant was asked to repeat the same arm/hand task 20 to 30 times during a single
9 treatment session. The treatment sessions lasted up to 45 minutes, 25 to 30 minutes of
10 which were used for active treatment alone. The remaining 15 to 20 minutes were used
11 for donning and doffing of the neuroprosthesis. During the arm/hand movements, the
12 ~~physio~~therapist guided the arm and assisted the patient with the neuroprosthesis in
13 performing the desired task. This assistance ensured that all movements were carried out
14 in a physiological way, i.e. neuroprosthesis induced movements did not oppose natural
15 joint movements and respected the anatomy of bone and soft tissue composition. **The**
16 **exact therapy dose is discussed in section Results.**

17 In stroke patients, the neuromuscular recovery typically starts proximally
18 followed by the recovery of distal neuromuscular compartments. Therefore, the
19 neuroprosthesis treatment began by training shoulder and upper arm muscles first.
20 *Anterior deltoid m.* and *biceps m.* were stimulated simultaneously to produce the arm
21 movement that resembled a feeding movement. Once the hand reached the mouth,
22 *posterior deltoid m.* and *triceps m.* were stimulated simultaneously to produce an arm
23 extension movement and place the arm in a relaxed position next to the body. Typically,

1 the shoulder flexion function recovered first (*anterior deltoid m.*) in all our participants,
2 followed by the recovery of the *biceps m.*, *posterior deltoid m.* and *triceps m.*,
3 respectively.

4

5

Figure 3 should be placed here

6

7 As soon as the patient showed signs of recovery of both the voluntary extension
8 and flexion of the shoulder, the *extensor digitorum m.* was stimulated together with the
9 *triceps m.* In this way, the patient was trained to extend the fingers when the elbow was
10 fully extended. Since a large number of hemiplegic patients with unilateral upper
11 extremity paralysis have spastic finger flexors, this stimulation protocol promoted finger
12 extension in the arm configuration that is the most challenging from the biomechanical
13 point of view to perform finger extension. This stimulation protocol helped reduce
14 spasticity and tone in the fingers allowing patients to better control finger flexion and
15 extension. The most difficult and time-consuming task was to train patients to
16 voluntarily extend the fingers or to relax them. This function is essential to allow patients
17 to voluntarily grasp and release objects.

18 Once the patient was able to voluntarily extend or relax the fingers, the *flexor*
19 *digitorum superficialis m.*, *flexor digitorum profundus m.*, *median nerve* (or *thenar m.*),
20 and *flexor pollicis longus m.* were stimulated to generate palmar and/or pinch grasp. This
21 phase of the treatment was terminated when the patient was able to perform voluntarily
22 palmar and/or pinch grasp combined with the reaching function.

1 In the study the following muscles and nerves were stimulated with surface
2 stimulation electrodes:

- 3 • *flexor digitorum superficialis m.* and the *flexor digitorum profundus m.* (finger
4 flexion)
- 5 • *median nerve* or *thenar m.*, and *flexor pollicis longus m.* (thumb opposition and
6 flexion)
- 7 • *extensor digitorum m.* (finger extension)
- 8 • *flexor carpi radialis m.* and *flexor carpi ulnaris m.* (wrist flexion)
- 9 • *extensor carpi radialis longus* and *brevis m.*, and *extensor carpi ulnaris m.* (wrist
10 extension)
- 11 • *biceps m.* (elbow flexion)
- 12 • *triceps m.* (elbow extension)
- 13 • *anterior and posterior deltoid m.* (shoulder flexion and extension, respectively)

14

15 Proper placements for the surface stimulation electrodes for the muscles and nerves listed
16 above can be found in [23]. Stimulation parameters used to stimulate the muscles and
17 nerves were:

- 18 • balanced, biphasic, current regulated electrical pulses
- 19 • pulse amplitude from 8 to 50 mA (typical values 17-30 mA)
- 20 • pulse width from 100 to 250 μ s (typical value 250 μ s)
- 21 • pulse frequency from 20 to 40 Hz (typical value 40 Hz)

22

1

2 **Statistical Analysis**

3

4 The following hypotheses were tested:

5

6 **Hypothesis 1:** On admission, Group A and Group B had the following scores equal:

7 1.1. REL Test - object manipulation

8 1.2. REL Test - wooden blocks

9 1.3. REL Test - forces

10 1.4. REL Test - torques

11 1.5. REL Test - eccentric load

12 1.6. FIM

13 1.7. BI

14 1.8. FMA

15 1.9. CMSMR

16

17 **Hypothesis 2:** On discharge, Group A and Group B had the differences of the following
18 scores, measured on discharge and admission, equal:

19 2.1. REL Test - object manipulation

20 2.2. REL Test - wooden blocks

21 2.3. REL Test - forces

22 2.4. REL Test - torques

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1 2.5. REL Test - eccentric load

