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Neuroplasticity of prehensile neural networks after quadriplegia

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3 *Franck Di Rienzo¹, Aymeric Guillot^{1,5}, Sébastien Mateo^{1,2}, Sébastien Daligault³, Claude Delpuech^{3,4},*
4
5 *Gilles Rode^{2,4} & Christian Collet¹*

6
7
8 ¹Université de Lyon, Université Claude Bernard Lyon 1, Centre de Recherche et d'Innovation sur le
9 Sport (EA 647), F-69622, Villeurbanne, France.

10
11 ²Hôpital Henri Gabrielle, Hospices Civils de Lyon, F-69230, Saint Genis-Laval, France.

12
13 ³CERMEP imagerie du vivant, Département MEG, F-69677, Bron, France.

14
15 ⁴INSERM U1028, CNRS UMR5292, Centre des neurosciences de Lyon, F-69000, Lyon, France.

16
17 ⁵Institut Universitaire de France, F-75000, Paris, France.

Corresponding author

18
19 Pr. Christian Collet

20
21 Université Claude Bernard Lyon 1

22
23 Centre de Recherche et d'Innovation sur le Sport

24
25 27-29 Boulevard du 11 Novembre 1918,

26
27 Villeurbanne, France, 69622

28
29 Mail: christian.collet@univ-lyon1.fr

30
31 Tél : (33) 472 431 092

32
33 Fax : (33) 472 448 010

Abstract

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3 Targeting cortical neuroplasticity through rehabilitation-based practice is believed to enhance
4 functional recovery after spinal cord injury (SCI). While prehensile performance is severely disturbed
5 after C6-C7 SCI, subjects with tetraplegia can learn a compensatory passive prehension using the
6 *tenodesis* effect. During tenodesis, the active wrist extension triggers a passive flexion of the fingers
7 allowing grasping. We investigated whether motor imagery training could promote activity-dependent
8 neuroplasticity and improve prehensile tenodesis performance. SCI participants ($n = 6$) and healthy
9 participants ($n = 6$) took part in a repeated measurement design. After an extended baseline period of
10 three weeks including repeated magnetoencephalography (MEG) measurements, MI training was
11 embedded within the classical course of physiotherapy for five additional weeks (3 sessions per week).
12 An immediate MEG post-test and a follow up at two months were performed. Before MI training,
13 compensatory activations and recruitment of deafferented cortical regions characterized the cortical
14 activity during actual and imagined prehension in SCI participants. After MI training, MEG data
15 yielded reduced compensatory activations. Cortical recruitment became similar to that in healthy
16 participants. Behavioral analysis evidenced decreased movement variability suggesting motor learning
17 of tenodesis. The data suggest that MI training participated to reverse compensatory neuroplasticity in
18 SCI participants, and promoted the integration of new upper limb prehensile coordination in the neural
19 networks functionally dedicated to the control of healthy prehension before injury.
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41 **Keywords:** Magnetoencephalography, rehabilitation, spinal cord injury
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1. Introduction

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3 Spinal Cord Injury (SCI) is the traumatic disruption of the neural pathways between the brain
4 and the peripheral effectors. Extensive cortical reorganizations due to neuroplasticity occur after SCI
5 (for a review, see Kokotilo et al., 2009). Transcranial magnetic stimulation studies evidenced higher
6 levels of corticospinal excitability in muscles innervated above the level of injury (Levy et al., 1990,
7 Topka et al., 1991, Streletz et al., 1995). Brain imaging studies provided evidence that disconnected
8 brain regions became progressively re-assigned to the control of spared movements represented in
9 adjacent sites of the cortical homonculus (Bruehlmeier et al., 1998, Lotze et al., 1999a, Curt et al.,
10 2002, Mikulis et al., 2002). Overall, cortical neuroplasticity after SCI appeared to “*maximize output*”
11 to the unaffected muscles (for a review, see Nardone et al., 2013). Jurkiewicz et al. (2007) reported
12 that concentration of activations within the primary motor cortex and decreased activity within
13 secondary brain motor regions during wrist extensions correlated with functional recovery during the
14 first year post-injury (see also Green et al., 1999). Targeting cortical neuroplasticity through
15 rehabilitation-based practice may thus lead to better understand the recovery processes after complete
16 SCI.
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35 Activity-dependent neuroplasticity inspired the development of rehabilitation strategies after
36 SCI (for review, see Dunlop, 2008, Harvey et al., 2009). These foremost involve PP-based training
37 (*e.g.*, physiotherapy, robot-assisted motor training). Interestingly, Motor Imagery (MI, the mental
38 representation of an action without engaging in its actual execution) represents an “*emerging avenue*”
39 to CNS stimulation after SCI (Dunlop, 2008). A large body of neuroscience research provided
40 evidence that MI and PP were functionally equivalent neural processes, *i.e.*, both tasks engage
41 overlapping structures within the brain motor network underlying actual motor preparation and
42 execution (Decety et al., 1994, Jeannerod, 1994, Porro et al., 1996, Lotze et al., 1999b, Ehrsson et al.,
43 2003, Lotze and Halsband, 2006, Szameitat et al., 2007b, a, Guillot et al., 2012a, Szameitat et al.,
44 2012, Burianova et al., 2013, Héту et al., 2013). Reduced activations intensities by 30 to 50 % are
45 usually recorded during MI compared to PP (Porro et al., 1996, Lotze and Halsband, 2006, Munzert et
46 al., 2009). Nonetheless, MI elicits sufficient CNS activation to stimulate cerebral neuroplasticity,
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thereby promoting motor learning and increased muscle performance in healthy participants (Pascual-Leone et al., 1995, Ranganathan et al., 2004). Functional equivalence between PP and MI is preserved for spared actions after complete SCI (Lacourse et al., 1999, Di Rienzo et al., 2013, Di Rienzo et al., 2014), and Cramer et al. (2007) provided evidence that SCI participants benefited from MI training to learn actions executed with muscles retaining a voluntary control.

