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Abstract: Procedural skills consist of several components that can be simultaneously acquired. During a motor-learning task we can distinguish between how a "movement" is performed (intrinsic component) and the spatial-related (extrinsic) component of this movement. The intrinsic movement component is thought to be supported by motor loops, including primary motor cortex (M1) as assessed with neuroimaging studies. Here we want to test further whether M1 makes a critical contribution to the movement rather than spatial-related component of skill-learning. To this purpose, we used repetitive Transcranial Magnetic Stimulation (rTMS) and the serial reaction time (SRT) task. Twenty right-handed participants performed the SRT-task starting with their left or right hand. After this learning session, participants switched to the untrained hand by

performing original (spatial-related) and mirror-ordered (movement-based) sequences. rTMS was applied to M1 ipsi- or contralateral to the transfer hand and both sequences were retested. Results revealed rTMS-interference with motor-skill transfer of mirror-ordered but not original sequences, showing that M1 is critically involved in the retrieval/transformation of the intrinsic but not the extrinsic movement coordinates. rTMS-interference in the mirror-condition consisted of both (i) disruption and (ii) release of motor-skill transfer depending on the stimulated hemisphere and on transfer-hand. The pattern of results suggests (i) contralateral (right) M1 involvement in retrieval/transformation of motor information during left hand reproduction of previously acquired right-hand motor-skills; and (ii) modulatory interactions of inhibitory nature from the dominant (left) to the non-dominant (right) M1 in the same transfer condition. These results provide further evidence that M1 is essential to intrinsic movement-based skill-learning and novel insight on models of motor-learning and hemispheric specialization, suggesting the involvement of interhemispheric inhibition.

Response to Reviewers: We thank the Reviewers and the Editors for their positive response. We are glad that our revised manuscript is now accepted for publication by the Guest Editors in CORTEX.

We have submitted our final revision, without the highlights and carefully checked for publication on the web.

Please let me know if additional information or any further changes are required.

Looking forward to hearing from you.

Best regards,

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1 To appear in the Special Issue: The contribution of TMS to structure-function mapping in the
2
3 human brain. Action, Perception and Higher Functions.
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11 **M1 contributes to the intrinsic but not the extrinsic components of motor skills**
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41 Running title: Intermanual transfer of motor-skills
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1 **Abstract**
2

3 Procedural skills consist of several components that can be simultaneously acquired. During a
4 motor-learning task we can distinguish between how a “movement” is performed (intrinsic
5 component) and the spatial-related (extrinsic) component of this movement. The intrinsic
6 movement component is thought to be supported by motor loops, including primary motor
7 cortex (M1) as assessed with neuroimaging studies. Here we want to test further whether M1
8 makes a critical contribution to the movement rather than spatial-related component of skill-
9 learning.
10

11 To this purpose, we used repetitive Transcranial Magnetic Stimulation (rTMS) and the serial
12 reaction time (SRT) task. Twenty right-handed participants performed the SRT-task starting
13 with their left or right hand. After this learning session, participants switched to the untrained
14 hand by performing original (spatial-related) and mirror-ordered (movement-based)
15 sequences. rTMS was applied to M1 ipsi- or contralateral to the transfer hand and both
16 sequences were retested. Results revealed rTMS-interference with motor-skill transfer of
17 mirror-ordered but not original sequences, showing that M1 is critically involved in the
18 retrieval/transformation of the intrinsic but not the extrinsic movement coordinates. rTMS-
19 interference in the mirror-condition consisted of both (i) disruption and (ii) release of motor-
20 skill transfer depending on the stimulated hemisphere and on transfer-hand. The pattern of
21 results suggests (i) contralateral (right) M1 involvement in retrieval/transformation of motor
22 information during left hand reproduction of previously acquired right-hand motor-skills; and
23 (ii) modulatory interactions of inhibitory nature from the dominant (left) to the non-dominant
24 (right) M1 in the same transfer condition. These results provide further evidence that M1 is
25 essential to intrinsic movement-based skill-learning and novel insight on models of motor-
26 learning and hemispheric specialization, suggesting the involvement of interhemispheric
27 inhibition.
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1 **Key Words** motor cortex, intermanual transfer, interhemispheric inhibition, procedural learning,
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3 Transcranial Magnetic Stimulation.
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8 **1. Introduction**