2 2.6. FIM

3 2.7. BI

4 2.8. FMA

5 2.9. CMSMR

6

7 **Hypothesis 3:** Group A had the following scores equal, on admission and discharge:

8 3.1. REL Test - object manipulation

9 3.2. REL Test - wooden blocks

10 3.3. REL Test - forces

11 3.4. REL Test - torques

12 3.5. REL Test - eccentric load

13 3.6. FIM

14 3.7. BI

15 3.8. FMA

16 3.9. CMSMR

17

18 The hypotheses were tested using a Wilcoxon rank-sum test, which is non-parametric and

19 robust to non-normal distributions of data. Since the outcome measures were expected to

20 produce highly skewed data distributions, the hypotheses could not be tested using the

21 standard Student's t-test

22

1

2

RESULTS

3

4 **Participants**

5

6 The study was conducted with 13 stroke patients who were randomly assigned to

7 **Group A:** the control group, and **Group B:** the treatment group:

8

9 Group A: Standard Therapy - Control Group

10

11 Eight subjects were assigned to Group A (Table 1). Five patients had strokes affecting
12 the right hemisphere and three patients had strokes affecting the left hemisphere. Five
13 patients were females and three were males. Their average age was 62 ± 20.3 years and
14 they joined the program 26 days post-stroke. At admission, the patients had the
15 following average functional test scores: 1) FIM was 59.5; 2) BI was 38.1; 3) CMSMR
16 pertaining to arm and hand functions was 3.6; 4) FMA upper limb score was 3.1; and 5)
17 REL scores were 0, 0, 0.5 Nm, 0.63 N, and 0 cm.

18

19

Table 1 should be placed here

20

1

2 Group B: Neuroprosthesis Intervention Group - Subjects who were administered the
3 neuroprosthesis (FES) treatment

4

5 Five subjects were assigned to Group B (Table 1). Three patients had strokes affecting
6 the left hemisphere and two patients had strokes affecting the right hemisphere. One
7 patient was female and four were males. Their average age was 57.6 ± 17.5 years. In
8 this particular case, we had a bimodal distribution of the time post-stroke: one patient was
9 recruited 338 days post-stroke and four patients were recruited at a mean of 30.8 days
10 post-stroke. Overall mean was 92 days. At admission, the patients had the following
11 average functional test scores: 1) FIM was 70.6; 2) BI was 48; 3) CMSMR pertaining to
12 arm and hand functions was 4.6; 4) FMA upper limb score was 3.6; and 5) REL scores
13 were 0.8, 2, 0.11 Nm, 7 N, and 0 cm.

14 **Therapy dose:** Subjects in Group B received FES therapy 45 minutes daily, 3 to
15 5 times per week, for 12 to 16 weeks. It is important to mention that some of the FES
16 therapies were combined with additional conventional physiotherapy and occupational
17 therapy. In particular, 36.3% of the total FES therapies delivered to Group B were carried
18 out in combination with additional conventional physiotherapy and occupational therapy
19 sessions. These additional therapies were primarily delivered during first 6-8 treatment
20 weeks. The exact number of hours of FES therapies and FES therapies combined with
21 physiotherapy and occupational therapy is presented in Table 2. Please note that subject
22 No. 4 received 19 weeks of therapy instead of 16 (maximum originally prescribed dose)

1 and that subject 5 received 9 weeks of therapy instead of 12 (minimum originally
2 prescribed dose).

3

4 *Table 2 should be placed here*

5

6

7 **Raw Data**

8

9 Tables 3 and 4 summarize the raw data obtained from both Groups A and B at admission
10 and discharge. The raw data was then scaled and presented as percentages of the
11 maximum scores that can be achieved with individual tests (Figure 4). The data was
12 scaled because the individual tests had very different ranges of scores and some tests had
13 physical units such as REL Test - forces & torques. Scaled data was then statistically
14 processed to obtain minimum, mean, maximum, and standard deviation values, which are
15 presented in Tables 3 and 4. The difference between mean scores obtained on discharge
16 and admission for both Groups A and B are shown in Figure 5. “Box and Whisker” plot
17 of the same data is provided in Figure 4. From Figures 4 and 5, and Tables 3 and 4 the
18 following conclusions can be drawn:

- 19
- Group A subjects (control group) who were administered standard physiotherapy
20 and occupational therapy appropriate for severe hemiplegic patients did not
21 improve their arm and hand functions substantially according to mean values of
22 the REL, FMA, and CMSMR tests. However, these subjects showed substantial
23 improvement in the FIM and BI scores.