Human prehension involves reaching and grasping objects within the haptic space (van de Kamp and Zaal, 2007). This function is severely disturbed after cervical SCI (Harvey, 1996, Snoek et al., 2004, Snoek et al., 2008). According to the surgical classification of Giens (McDowell et al., 1986), finger and forearm muscles are paralyzed from the C6/C7 level. Accordingly, how can C6/C7 quadriplegic SCI participants achieve manual prehension in spite of finger and forearm muscles paralysis? SCI participants must learn a different pattern of prehension through extensive rehabilitation. Voluntary control of shoulder muscles is preserved, while active elbow and wrist extension remain possible due to residual control of the *triceps brachii* and *extensors carpi radialis*. Arm and hand positions during reaching can be controlled by proximal shoulder muscles while grasping is achieved with the tenodesis effect, *i.e.*, an active extension of the wrist triggers a passive flexion of the fingers (Harvey et al., 2001, Mateo et al., 2012). Tenodesis prehension (TP) is thus a compensatory prehension that require new motor programs (*e.g.*, Mateo et al., 2012). Recent findings provided evidence that MI training improved the kinematic parameters of TP after cervical SCI, particularly movement speed and accuracy (Grangeon et al., 2010, Grangeon et al., 2012). MI was assumed to stimulate activity-dependent neuroplasticity. Grangeon et al. (2012) nonetheless underlined that their results were to be replicated on larger sample of SCI participants.

Prehension is controlled by a widespread cortical network involving frontal, parietal and occipital associative cortices interacting with primary somatosensory and motor structures (Jeannerod et al., 1995, Rizzolatti et al., 1996, Binkofski et al., 1998, Kuhtz-Buschbeck et al., 2001, Grafton, 2010). Whether similar neural networks underpin TP in C6/C7 quadriplegic participants is a first interest. A second issue relates the effect of MI training on TP, and the associated effects on the neural networks controlling PP and MI of prehension. Also, previous studies reporting the preservation of

1 functional equivalence between MI and PP after SCI foremost involved *simple* motor sequences which
2 could be easily executed physically (Lacourse et al., 1999, Sabbah et al., 2002, Di Rienzo et al., 2013).
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4 However, Olsson (2012) showed reduced recruitment of the motor system during MI of *complex*
5 motor sequences that were impossible to perform physically after SCI. Olsson (2012) argued that the
6 lack of PP due to chronic deafferentation and deafferentation led to the degradation of complex motor
7 representations. Whether C6/C7 quadriplegic participants are able to achieve MI of TP with a high
8 degree of functional equivalence in spite the complexity of this skill is a final issue of interest. Using
9 magnetoencephalography (MEG), we examined the effect of 5-week of MI training on TP
10 performance in C6/C7 SCI participants. MI was integrated to the course of physiotherapy. MEG
11 afforded investigation of cortical activity underlying actual and imagined TP.
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23 **2. Experimental procedures**

24 *2.1. Participants*

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29 SCI participants ($n = 6$) (5 right handed, 2 females) were recruited from the Henri Gabrielle
30 hospital (St Genis Laval, France) over a 1 year period of inclusion. Inclusion criteria were: *i*) age range
31 18-55 years, *ii*) SCI at the C6/C7 level eliciting complete motor deficit according to the American
32 Spinal Injury Association (ASIA) impairment scale (Maynard et al., 1997), *iii*) post-traumatic period
33 superior to 6 months (*i.e.*, corresponding to the spontaneous motor recovery plateau; Waters et al.,
34 1993, Yakura, 1996). Exclusion criteria were: *i*) non-stabilized hypertension or pathological
35 dysfunction of the autonomic nervous system, *ii*) cerebral damage and / or cognitive deficit, *iii*) elbow
36 or shoulder joint amplitude restriction, upper limb para osteo-arthritis, *iv*) simultaneous inclusion
37 to another study, and *v*) presence of metallic objects within the body (*e.g.* pacemaker, auditory device
38 or brace) incompatible with MEG or fMRI recordings. HPs matched to SCI participants according to
39 gender, age (± 1 year) and handedness were recruited as controls.
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55 All participants provided informed written consent according to the statements of the
56 Declaration of Helsinki. This study was performed under approval of the Lyon Civil Hospices ethic
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2 committee (CPP 2009-051-B), and was part of the Hospital Program for Clinical Research n° 2010-
3 541/142 registered under the trial number ACTRN12612001030864.
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5 2.2. *Experimental design*

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8 SCI participants were hospitalized across the duration of experiments, and underwent daily
9 standard medical care including physiotherapy (*e.g.*, passive limb mobilization, muscle strengthening
10 above the lesion level, etc.) and occupational therapy.
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14 We conducted repeated pre-test assessments over a five weeks period to define the baseline
15 level (Figure 1). Pre-tests were separated from each other by a minimum period of one week. Then,
16 individual MI sessions were embedded to the classical course of physiotherapy (3 sessions of 45 min
17 per week). MI sessions were delivered in a quiet room at the hospital. Spinal cord injury (SCI)
18 participants were seated on their wheelchair, in front of a table and performed imagined prehensile
19 actions with tenodesis in an ecological environment. All tasks were goal-directed. During the first
20 week, the experimenter showed the movement before the participant physically or mentally performed
21 it. Experimenter was assisted by physiotherapists who helped the SCI participant to achieve execution
22 of complex motor tasks. Training sessions were of increased complexity along the course of training,
23 based on SCI participants' abilities (*i.e.*, from simple pointing actions during familiarization to
24 complex sequences involving more rapid reaching/grasping of smaller, larger, or heavier objects
25 placed in the haptic space). Visual and kinesthetic imagery were both used during training, promoting
26 analysis of the kinematics and correcting inadequate executions. PP vs. MI training ratio was 1 to 5
27 and increased each week up to 1 to 9.
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47 The intervention period was followed by an immediate post-test and a follow-up at 2 months
48 (Figure 1). HPs underwent an identical procedure but performed a control task (*i.e.*, visualization of
49 geometric forms) during the 5 weeks allocated to MI training in the SCI group. The HPs group thus
50 only controlled for the general effect of MI training. The prehension used by HPs differed from TP,
51 and thus potential transfer of MI training to healthy prehension would be limited for a similar training
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*** Insert Figure 1 about here ***

2.3. Experimental sessions

Experimental sessions included MI assessments and MEG recordings (Figure 1).