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10 Every time we are engaged in a new task the first steps will require an effort to improve our
11 performance. By repeating the task, it will become easier, better performed and almost
12 automatic. This process is known as “procedural learning” as it provides the encoding in
13 memory of new procedures by distinct mechanisms and neural networks (Hikosaka et al,
14 2002). Procedural skills consist of several components that can be simultaneously acquired
15 (Verwey and Clegg, 2005). For example, a sequence of movements can be represented by a
16 spatial and a motor component. The spatial component of the sequence is thought to be
17 supported by parietal-prefrontal cortical loops, as it encodes spatial (kinematic) coordinates
18 and is supposed to be independent of the effectors, whereas the motor component is thought
19 to be supported by motor loops including primary motor cortex (M1) and to be therefore
20 effector-dependent (Hikosaka et al., 2002). Consistent with this idea, functional neuroimaging
21 studies on humans suggest that motor-skill learning is associated with activation of many
22 brain areas including fronto-parietal cortices and that M1 makes a critical contribution to
23 effector-dependent but not -independent skill-learning (Grafton et al., 1998; 2002).
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44 Here, we use the serial reaction time (SRT) task (Nissen and Bullemer, 1987) for implicit
45 (Robertson, 2007) unimanual skill-learning and its intermanual transfer (Cohen et al., 2005)
46 in mirror-reversal (movement-based) and original sequence (spatial-related) order. By
47 applying an offline repetitive TMS (rTMS) paradigm over ipsi- or contralateral M1 to the
48 transfer hand, we test for M1 contribution to transfer of previously acquired movement-
49 versus spatial-related skill-learning.
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2. Materials and Methods

2.1. Participants

Twenty-four healthy, right-handed (Oldfield, 1971) volunteers (12 females, 19-32yrs) gave written informed consent to the study that had been approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center. All were naive to the SRT paradigm and none had a personal or family history of neurological or psychiatric disorders.

2.2. Paradigm

We used a modified version of the SRT-task originally developed by Nissen and Bullemer (1987). Participants viewed a computer monitor (at 60cm distance from the screen) with their index, middle, ring and little fingers of one hand placed on a four-button response box (Cedrus RB-410, San Pedro, CA). The visual stimulus prompting manual responses consisted of a circle (3.5cm diameter) that could appear at one of four possible, equally spaced positions aligned on the horizontal midline of the computer screen. Participants were instructed to respond as quickly and accurately as possible to the stimulus position by pressing the spatially corresponding button on the response board. Upon giving a correct response, the visual stimulus disappeared for 200msec before the onset of the next target. After incorrect responses, the stimulus remained on the screen until correct button selection.

The SRT-task involved blocks of stimulus presentation at randomly alternating positions for assessing baseline performance and blocks of trials with presentation of stimuli in a predefined spatial sequence (hidden to the participants) repeated over several blocks to induce implicit learning (Robertson, 2007). Learning trials were performed first with either the dominant or the non-dominant hand and then transferred (in original and mirror-ordered sequences) to the opposite hand. In the original transfer condition, spatial stimulus sequence and series of response locations remained unchanged. In the mirror-ordered transfer

1 condition, the stimulus sequence and series of response locations were reversed but the
2
3 response sequence involved finger movements that were homologous to those used during
4
5 previous learning. Stimulus presentation and response time collection was controlled by
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7 Superlab Pro (Cedrus, San Pedro, CA).
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10 11 12 *2.3. Experimental procedure* 13