1

2

Figures 4 and 3 should be placed here

3

4

5 **Results of the Statistical Analysis**

6

7 The results of the statistical analysis are presented in Table 5. In Table 5, items with dark
8 gray background and white bold font indicate that the hypothesis can be accepted, and the
9 items with light gray background and bold black fonts indicate that the hypothesis should
10 be rejected. In summary, the results of the analysis suggest the following:

11

- 12 1. Subjects in Groups A and B were selected in random fashion, i.e. Hypothesis 1
13 could not be rejected. Subjects in both groups had similar arm and hand
14 functions, and had similar abilities to perform ADL when they were assigned to
15 the groups.
- 16 2. Subjects in Group A, after the treatment was completed, only improved the FIM
17 and BI scores; the arm and hand function scores (REL, FMA and CMSMR
18 scores) did not improve significantly. In other words, Hypotheses 3.6 and 3.7
19 were rejected with alphas 0.005 ($P = 0.001$) and 0.01 ($P = 0.007$), respectively,
20 while Hypotheses 3.1, 3.2, 3.3, 3.4, 3.5, 3.8 and 3.9 could not be rejected.
- 21 3. When Group A and Group B subjects were compared on discharge, subjects in
22 Group B showed significant improvement in the arm and hand functions
23 compared to Group A subjects, as shown with the REL Test - object

1 manipulation, REL Test – forces, REL Test - torques, FMA, BI, and CMSMR
2 scores. Also, the FIM, REL Test – blocks and REL Test - eccentric load showed
3 improvements in function; however, the significance of the changes could not be
4 demonstrated with the given number of subjects. In other words, Hypotheses 2.1,
5 2.3, 2.4, 2.7, 2.8 and 2.9 were rejected with alphas 0.005 ($P = 0.002$), 0.01 ($P =$
6 0.008), 0.005 ($P = 0.002$), 0.05 ($P = 0.048$), 0.005 ($P = 0.002$), and 0.05 ($P =$
7 0.025), respectively, while Hypotheses 2.2, 2.5 and 2.6 could not be rejected.

8

9

Table 5 should be placed here

10

11 In summary, the statistical analysis confirmed our hypothesis that the neuroprosthesis
12 therapy gives rise to greater improvement in arm and hand functions, compared to
13 traditional physiotherapy and occupational therapy alone.

14

15

16 **Observations Pertaining to Group B Subjects:**

17

18 During the treatment, all patients reached a functional plateau after twelve to sixteen
19 weeks of neuroprosthesis treatment. In addition to arm/hand function improvement, the
20 subjects also improved the way they controlled their upper body during sitting, standing,
21 and walking. All subjects reported that they felt more natural with respect to their arm,
22 and that the arm “followed” the natural movements of the body after the FES treatment
23 was completed. In addition, subjects who had shoulder subluxation and had to take pain

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1 medication because of it (Group B, subjects 3 and 4), did not have shoulder subluxation
2 after the neuroprosthesis treatment and stopped taking the pain medication.

3 We have observed that the initial improvements in reaching and grasping
4 functions due to the neuroprosthesis training have strongly motivated patients to continue
5 participating in the program. Furthermore, the reinforced motivation and the regained
6 function encouraged patients to increase active use of the paralyzed arm and hand in
7 ADL, which further promoted recovery and gradually eliminated the “learned non-use
8 pattern” typical for these patients.

9

1

2

DISCUSSION

3

4 We compared the outcomes of two groups of hemiplegic stroke subjects with severe
5 unilateral upper extremity paralysis. One group of subjects was administered
6 conventional occupational therapy and physiotherapy, commonly applied to rehabilitate
7 these patients. The other group was administered neuroprosthesis therapy. The results of
8 this study have shown that the subjects who were treated with the neuroprosthesis for
9 reaching and grasping improved significantly compared to control subjects.

10 Our study differs from previously published results in the following ways. First,
11 our patients were unable to move the paralyzed arm at all or were able to perform very
12 limited movements with the arm, and as such, were not candidates for constraint induced
13 therapy [9,10], or FES therapy proposed by Popovic et al. [11] and Cauraugh et al. [12],
14 or biofeedback therapy [13-15]. As the patients regained some components of the
15 voluntary active movement of the arm and hand, the FES support for those recovered
16 components of the movement were phased out. Second, the recovery achieved with our
17 treatment produced radical improvements in arm and hand functions, instead of
18 incremental improvements observed with constraint induced therapy and FES therapy
19 proposed by Popovic et al. and Cauraugh et al. [11,12]

20 We believe that our results provide more compelling evidence that FES therapy
21 can be successfully used, not only to treat mild and moderate arm paralysis in hemiplegic
22 patients, but also to treat patients with severe paralysis. Second, our treatment protocol
23 stresses the importance of applying surface FES treatment that can be tailored/adjusted to