2.3.1. Motor imagery ability assessment

During the first session, the participants completed the Kinesthetic and Visual Imagery Questionnaire (KVIQ; Malouin et al., 2007) (Figure 1). The KVIQ was aimed at testing whether HPs and SCI participants share comparable capacities to achieve vivid MI. It is made of 20 items involving axial movements with head and trunk, as well as upper and lower limb movements. Each participant reported immediately after completion of actual movement the level of MI vividness on a 5-point Likert scale using first person visual or kinesthetic MI. If the participant was not able to physically perform the movement, he was requested to observe its execution by the experimenter before each trial. Only KVIQ data related to MI of the dominant upper limb were processed.

The capacity to achieve temporal equivalence between PP and MI durations was used as behavioral index of MI accuracy (Guillot and Collet, 2005, Collet et al., 2011, Guillot et al., 2012b). The participants were requested to point to four cardinal points drawn on a 10 cm circle target in the clockwise direction with their dominant upper limb. They completed two PP and MI trials at each phase of the experimental procedure (Figure 1).

2.3.2. Magnetoencephalography recordings

The MEG was a CTF-MEG system (CERMEP, F-69677), with 275 radial gradiometers over the scalp and 33 reference channels for ambient field correction. MEG signals were digitalized at sampling rate of 600 Hz and low-pass filtered (0 - 150 Hz). Head position was controlled in real-time using three head coils placed on the nasion and pre-auricular points prior to scanning. Each participant was installed on the MEG seat by two physiotherapists under the supervision of a medical doctor. A wooden table was placed above their knees standardizing the position of the dominant hand and making the non-dominant arm lying in a comfortable position (Figure 2A). A fake apple was the target

1 placed in the sagittal plane within 60 % of the haptic space. Participants were requested to reach and
2 grasp the apple, to put it into contact with their mouth and then to place it back on the initial position
3 (Figure 2A). This motor sequence was selected for its complexity and its functionality.
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10 Participants were instructed to complete 10 successive trials of the prehensile sequence (PP
11 condition). Movement time (MT, from movement initiation until the participant has put the apple
12 again to its initial position) was recorded using optical fiber switch system (Figure 2BC). Each
13 participant also performed 10 MI trials of the same sequence using first-person and kinesthetic MI
14 concurrently (MI condition). Finally, they were instructed to remain motionless during 10 trials
15 (CONTROL condition). An auditory soundtrack provided instructions regarding each experimental
16 condition and triggered each trial every 15s. Experimental conditions were randomly presented three
17 times each within a block-design for a total of 30 trials in each condition. The number of trials was
18 expected to preserve SCI participants from deleterious effects of physical and mental fatigue.
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31 Anatomical MRI was recorded during the week preceding the first pretest for co-registration
32 with MEG data. A 1.5T Siemens Magnetom scanner (CERMEP, France - Siemens AG, Erlangen,
33 Germany) computed 3-dimensional anatomical T1 weighted pictures covering the whole brain with 1
34 mm³ cubic voxels (TR: 9.7 ms, TE: 4 ms).
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41 *2.3.3. Magnetoencephalography data processing*

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44 We used Synthetic Aperture Magnetometry (SAM) as beamformer to map the distribution of
45 event-related synchronization (ERS) and desynchronization (ERD) of brain oscillations. We
46 investigated MEG beta signals (15-30 Hz), as this frequency domain was shown particularly relevant
47 for the study of MI and motor execution networks in both HPs and SCI subjects (Burianova et al.,
48 2013, Di Rienzo et al., 2013). Brain rhythms encompassing few frequencies (*e.g.*, the mu-sensorimotor
49 rhythm) were not investigated. Considering the number of trials, beamforming imaging was expected
50 to be more powerful/reliable carried on MEG signals encompassing larger frequency domains
51 (Brookes et al., 2008). SAM displays the spatial distribution of event-related changes of power in
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1 defined brain rhythms using t-paired Jackknife statistics between an active and a control state. In the
2 present experiment, the active state duration corresponded to the median duration of the prehensile
3 sequence (PP condition). Depending on participants' ability to achieve temporal equivalence between
4 MI and PP, active state duration would remain unchanged between MI and PP conditions, otherwise
5 increased or shortened. Control state was placed before stimulus onset for each condition, and its
6 duration corresponded to the median PP duration throughout sessions and participants, thus ensuring
7 an identical reference period for computation of MEG contrasts.
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16 In the present design, the sample size was due to the highly specific inclusion criteria and
17 restricted inclusion period. We used a unique approach to delineate the neural underpinnings of actual
18 and imagined prehensile actions in HPs and SCI groups. SAM computes and displays t-contrast values
19 between active and control states at each point of a 3-dimensional cubic grid (5 mm) overlaid to the
20 anatomical MRI brain volume of each individual. We applied a statistical mask to each SAM map for
21 each experimental condition: SAM sites displaying t-contrast values between active and control states
22 inferior or equal to $t = 2$ were coded 0. SAM sites which displayed t-contrast values strictly superior to
23 $t = 2$ were coded 1. For each participant, masked SAM maps corresponding to each pretest were
24 summed for each experimental condition. Only SAM sites displaying maximal values (corresponding
25 to brain sites which elicited t-contrast ratios higher than $t = 2$ during each of the three pre-tests) were
26 considered part of the task-specific neural network (*i.e.*, each site thus corresponded to a $p = 1.10^{-4}$
27 level of statistical significance as SAM t-contrast values were computed on the basis of paired t-tests
28 with 30 trials per condition). For group analysis, we combined and normalized pre-tests masked SAM
29 maps for each experimental condition within the Talairach and Tournoux space (Talairach and
30 Tournoux, 1988) using AFNI® functions (<http://afni.nimh.nih.gov/>). Again, only SAM sites
31 displaying the maximal values were considered part of the task-related network of the group ($p = 1.10^{-4}$
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53 54 55 2.4. Statistical procedure 56 57 58 59 60 61 62 63 64 65