14 Each participant was tested on left-to-right as well as right-to-left hand transfer at two
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16 separate days (one week apart). The involvement of ipsi- or contralateral M1 in the transfer of
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18 previously learned motor-skills was tested by applying rTMS in one half of the participants
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20 over M1 contralateral to the transfer hand and in the other half ipsilaterally. Per experimental
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22 day, participants performed the SRT-task in pure random trials first (Random session),
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24 followed by sequence trials (Learning session) that had to be subsequently transferred to the
25
26 opposite hand (Transfer session: test). rTMS was applied and participants performed again the
27
28 transfer session (Transfer session: retest). At the end, we asked participants to try to recall a
29
30 sequence whenever they thought there was one in at least one of the two sessions.
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36 *Random session.* This session was divided in two blocks of 120 stimuli per hand and
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38 provided baseline measures to compare performance of both hands.
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41 *Learning session.* The learning session was performed over a total of 10 blocks. Each
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43 block consisted of intermixed series of random (R) and sequence (S) trials (n=12 trials per
44
45 series) arranged in a fixed pattern (R-SS-R-SS-R-SS-R). R-trials were introduced to control
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47 for learning by comparing reaction times between R- and S-trials within each block and also
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49 helped to mask the presence of a recurrent sequence preventing explicit recognition. The end
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51 of each 12-trial sequence and the beginning of the next was not marked and each block
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53 appeared as a continuous series of 120 trials. Each participant was presented with two
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55 different sequences, one for each day of the experiment (sequence A: 1-2-1-4-2-3-4-1-3-2-4-
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1 3, sequence B: 1-4-2-3-1-3-2-4-3-2-1-4, mirror-reversal A: 4-3-4-1-3-2-1-4-2-3-1-2, mirror-
2 reversal B: 4-1-3-2-4-2-3-1-2-3-4-1). These sequences were counterbalanced between
3 participants, such that the two sequences and their mirror-reversed versions were evenly
4 distributed over conditions (learning- and transfer-hands), to avoid possible effects due to
5 differences in complexity of the associated finger movement sequences.
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13 *Transfer session (test-retest).* The transfer session was divided in two parts: an initial 4
14 consecutive test blocks (skill-1) of intermixed series of random and sequence trials (2 mirror-
15 ordered and 2 original-ordered blocks), arranged in analogy to the learning sessions (R-OO-
16 R-OO-R-OO-R, R-MM-R-MM-R-MM-R), followed by rTMS, and a final 4 re-test blocks of
17 transfer (skill-2) designed to assess the specific contribution of M1 in transfer of either
18 intrinsic or extrinsic motor-skill. The order of the original and mirror-ordered transfers was
19 counterbalanced between participants, during the first presentation (test) as well as after
20 rTMS (retest).
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35 2.4. Transcranial Magnetic Stimulation (TMS)

36 TMS was delivered with a 70mm figure-of-eight coil and a Magstim Super Rapid
37 Transcranial Magnetic Stimulator (Magstim Company, Dyfed, UK). We first searched for the
38 scalp position from which TMS elicited motor evoked potentials of maximal amplitude in the
39 contralateral *abductor digit minimi* muscle, and determined the corresponding resting motor
40 threshold (rMT). This position was taken to represent the location of M1. During repetitive
41 stimulation, TMS was applied at 90% of individual rMT for 10 minutes at 1 Hz frequency.
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52 The coil was positioned tangentially to the scalp with the coil handle pointing posteriorly and
53 oriented 135° from the midsagittal axis of the participant's head.
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3. Data Analysis

Median response times (RT) were calculated separately for both random and sequential trials in each block and condition for each subject. The mean of the median manual RT to visual stimulus onsets of correct response trials were included in the analyses. Four out of 24 participants were excluded from the analyses because they became aware of the hidden sequence. To evaluate the implicit motor learning effect, an average of each 2 consecutive blocks was computed for both random and sequence trials: 1-2=1, 3-4=2, 5-6=3, 7-8=4, 9-10=5. A motor-skill index was calculated by subtracting the median RT of random trials from those of sequential trials within each block. Finally, the effects of M1 stimulation on movement- and spatial-related motor-skill were assessed by comparing the motor-skill index for the untrained hand before rTMS (skill-1) and after rTMS (skill-2) via subtraction (skill-2 – skill-1).

4. Results

4.1. Baseline motor performance

In the random session, a paired t-test showed RTs to be significantly faster for right than left-hand trials (mean±SE: 367±9.81msec vs. 379±11.56msec; $t_{19}=-2.82$; $p<.01$) corresponding to a general right-hand advantage of the right-handed participants, in line with left-hemispheric motor dominance.