1 patients' needs on a daily basis and can evolve as the patients improve their function.
2 Third, our findings suggest that if a hemiplegic patient who strains to execute a reaching
3 or grasping task is assisted with the FES to carry out that task, he/she is effectively
4 voluntarily generating the motor command (desire to move the arm, i.e. *command input*)
5 and FES is providing the afferent feedbacks (*system's output*), indicating that the
6 command was executed successfully. We hypothesize that, by providing both the
7 command input and system's output to the central nervous system repetitively for
8 prolonged periods of time, this type of treatment facilitates functional reorganization and
9 retraining of intact parts of the of central nervous system and allows them to take over the
10 function of the damaged part of the central nervous system. It is important to add that
11 during the treatment, the subjects were performing reaching and grasping tasks
12 repetitively. However, the exact reaching and grasping tasks differed from day to day to
13 encompass as many different reaching and grasping strategies and arm kinematic
14 configurations as possible. We believe that diversity of meaningful tasks combined with
15 high repetition may play an important role in retraining reaching and grasping functions.
16 Similar findings were also reported by Hesse et al. [16]

17 The results presented in this article clearly indicate that in severe hemiplegic
18 patients, improvement of the unilateral arm function when the other arm is fully
19 functional have little or no effect on the improvement in FIM scores. Second, the results
20 also indicate that a hemiplegic subject can achieve high FIM and BI scores in spite of
21 having one arm completely paralyzed. Third, the results also suggest that established
22 physiotherapy and occupational therapy commonly administered to severe hemiplegic
23 subjects have a positive effect on the improvement of the unilateral arm and hand

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1 functions. However, these positive changes have very limited impact on object
2 manipulation tasks, i.e., in spite of improvement, subjects still have very limited ability to
3 grasp and manipulate objects in ADL, as shown by the REL Test scores, CMSMR and
4 FMA. On the other hand, subjects that were administered the neuroprosthesis treatment
5 achieved substantially greater improvements in the arm and hand functions compared to
6 the control subjects, and were able to apply them effectively in ADL, as shown by the
7 REL Test scores, CMSMR and FMA.

8 Although this is an ongoing study, and thus far only 13 subjects participated, (five
9 who were administered the neuroprosthesis therapy and eight control subjects) the
10 obtained results are statistically significant. This clearly indicates that the
11 neuroprosthesis treatment provides significant and radical improvement in reaching and
12 grasping function in severe hemiplegic patients with unilateral arm deficit, compared to
13 established rehabilitation techniques. Since the number of subjects used to produce these
14 results was very low, we feel confident that additional subjects will further reinforce
15 these findings and would help reject hypotheses 2.2 and 2.5 (the differences for the REL
16 Test – blocks and REL Test - eccentric load tests for Group A and Group B, before and
17 after the therapy are the same). Our future work is aimed at better understanding the
18 mechanisms responsible for the success of the proposed neuroprosthesis therapy.

19

1

2 **Weaknesses of the Study**

3

4 The nature of the neuroprosthesis therapy did not allow us to blind the therapists and
5 participants from the knowledge of which participant received the neuroprosthesis
6 therapy and which participants were controls. Furthermore, despite our efforts to blind
7 the assessor from the knowledge of which of the two groups individual patients were
8 assigned to, the assessor was able to realize which subjects received the neuroprosthesis
9 therapy. The reason for this was substantial difference in final outcomes in patients that
10 participated in the neuroprosthesis therapy compared to controls.

11

12

13 **CONCLUSIONS**

14

15 A neuroprosthesis that applies surface FES technology can be successfully used to
16 improve reaching and grasping functions in both acute and long-term hemiplegic patients
17 with severe arm paralysis. The key to the success of this therapy is a repetitive and
18 intensive neuroprosthesis treatment that can be tailored to a patient's needs on a daily
19 basis and can evolve as the patient improves his/her arm and hand functions.

20

1

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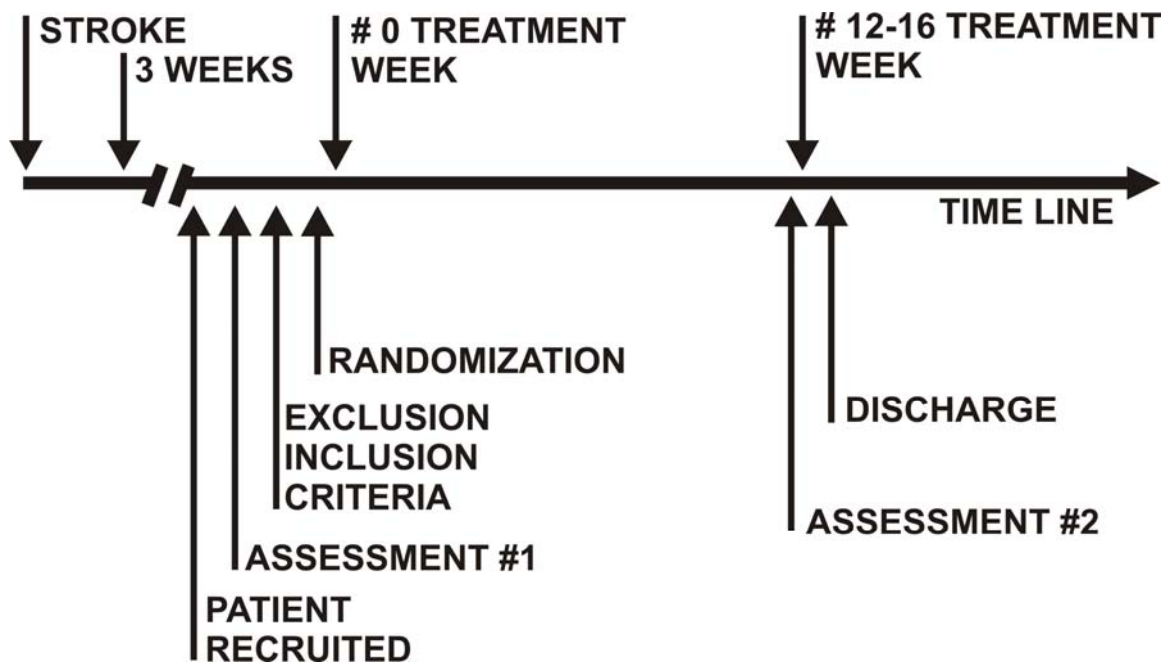
10 Program, Los Amigos Research and Education Institute, Rancho Los Amigos