1 We performed the statistical analyses with R (R Core Team, 2014). Data normality was
2 checked through visual inspection of Q-Q plots, and the type 1 error rate settled at $\alpha = .05$.

3 4 5 *2.4.1. Motor imagery evaluations*

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8 Student's t-tests were used to compare KVIQ scores between groups. We tested the temporal
9 equivalence between PP and MI durations. We calculated Pearson's product-moment correlation
10 between PP and MI durations, and compared median PP and MI durations using a paired Student's t-
11 test.
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16 17 18 *2.4.1. Motor performance*

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21 MT and movement variability (MV, the variance of MT) were bootstrapped at the individual
22 level for each experimental session. We used R (R Core Team, 2014) and *lme4* (Bates et al., 2014) to
23 perform a linear mixed effects analysis (Winter, 2013). A rank transformation of MT and MV was
24 applied to increase the statistical power (Baguley, 2012). As fixed effect, we entered the interaction
25 between group and experimental session. As random effect, we had intercepts by subjects. Visual
26 inspection of the residual plots did not reveal any deviations from homoscedasticity or normality. The
27 *p*-values were obtained using likelihood ratio tests of the full model against the model without the
28 effect in question. For post-hoc investigations, mixed linear models were applied on datasets from
29 which classes of the factors considered were removed to allow dual comparisons. Holm's sequential
30 corrections were applied to control the false discovery rate (Holm, 1979).
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44 *2.4.1. MEG*

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47 Due to the stringent procedure used to disclose MEG activation sources underlying actual and
48 imagined prehensile actions in HPs and SCI groups (see above), we opted for descriptive between- and
49 intra-group comparisons.
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54 **3. Results**

55 56 57 58 *3.1. Motor imagery evaluations*

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2 Mean ($\pm SD$) KVIQ visual (HPs = 4.33 ± 0.47 ; SCI = 3.55 ± 0.95) and kinesthetic sub scores
3 (HPs = 3.66 ± 0.44 ; SCI = 3.83 ± 0.91), as well as KVIQ total scores (HPs = 3.91 ± 0.41 ; SCI = $3.66 \pm$
4 0.91), were comparable in both the HCs and the SCI group ($t = -1.78, p = 0.12$; $t = 0.54, p = 0.60$; $t = -$
5 $0.67, p = 0.52$; respectively). Data from the mental chronometry task showed significant correlation
6 between MI and PP durations at the whole-group level ($r = 0.94, p < .001$). No significant difference
7 emerged between MI and PP durations ($t = 0.46, p = 0.66$). Accordingly, we used similar SAM time
8 windows for MEG data analysis during PP and MI conditions.
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10 11 12 13 14 15 16 3.2. Motor performance data 17

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19 Mixed linear models revealed the significant interaction between group and experimental
20 session on MV ($\chi^2(4) = 25.60, p < .01$), but not on MT ($\chi^2(4) = 7.56, p = .11$). The statistical power
21 of the test for MV was .83. Post-hoc investigations revealed a higher MV during the pre-test 3 as
22 compared to the pre-test 2 in HPs ($p < .05$) whereas, in the SCI group, MV during the post-test 1 was
23 lower than during each of the pre-tests by 70-76 % (all $p < .01$), see Figure 3.
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35 Linear models also yielded significant group effects on MT ($\chi^2(4) = 19.15, p < .001$) and MV
36 ($\chi^2(4) = 19.74, p < .001$), with a statistical power of .98 and .99, respectively. As shown in Figure 3,
37 comparisons between groups showed lower MT and MV in HPs compared to SCI subjects, for each
38 experimental session (all $p < .01$). MT values ranged between 3.62 to 4.30 s in HPs and 7.00 to 8.00 s
39 in SCI groups. Based on MT data, SAM control state duration was settled at 5.75 s (see methods).
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50 SAM maps yielded clear ERD patterns during PP and MI conditions in both groups. No brain
51 region reached the required level of statistical significance during the CONTROL condition in both
52 groups.
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56 57 3.3.1. Pre-tests 58 59 60 61 62 63 64 65

1 During PP, both SCI and HP groups recruited a widespread cortical network that encompassed
2 the contralateral pre-central gyrus, left inferior parietal lobe and precuneus (Figure 4 and Table 1). HPs
3 recruited portions of the contralateral pre-central gyrus corresponding to the hand area, whereas
4 portions of the pre-central gyrus corresponding to the representation of the legs were activated in SCI
5 participants (*i.e.*, activation located more medially) (Figure 4). Finally recruitment of the contralateral
6 post-central gyrus was observed in the HP but not in the SCI group, while contralateral precuneus
7 activations extended anteriorly towards the paracentral lobe in SCI subjects only. Ipsilateral
8 activations were also present. Both groups recruited the ipsilateral pre- and post-central gyrii, and
9 inferior parietal lobe (Figure 4 and Table 1).