4.2. Implicit motor learning

A repeated-measure analysis of variance (ANOVA) performed with the within-subject factors hand (left-trained vs. right-trained hand) and blocks showed an implicit motor learning effect. This was reflected in the significant increase of motor-skill over blocks (Fig.1, lower panel; main effects of block: $F_{4,76}=20.16$; $p<.0001$) that was independent of performing hand

1 (interaction block*hand: $F_{4,76}=1.36$; n.s.). Also, there was no main effect of hand ($F_{1,19}=0.03$;
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3 n.s.), indicating that, despite a baseline difference in speed between hands, there was no hand
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5 difference in the amount of learning across blocks.
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15 *4.3. Transfer of implicit motor-skill between hands*

16 An ANOVA with the within-subject factors transfer-direction (left-to-right vs. right-to-left
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18 hand)*transfer-type (last learning-blocks vs. original- and, mirrored-ordered transfer) showed
19
20 a significant main effect of transfer-type ($F_{2,38}=4.39$; $p=.02$), explained by a motor-skill
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22 reduction during mirror-ordered transfer relative to both the acquired motor-skill after training
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24 (opposite-hand training; $p<.01$) and the original transfer performance (same-hand; $p<.05$).
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26 This shows that while the previously acquired motor-skill can be transferred to the opposite,
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28 untrained hand when reproduced in the original sequence, motor-skill transfer from the
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30 trained to the untrained hand is reduced when the mirror-ordered sequence is presented,
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32 suggesting that the two forms of transfer are governed by different mechanisms (Fig.2).
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40 Additionally, the ANOVA showed a significant interaction of transfer-type*transfer-
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42 direction ($F_{2,38}=3.72$; $p=.03$), explained by a significant loss of motor-skill for left-to-right
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44 hand transfer of mirror-ordered sequence, relative to all other conditions (all $p<.05$, Fig.2).
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54 *4.4. Effects of rTMS over M1 on motor-skill transfer*

55 The difference values skill-2 – skill-1, indexing the rTMS effect on motor-skill transfer, were
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57 subjected to an ANOVA with the transfer-condition (original vs. mirror) and transfer-
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1 direction (left-to-right vs. right-to-left) as within-subject factors and the TMS (Ipsi- vs.
2
3 Contralateral) as between-subject factors. Results showed a trend for a main effects of TMS
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5 ($F_{1,18}=4.0$; $p=.06$), a 2-way interaction of TMS with transfer-direction ($F_{1,18}=5.06$; $p=.037$) as
6
7 well as a significant 3-way interaction ($F_{1,18}=6.34$; $p=.021$).
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10 The trend for the factor TMS is suggestive of an overall difference between rTMS
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12 over ipsi- versus contralateral M1, with ipsilateral M1-stimulation producing a motor-skill
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14 improvement and contralateral M1-stimulation resulting in a motor-skill reduction. However,
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16 these effects mainly occur for right-to-left hand transfer directions (interaction TMS*transfer-
17
18 direction) and most prominently so when the mirror-order sequence is transferred (3-way
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20 interaction; see Fig.3). In fact, the two-way interaction of TMS*transfer-direction was
21
22 significant only in the mirror-ordered ($F_{1,18}=9.13$; $p=.007$) but not in the original condition
23
24 ($F_{1,18}=0.29$; $p=.60$), and is explained by an effect of ipsi- versus contralateral TMS on mirror
25
26 transfer that is present only for right-to-left hand ($F_{1,18}=12.86$, $p=.002$) but not left-to-right
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28 hand transfer ($F_{1,18}=0.61$, $p=.44$).
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35 Paired t-tests computed for the right-to-left hand, mirror-ordered condition revealed
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37 that the amount of transfer was significantly reduced after contralateral M1-stimulation ($t_9=-$
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39 2.63 ; $p=.027$) and significantly increased after ipsilateral stimulation ($t_9=2.53$; $P=.03$).
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41 Exploratory comparisons via t-tests computed for all the other conditions showed no
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43 significant changes after rTMS stimulation.
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52 **5. Discussion**