11 Medical Center, 2000.

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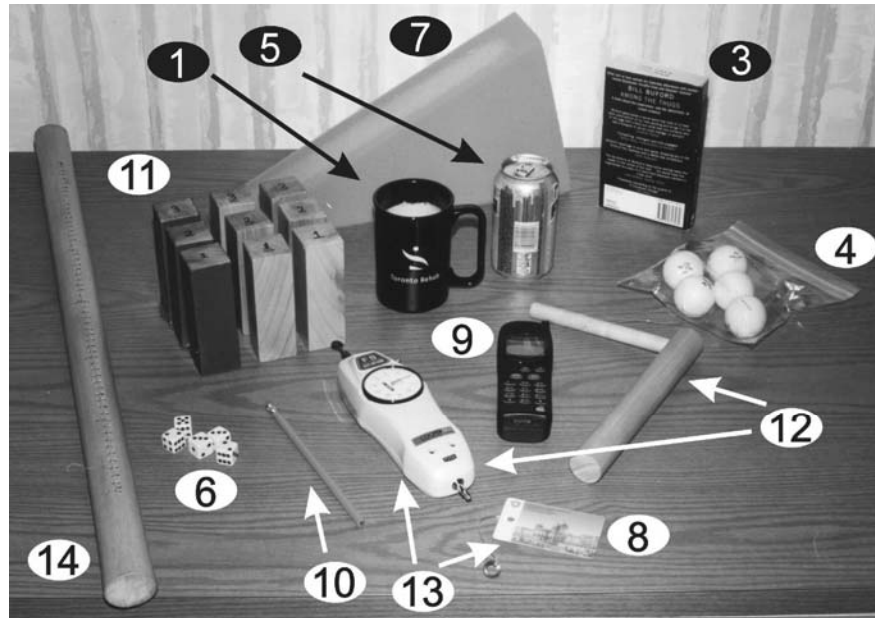
5 Figure 1: The flow chart of the recruitment, therapies and assessments that were applied
 6 to both controls and patients who participated in the neuroprosthesis (FES) therapy.

7

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5 Figure 2: The REL Hand Function Test: Itemized objects used in the test.

6

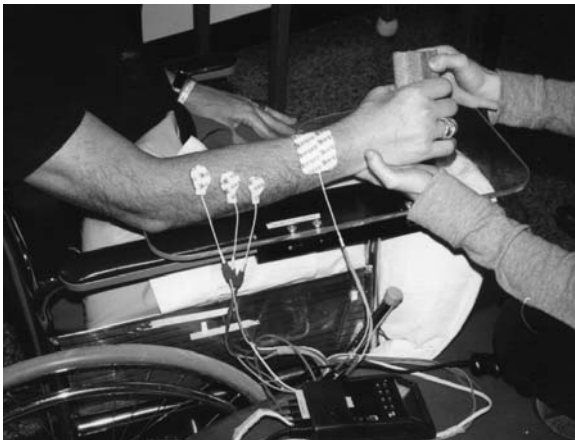
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3 a)