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21 During MI, no ipsilateral activations were detected in SCI and HPs groups. Strong overlap
22 with contralateral brain regions activated during PP was noted. Activations were detected in both
23 groups in the pre- and post-central gyrii, superior parietal lobe and precuneus. Compared to HPs, no
24 activation of the inferior parietal lobe was present in SCI subjects. Similarly as during PP, precuneus
25 activations extended to the paracentral lobe in SCI participants but not in HPs. SCI participants
26 recruited portions of the post-central gyrus corresponding to the representation of lower limbs within
27 the sensory homunculus, whereas HPs recruited sites corresponding to hand representation (see Figure
28 4 and Table 1). Surprisingly, however, SCI and HPs both recruited portions of the pre-central gyrus
29 corresponding to the hand motor area (see Table 1).

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44 3.3.2. *Post-test*

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48 There was no MV difference between post-test 1 and 2 in SCI participants ($p > .05$), albeit
49 mean MV slightly increased in post-test 2 (Figure 3). Accordingly, masked post-test 1 and 2 SAM
50 activation maps were combined to increase the statistical power of post-test MEG analyses. We used
51 the same procedure for pre-tests SAM activation maps. Only sites showing the maximal score were
52 taken into account (*i.e.*, corresponding to a $p < 1.10^{-15}$ level of statistical significance).
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1 During PP, both groups recruited the contralateral pre- and post-central gyrii, inferior parietal
2 lobe and precuneus. Recruitment of the upper limb motor representation within the motor and
3 somatosensory homunculi was present in both groups, whereas it was not the case in SCI subjects
4 during the pre-tests (Figure 4 and Table 1). Furthermore, activation of the the contralateral superior
5 parietal lobe was recorded in SCI subjects only. SCI subjects finally showed reduced ipsilateral
6 involvement of the pre- and post-central gyrii as compared to HPs.
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13 Only contralateral activity was present in HP and SCI groups, similarly as during the pre-tests.
14 Brain activation during MI was congruent with that during PP. Pre- and post-central gyrii activations
15 were observed at sites corresponding to the hand representation within the motor and somatosensory
16 homunculi (Figure 4 and Table 1). We also observed the activation of the inferior parietal lobe while
17 the superior part was activated in HPs but not in SCI participants (Table 1).
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4. Discussion

This study addressed the neural networks controlling actual and imagined prehension in participants with SCI at C6-C7 level, before and after embedding MI training to the classical course of rehabilitation. In HCs, post-tests networks were similar to those activated during the pre-tests. As the HCs group did not receive any specific training intervention, this supports reliability of the MEG analysis procedure applied ensure power/reproducibility of the findings (Button et al., 2013).

4.1. Pre-tests data

MT and MV remained stable in HPs and SCI participants across the three pre-tests. TP is an intrinsically distinct skill from the usual pattern of healthy prehension (Laffont et al., 2000, Mateo et al., 2013). Nonetheless, MEG data yielded overlapping brain activations within bilateral pre-central gyrii, inferior parietal lobe and contralateral precuneus in both HCs and SCI groups. These regions are known to be part of the reaching and grasping networks (Jeannerod et al., 1995, Binkofski et al., 1998, Grafton, 2010, Davare et al., 2011). Particularly, the precuneus is involved in attention switches during target selection and visuo-motor processing during pointing to grasp sequences (for reviews, see Kawashima et al., 1995, Cavanna and Trimble, 2006). Contralateral paracentral lobe, superior parietal lobe and pre-motor cortex activation was observed only in SCI subjects. This may reflect the recruitment of a compensatory network during TP. Interestingly, the same pattern of pre-motor/parietal compensation was reported during attempted movements that were impossible to perform physically in SCI participants (Hotz-Boendermaker et al., 2008). Here, SCI participants also recruited cortical sites corresponding to the representation of limbs distal to the level of spinal injury within the primary motor cortex. This finding is congruent with data related to spontaneous neuroplasticity after SCI (e.g., Bruehlmeier et al., 1998, Lotze et al., 1999a, Mikulis et al., 2002, Lotze et al., 2006). Overall, compensatory activations and recruitment of deafferented motor networks support the hypothesis of low central integration of TP motor programs. Lastly, no contralateral post-central activation was evidenced during TP in SCI participants. Albeit SCI participants received

1 proprioceptive input from proximal upper limb body parts and forearm wrist extensors muscles during
2 TP, these may have been insufficient to elicit primary somatosensory cortex activation.
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5 SCI and HPs groups had comparable MI capacities based on psychometric and behavioral
6 evaluations. During MI, pre-tests MEG data yielded contralateral activations only. This result
7 contrasts with the bilateral cortical involvement observed during PP, but is in congruent with previous
8 brain imaging reports of MI (*e.g.*, Ehrsson et al., 2003, Michelon et al., 2006). Functional overlap
9 between MI and PP was present in both groups within the contralateral hemisphere (Figure 4 and
10 Table 1). The neural networks controlling imagined TP during the pre-tests were close to those
11 observed during PP. This result supports intact functional equivalence in spite the complexity of the
12 tenodesis sequence. Particularly, MI mirrored increased recruitment of the pre-motor network in SCI
13 subjects compared to HPs. Recruitment of cortical sites controlling the lower limbs within the primary
14 somatosensory cortex was also noted. Such pattern of activation may originate from kinesthetic
15 information processing during MI within a reorganized somatosensory system (Guillot et al., 2009).
16 Surprisingly, SCI participants recruited the hand motor representation within the pre-central gyrus,
17 similarly as HPs (Figure 4). The effector-specific recruitment of the primary motor cortex during
18 imagined, but not during actual, TP was not expected. Hypothetically, the representation of prehension
19 may be alimented and maintained by other sources of sensory input than proprioception (*e.g.*, action
20 observation engaging motor stimulation) (Vogt et al., 2013).
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41 *4.2. Post-tests data*