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54 We found M1 to represent a fundamental component of the motor loop engaged in the
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56 intrinsic but not the extrinsic movement components of skill-learning (Hikosaka et al 2002) in
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58 line with previous neuroimaging studies (Grafton et al., 1998; 2002).
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1 Our main findings and conclusions are that: (i) the behavioural benefit from previous,
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3 opposite hand learning depends on whether mirror-ordered or original movement sequences
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5 have to be transferred between hands, suggesting distinct mechanisms and neuronal substrates
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7 for movement- and spatial-related skill-learning; (ii) only the movement-based skill-learning
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9 critically depends on M1, as only mirror-ordered transfer was influenced by M1-disruption;
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11 (iii) M1 contralateral to the transfer-hand has a supportive function in transformation of
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13 movement-based coordinates, as rTMS over this site impaired transfer; (iv) M1 ipsilateral to
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15 the transfer-hand plays an inhibitory/modulatory role in retrieval/transformation of the
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17 previously acquired motor-skill, most likely through callosal interactions, leading to a motor-
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19 skill release after its disruption. Finally, our data show that (v) these effects depend on
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21 transfer direction and are thus under the influence of hemispheric dominance and motor
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23 proficiency. Finally, our data show that (v) these effects depend on
24
25 transfer direction and are thus under the influence of hemispheric dominance and motor
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27 proficiency.

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29 TMS has been successfully applied to investigate the role of M1 in several aspects of motor
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31 learning including execution (Hotermans et al., 2008), acquisition (Richardson et al., 2005),
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33 observation (Stephan et al., 2005), retention (Muellbacher et al., 2002; Hadipour-Niktarash et
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35 al., 2008), consolidation (Robertson et al., 2005), and interhemispheric interactions (Perez et
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37 al., 2007a, 2007b; Duque et al., 2008). Our results provide novel insight into the contributions
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39 of opposite M1 to transfer of procedural learning by showing that the role of M1 depends on
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41 its localization relative to the dominant hemisphere as well as on transfer direction.
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47 On the one hand, M1 stimulation of the right non-dominant hemisphere impaired movement-
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49 based skill when transferred from the right to the left hand. This significant impairment of
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51 left-hand motor function after right M1-stimulation is specific for motor-skill and cannot be
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53 explained by interference with motor execution per se, because the latter effects are parcelled
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55 out through our design via subtraction (RT-sequence trials minus RT-random trials leading to
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57 the motor-skill score). It could be argued that the learning effect of the S-series persisted in
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1 the R-series, thus slowing down the performance of the subsequent R-series due to the
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3 incongruence between the expected S- and the actual R-stimulus. This would lead to an
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5 artefactual larger difference between the R- versus S-RTs (i.e. higher motor skill scores).
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7 However this is not the case since the raw RTs in the R-series is constant across blocks (see
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9 Fig 1), which means that the implicit learning occurring in the S-series did not interfere with
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11 the motor performance of the R-series. We therefore conclude that M1 is actively involved in
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13 the retrieval/transformation of movement-based coordinate representations, required during
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15 transfer of mirror-ordered movement sequences to the non-dominant hand.
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20 On the other hand, M1-stimulation of the dominant left hemisphere improved movement-
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22 based skill-learning, when transferred from the right to the left hand. This is best explained by
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24 an uncovering of a left-hand (right-hemispheric) motor function due to rTMS-interference
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26 with inhibitory interactions from the stimulated motor-dominant towards the non-dominant
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28 hemisphere. In other words, this shows that a virtual lesion of the ipsilateral left M1 cancels
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30 out the inhibitory drive towards the right M1 and therefore improves motor performance of
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32 the left hand.
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37 Intermanual transfer of motor-skills has been shown to require intact callosal fibers (Thut et
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39 al., 1997; de Guise et al., 1999; Chicoine et al., 2000). Also, it has been suggested that
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41 bilateral activation of M1 during unilateral simple or complex motor tasks with the non-
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43 dominant hand is related to interhemispheric inhibitory interactions at the level of M1
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45 (Kobayashi et al., 2003) and that some of the effects of intermanual transfer of training are
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47 driven by callosally mediated interactions of inhibitory nature (Thut et al., 1996, 1997). Given
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49 these findings, the release of right-hemispheric/left hand motor function found in the present
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51 study is likely to reflect interference at the level of interhemispheric inhibitory interactions,
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53 previously shown to be of importance both in animals (Matsunami and Hamada, 1984;
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55 Nakamura et al., 1971), healthy human controls (Ferbart et al., 1992; Di Lazzaro et al., 1999;
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1 Romei et al., 2008) and patients with callosal damage (Meyer et al., 1995). Some TMS studies
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3 have furthermore noted an asymmetry in transcallosal inhibition when TMS was applied at
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5 low intensities suggesting more prominent inhibition from the left, dominant to the right, non-
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7 dominant M1 (Netz et al., 1995; Kobayashi et al., 2003). In the light of these collective
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9 results, our data suggest that the change in callosal inhibition from the dominant to the non-
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11 dominant hemisphere due to previous right-hand learning does not have the same behavioural
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13 impact on motor-skill as compared to motor execution. Following left hemispheric/right hand
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15 learning, inhibitory interaction from the left to the right hemisphere appear to be associated
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17 with a higher effect strength on complex skills relative to simple execution, leading to an
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19 uncovering of motor-skill (enhanced motor-skill score) after transient disruption of left M1.
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21 This seems to be at odds with Perez et al. (2007a) showing that learning-related changes in
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23 transcallosal inhibition as tested through paired-pulse TMS are correlated with motor
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25 execution but not skill score during transfer. However, it is conceivable that inhibition as
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27 probed through paired-pulse TMS rather emphasizes the interactions associated with simple
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29 movements.
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37 Finally, the transynaptic effect of rTMS (Rothwell, 1997), which is likely to affect the activity
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39 of distant cortical areas (Bestmann et al., 2004), has to be taken into account when
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41 interpreting the present data. It is conceivable that rTMS affected participants' performance
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43 via cortico-cortical pathways, e.g. interhemispheric interactions originating from premotor
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45 areas (Duque et al., 2008; Perez et al., 2007b), which exert inhibitory influences on the
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47 contralateral M1 (Mochizuki et al., 2004).
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52 In conclusion, we provide further evidence for M1 contribution to movement- but not
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54 spatial-related motor-skill learning and suggest involvement of interhemispheric inhibition in
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56 hemispheric specialization for motor-skill. The study of the neuronal underpinning of skill-
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learning, through intermanual transfer of training and TMS, can provide further clues for the understanding of motor-skills acquisition and cerebral laterality.