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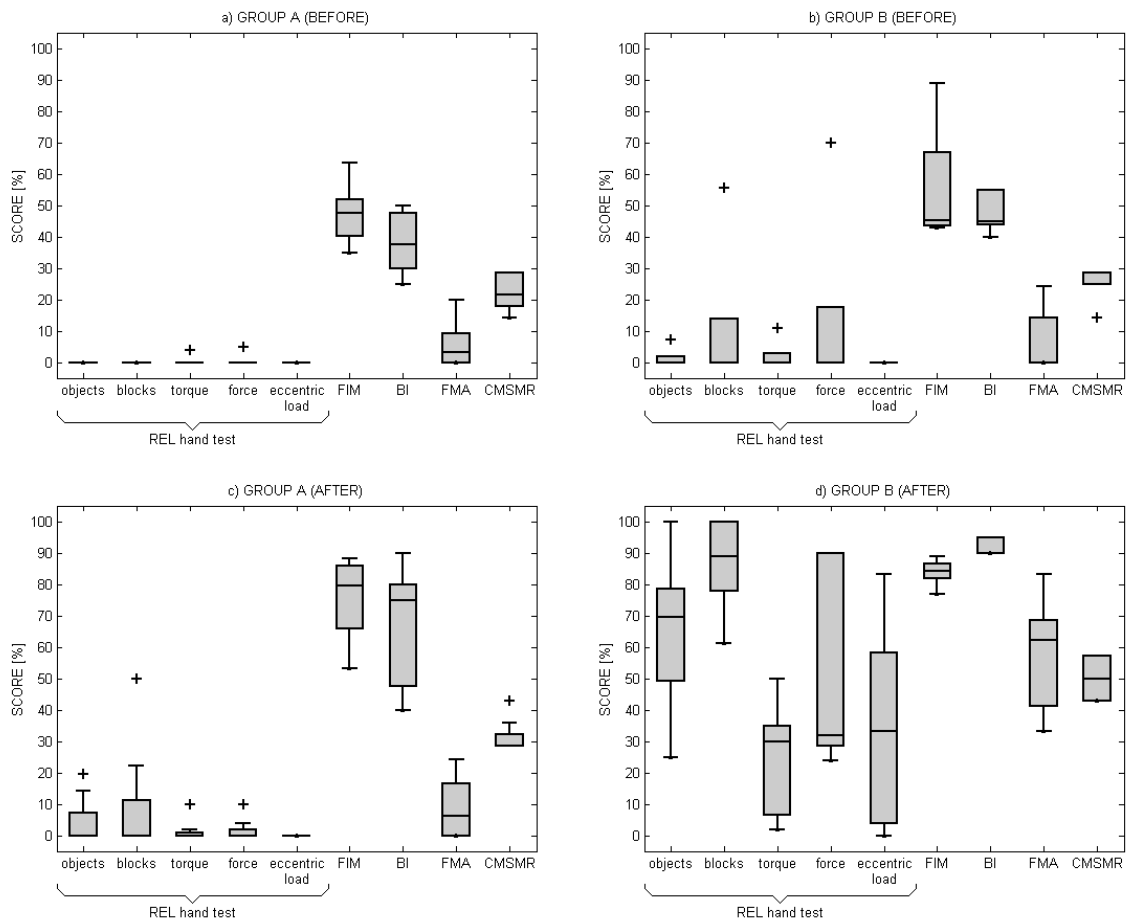
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6 b)

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8 Figure 3: a) Finger extension generated with the neuroprosthesis (FES) and b) Voluntary
9 finger flexion.

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4 Figure 4: “Box and Whisker” plots of the scaled data for REL Tests: object manipulation,

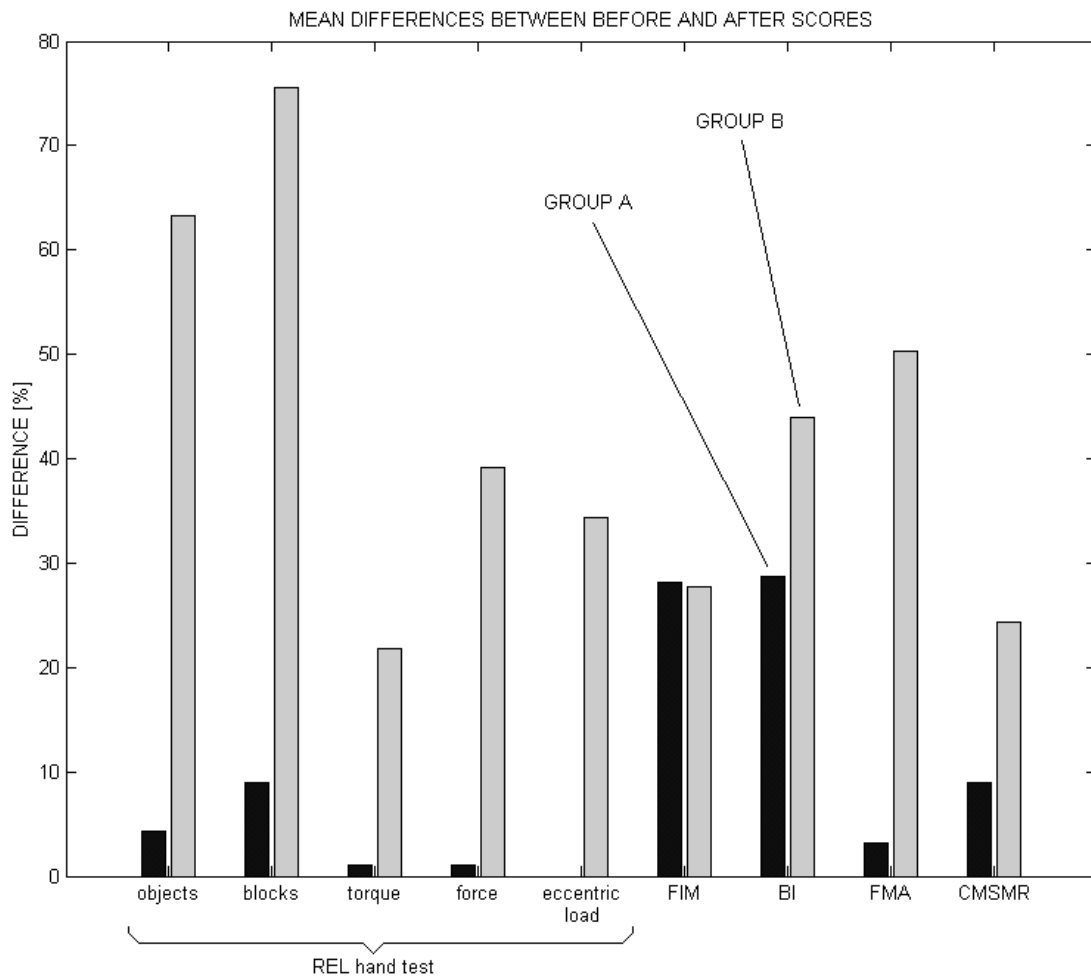
5 wooden blocks, torques, forces, and eccentric load; FIM; BI; FMA; and CMSMR tests: a)