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45 MT and MV were higher in SCI subjects compared to HPs, which reflects the impaired
46 performance in the case of SCI (Mateo et al., 2013). MT remained unchanged after inclusion of MI
47 training in the rehabilitation program. MI practice focused on the kinematic aspects of tenodesis (see
48 Appendix 1), and did not involve instructions as regards movement speed. Accordingly, absence of
49 MT change is not surprising (Louis et al., 2008). During the post-test 1, MV was significantly lower in
50 SCI participants as compared to pre-tests values, thus attesting improved performance (Figure 4).
51 Embedding MI training within the rehabilitation program increased movement consistency. This effect
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1 was maintained two months after the intervention. MV no longer differed from pre-tests values (see
2 Grangeon et al., 2012 for an analogous patten of results). Baseline and intervention periods were of
3 equivalent duration in this design. TP improvements may thus be imputable to the adjunction of MI
4 training in the classical hospitalization program (*i.e.*, including physiotherapy). However, the present
5 study does not provide straightforward evidence of MI efficacy. Such hypothesis would require a
6 randomized controlled trial. For ethical reasons, a group of SCI participants not receiving MI training
7 program could not be included (*i.e.*, risk of unbalance between additional costs and potential benefits
8 associated with participation in the design for SCI participants in the control group)¹.
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18 The features of TP networks in SCI participants closely resembled those in HPs during the
19 post- tests as compared to pre-tests. Compensatory activations were no longer present. A striking
20 finding is that primary motor cortex recruitment switched back to the hand motor representation.
21 Accordingly, MI may have contributed to strengthen the task-specific recruitment of upper limb motor
22 networks. Activation of the contralateral superior parietal lobe was also noted in SCI but not in HPs.
23 The superior parietal lobe plays a crucial role in the preparation and online control of prehension
24 (Jeannerod et al., 1995, Grafton, 2010). During MI, precuneus activation was no longer present in both
25 HPs and SCI groups. This might reflect the habituation to the MI task in a repeated measures design.
26 Indeed, Guillot et al. (2008) highlighted the role of cuneus regions in the generation of motor images.
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39 Overall, post-test MEG data provided evidence for reversed cortical neuroplasticity underlying
40 reinforcement of TP programs. The networks were similar to those recorded in HPs performing
41 healthy prehensions. This original result shows that TP, a *compensatory* prehension, became
42 progressively integrated within neural networks functionally dedicated to the control of prehension.
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52 ¹ Counterbalanced interventions were also rejected due to risk of inequities during the early
53 stages of training (*i.e.*, as a group of SCI subjects would be receiving MI practice while the other not),
54 resulting in differential effects on motor recovery (higher gains are usually achieved during the early
55 stages of training).
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4.3. Limitations

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3 In this MEG experiment, we primarily observed cortical activations. Cramer et al. (2007)
4 reported plastic changes at the subcortical level after MI training in SCI subjects. This study required
5 memorization of sequences of foot and tongue movements. Here, TP was perceptually driven by the
6 functional purpose of grasping and placing an apple to the mouth. It is therefore obvious that changes
7 should primarily be observed within the cortical network underlying online control of TP, rather than
8 within sub-cortical centers of motor memory. Further, MEG is primarily sensitive to post-synaptic
9 current from apical dendrites of pyramidal neurons (Hari, 2005, Lopes da Silva and van Rotterdam,
10 2005). Detection of subcortical activity is usually achieved by a considerable number of trials, which
11 we could not afford here due to fatigability of SCI participants and risk of excessive duration allocated
12 to MEG recordings. The stringent procedure implemented for source localization, has made difficult
13 the detection of isolated subcortical sources. We did not detect frontal cortex activity during pre- and
14 post-tests in both groups, a structure with well-identified roles in the control of prehension (*e.g.*,
15 Jeannerod et al., 1995, Grol et al., 2007). This may be due to long SAM active state duration, which
16 encompassed all aspects of prehension sequences with MEG. Frontal regions are primarily involved in
17 visuo-motor processing during preparation of prehension (Botvinick et al., 2009, Grafton, 2010).
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5. Conclusions

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40 The present study investigated the neural underpinnings of TP before and after embedding MI
41 training to the classical course of rehabilitation. Functional equivalence between MI and PP was
42 preserved in SCI participants and reflected compensatory neuroplasticity during the pre-tests. MI
43 training restored effector-specific patterns of activity within the primary motor and somatosensory
44 cortices. These changes were associated with reduced movement variability suggesting increased
45 motor efficiency.
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Conflict of interest

The authors declare no conflict of interest.

Contributors

CC, GR, CD and AG designed the experiment. All authors participated to the experimental recordings. CD, SD, SM and FDR performed the MEG analyses. FDR carried on the statistical analyses and drafted the manuscript. All authors corrected and approved the final version of the manuscript.

Figure captions

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3 Figure 1. Experimental design including five experimental sessions (*i.e.*, 3 pre-tests and 2
4 post-tests).
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8 Figure 2. Experimental settings. A: Installation of participants within the MEG seat. The onset
9 of the 3 phases of prehension is provided. B: Optical fiber switch systems spotting hand and apple
10 movements from their standardized start positions. C: CTF® software displaying the sudden drops in
11 the optical fiber baseline for the hand and apple switch systems, thus spotting start and end of the
12 prehension.
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20 Figure 3. A: Median duration (*SD*) of prehension in SCI and HP across experimental sessions.
21 B: Median movement variability (*SD*) in the two groups. During pre-tests 2 and post-test 1, movement
22 variability was extremely low in HP. HP: Healthy participants, SCI: spinal cord injury.
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28 Figure 4. Neural networks controlling actual and imagined prehension during the three pre-
29 and the two post-tests, in healthy and spinal cord injury participants. The statistical threshold for
30 detection of activations in post-test is higher than that in the pre-tests since only two masked activation
31 maps were combined.
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Experimental session	Anatomical area	Brodmann area	Physical practice						Motor imagery					
			Healthy participants			SCI participants			Healthy participants			SCI participants		
			x	y	z	x	y	z	x	Y	z	x	y	z
Pre-tests 1-3	Left middle frontal gyrus	6				2	16	65				26	8	52
	Left precentral gyrus	4	32	24	55	10	25	62	29	25	60	33	11	50
	Left postcentral gyrus	1 - 3	34	38	58				30	36	58	17	37	54
	Left inferior parietal lobe	39 - 40	39	44	57	39	40	41	38	55	44			
	Left superior parietal lobe	5 - 7				31	55	51	30	56	56	20	49	59
	Left precuneus	7	3	54	57	16	54	39	15	48	45	12	42	52
	Left paracentral lobe	5				6	32	52				13	36	49
	Right precentral gyrus	4	-29	28	62	-38	14	52						
	Right postcentral gyrus	1 - 3	-29	36	55	-31	39	58						
Right inferior parietal lobe	39 - 40	-39	36	51	-39	43	42							
Post-tests 1-2	Left precentral gyrus	4	35	20	55	37	23	58	33	27	57	32	27	52
	Left postcentral gyrus	1 - 3	40	35	53	39	36	57	42	33	53	34	33	51
	Left inferior parietal lobe	39 - 40	31	45	47	41	41	45	39	40	46	35	41	39
	Left superior parietal lobe	5 - 7				28	56	55	33	57	56			
	Left precuneus	7	16	44	48	10	57	46						
	Right precentral gyrus	4	-32	28	62									
	Right postcentral gyrus	1 - 3	-39	36	56									
	Right inferior parietal lobe	39 - 40	-44	39	45	-38	48	45						

Table 1. Cerebral regions recruited during physical practice and motor imagery of the prehension task in pre- and post-tests, in healthy and spinal cord injury participants. Coordinates of the center of gravity is provided for each region. SCI: Spinal Cord Injury.