6 Group A scores before the treatment; b) Group B scores before the treatment; c) Group A

7 scores after the treatment; and d) Group B scores after the treatment.

8

1



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3

4 Figure 5: Differences between the after and before mean scores for: 1) REL Test - object
 5 manipulation; 2) REL Test - wooden blocks; 3) REL Test - torques; 4) REL Test - forces;
 6 5) REL Test - eccentric load; 6) FIM; 7) BI; 8) FMA; and 9) CMSMR tests. The black
 7 bars represent the differences for Group A and the light gray bars represent the
 8 differences for Group B.

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1

Group A: Standard Therapy - Control Group

Subject	Sex	Age	Diagnosis	Affected arm	Treatment start date in days after stroke
1	F	48	Right cerebral infarct	Left	21
2	F	78	Right middle cerebral artery internal capsule stroke	Left	21
3	F	73	Right parietal bleed with mass effect	Left	19
4	M	69	Right thalamic stroke	Left	47
5	M	79	Right internal capsule stroke	Left	33
6	M	81	Left middle cerebral artery territory infarct	Right	46
7	F	39	Intracerebral hemorrhage in the left basal ganglia	Right	40
8	F	29	Right intracerebral hemorrhage	Right	33

Group B: Neuroprosthesis Intervention Group - Subjects who were administered the neuroprosthesis (FES) treatment

Subject	Sex	Age	Diagnosis	Affected arm	Treatment start date in days after stroke
1	M	73	Corona radiate, ischemic stroke	Right	338
2	M	32	Hemorrhage in the left lentiform nucleus	Left	19
3	F	50	Right introcranial hemorrhage	Left	57
4	M	59	Ischemic stroke in the left pons	Right	31
5	M	74	Cerebral vascular accident in the left hemisphere	Right	16

2

3 Table 1: Subjects' demographic data and stroke diagnosis

1

2

Subject	Number of delivered FES therapies <u>combined with</u> physiotherapy and occupational therapy	Number of delivered FES therapies <u>that were not combined with</u> physiotherapy and occupational therapy
1	0	77
2	36	0
3	18	59
4	31	62
5	28	0

3

4 Table 2: The exact number of therapy sessions delivered to Group B.

5

1

Group A: Standard Therapy - Control Group

Admissions Test (BEFORE)

Subject	REL Test					FIM	BI	FMA	CMSMR
	objects	blocks	torques (Nm)	forces (N)	eccentric load				
1	0	0	0	0	0	66	35	0	3
2	0	0	0	0	0	80	50	8	3
3	0	0	0	0	0	56	50	13	4
4	0	0	0.2	2.5	0	45	25	4	2
5	0	0	0	0	0	44	40	0	4
6	0	0	0	0	0	61	30	4	3
7	0	0	0	0	0	59	45	0	4
8	0	0	0	0	0	65	30	0	2
Upper limit	56	18	5	50	60	126	100	66	14

Statistically processed data presented in % of the maximum scores that can be achieved with the individual tests

Min.	0	0	0	0	0	34.9	25	0	14.3
Mean	0	0	0.5	0.63	0	47.2	38.1	5.49	22.3
Max.	0	0	4	5	0	63.5	50	19.7	28.6
S.D.	0	0	1.41	1.76	0	9.28	9.61	7.24	5.96

Discharge Test (AFTER)

Subject	REL Test					FIM	BI	FMA	CMSMR
	objects	blocks	torques (Nm)	forces (N)	eccentric load				
1	0	0	0	0	0	111	75	0	4
2	0	0	0	0	0	103	80	8	4
3	8	4	0.1	2	0	97	80	16	6
4	11	9	0.5	5	0	92	40	14	5
5	0	0	0	0	0	67	50	0	4
6	0	0	0	0	0	74	45	4	4
7	0	0	0	0	0	110	90	0	4
8	0	0	0	0	0	106	75	4	4
Upper limit	56	18	5	50	60	126	100	66	14

Statistically processed data presented in % of the maximum scores that can be achieved with the individual tests

Min.	0	0	0	0	0	53.17	40	0	28.57
Mean	4.24	9.03	1.5	1.75	0	75.40	66.88	8.712	31.25
Max.	19.6	50	10	10	0	88.10	90	24.24	42.86
S.D.	7.982	18.29	3.505	3.615	0	13.09	18.89	9.642	5.314

2

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- 1 Table 3: Raw data collected with Group A (control group) at admission and discharge,
- 2 and the statistics of the collected data.

1

Group B: Neuroprosthesis Intervention Group - Subjects who were administered the neuroprosthesis (FES) treatment

Admissions Test (BEFORE)

Subject	REL Test					FIM	BI	FMA	CMSMR
	objects	blocks	torques (Nm)	Forces (N)	eccentric load				
1	4	10	0.55	35	0	112	55	16	4
2	0	0	0	0	0	57	45	0	2
3	0	0	0	0	0	75	40	0	4
4	0	0	0	0	0	54	55	0	4
5	0	0	0	0	0	55	45	7	4
Upper limit	56	18	5	50	60	126	100	66	14

Statistically processed data presented in % of the maximum scores that can be achieved with the individual tests

Min.	0	0	0	0	0	42.86	40	0	14.29
Mean	1.429	11.11	2.2	14	0	56.03	48	6.970	25.71
Max.	7.143	55.56	11	70	0	88.89	55	24.24	28.57
S.D.	3.194	24.85	4.919	31.31	0	19.59	6.708	10.69	6.389

Discharge Test (AFTER)

Subject	REL Test					FIM	BI	FMA	CMSMR
	objects	blocks	torques (Nm)	Forces (N)	eccentric load				
1	32	18	2.5	45	50	112	95	42	8
2	39	15	1.5	12	3	108	95	41	8
3	14	11	0.4	16	0	106	90	22	7
4	40	16	1.5	45	30	105	90	41	6
5	56	18	0.1	15	20	97	90	55	6
Upper limit	56	18	5	50	60	126	100	66	14

Statistically processed data presented in % of the maximum scores that can be achieved with the individual tests

Min.	25	61.11	2	24	0	76.98	90	33.33	42.86
Mean	64.64	86.67	24	53.2	34.33	83.81	92	60.919	50
Max.	100	100	50	90	83.33	88.89	95	83.33	57.14
S.D.	27.15	16.01	19.29	33.72	34.23	4.369	2.739	17.84	7.143

2

3 Table 4: Raw data collected with Group B (intervention group) on admission and
 4 discharge, and the statistics of the collected data.

1

	Statistics	REL Test					FIM	BI	FMA	CMSMR
		objects	blocks	torques	forces	eccentric load				
Hypothesis		1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9
Group A before versus Group B before	T-stat	39	39	37	37	35	37	46.5	34	39
	p-value	0.769	0.769	0.769	0.769	1.000	0.833	0.099	0.957	0.769

	Statistics	REL Test					FIM	BI	FMA	CMSMR
		objects	blocks	torques	forces	eccentric load				
Hypothesis		2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9
Group A delta versus Group B delta	T-stat	55	48	52.5	55	47	38	48.5	55	50.05
	p-value	0.002	0.053	0.008	0.002	0.070	0.681	0.048	0.002	0.025

	Statistics	REL Test					FIM	BI	FMA	CMSMR
		objects	blocks	torques	forces	eccentric load				
Hypothesis		3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9
Group A before versus Group A after	T-stat	60	60	64	64	68	38	43	64.5	60
	p-value	0.467	0.467	0.733	0.733	1	0.001	0.007	0.761	0.467

2

3 Table 5: Results of the Wilcoxon rank-sum analysis conducted to test Hypotheses: 1.1 –

4 1.9, 2.1 – 2.9 and 3.1 – 3.9. Items with dark gray background and white bold fonts

5 indicate that the hypothesis can be rejected ($p < 0.05$). Items with light gray background6 and black bold fonts indicate that the hypothesis could not be rejected ($p > 0.05$).

7

8