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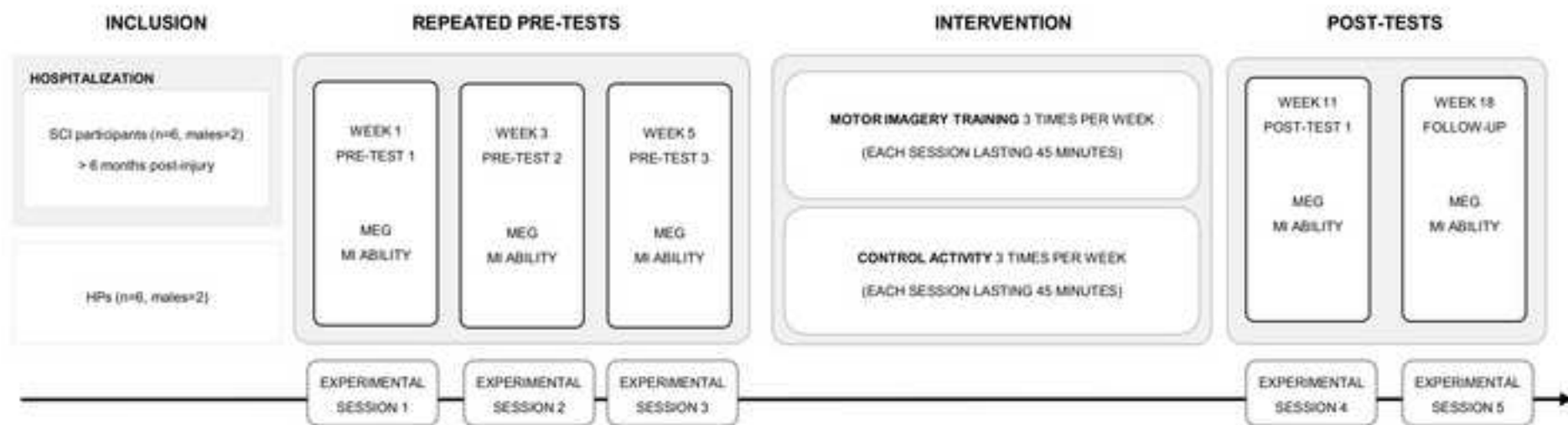
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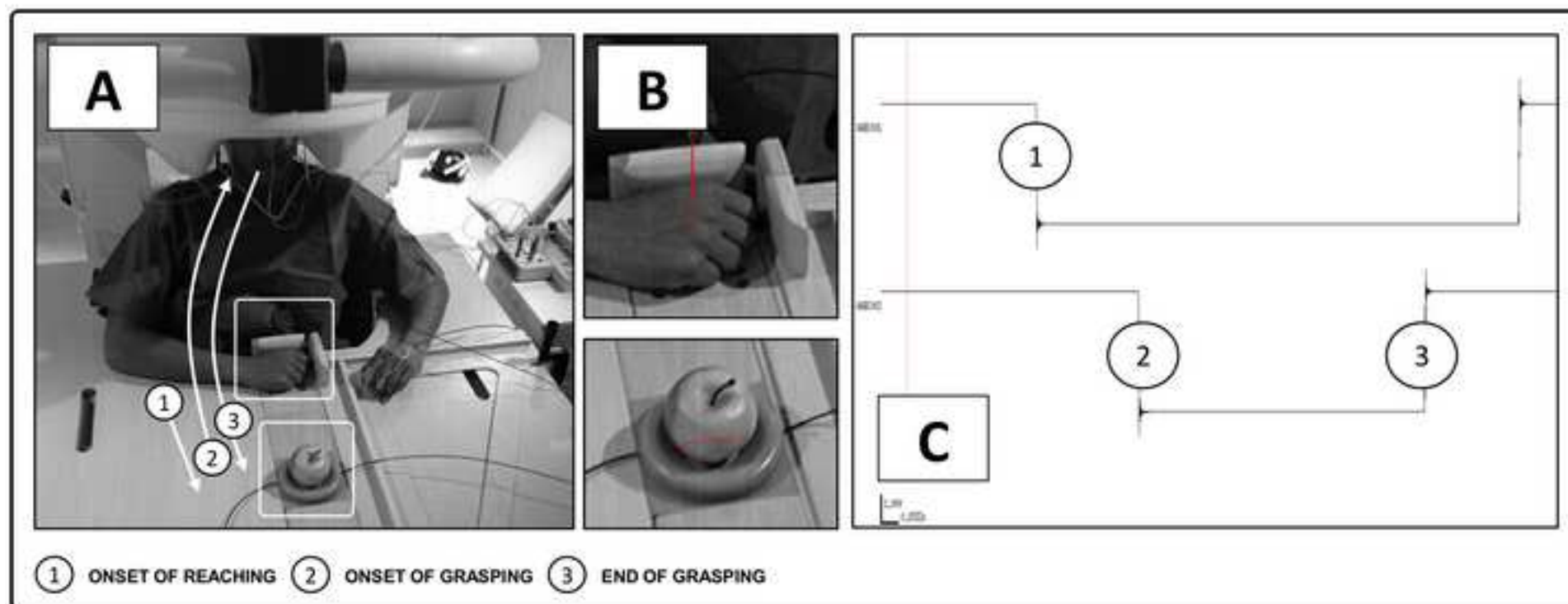
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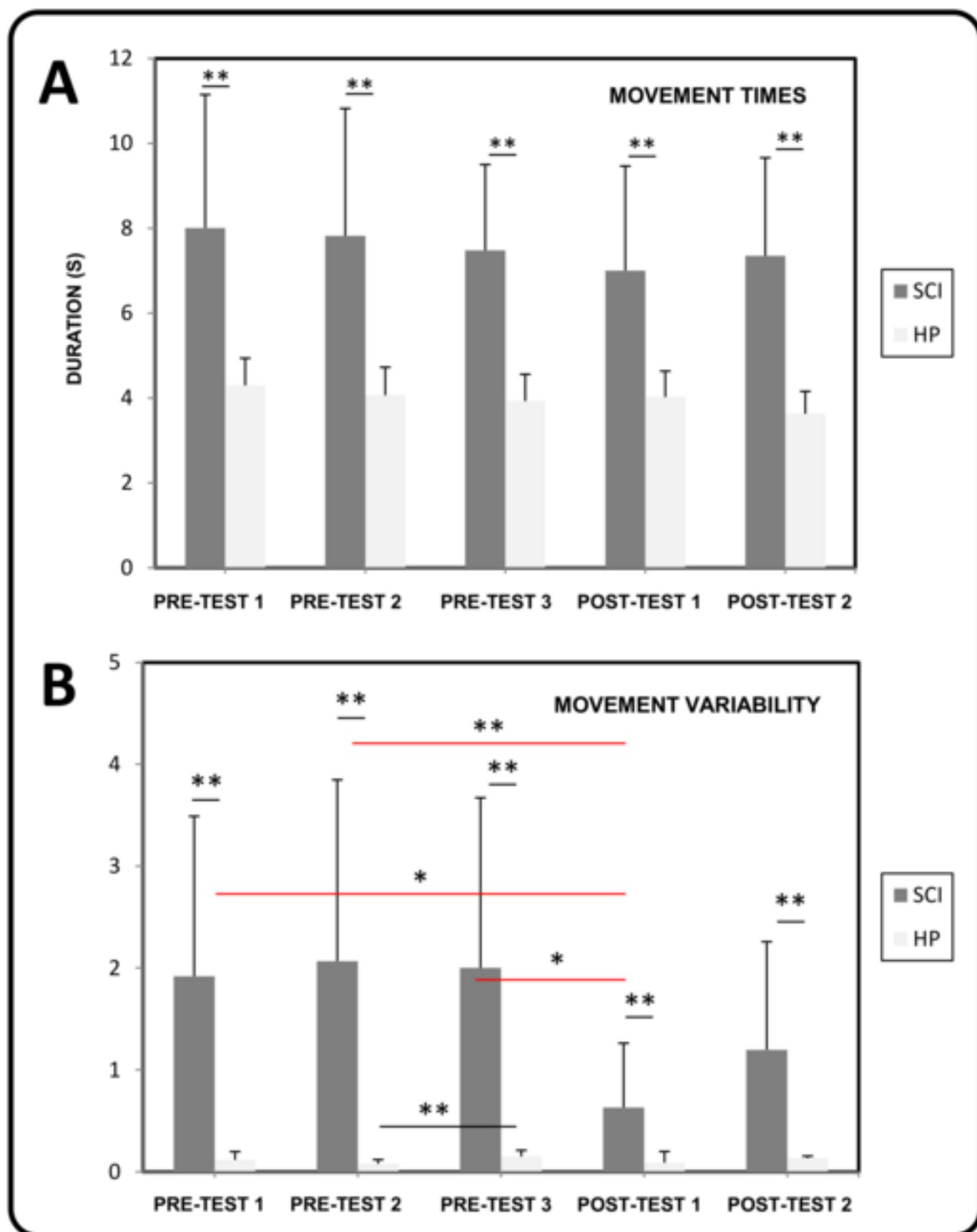
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