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1 **Figure 1.** Mean of the median response times (RT) to visual stimuli of random (square \pm SE)
2 and sequential (circle \pm SE) trials per hand and across learning blocks (upper panel) and
3 derived procedural learning scores (indexing motor-skill improvement: RT sequential trials –
4 RT random trials), which correct for the general difference in speed between hands (lower
5 panel). Error bars depict Standard Errors. No differences between hands were observed across
6 blocks.
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16 **Figure 2.** Motor-skill scores at the end of training immediately before transfer, as well as for
17 subsequent transfer to the untrained hand, for right-to-left (left panel) and left-to-right (right
18 panel) transfer in original and mirror-ordered sequences. A significant transfer asymmetry
19 was observed only in the mirror-ordered sequence with a benefit for right-to-left as compared
20 to left-to-right hand transfer. Asterisks point to the significance of differences in the amount
21 of motor-skills transferred: *** $p < .0001$.
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34 **Figure 3.** rTMS over M1 interfered with transfer of the mirror but not the original sequence,
35 suggesting that M1 is not actively involved in original transfer. Within the mirror transfer
36 conditions, rTMS had an impact on right-to-left hand transfer by enhancing transfer gain
37 when applied over ipsilateral (left) M1 and inhibiting transfer gain when applied over
38 contralateral (right) M1. Ipsilateral and contralateral M1 refer to the transfer hand. No
39 inhibition, nor release was found for transfer in the opposite (left-to-right) direction. Asterisks
40 point to statistical significance: * $p < .05$).
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Figure 1

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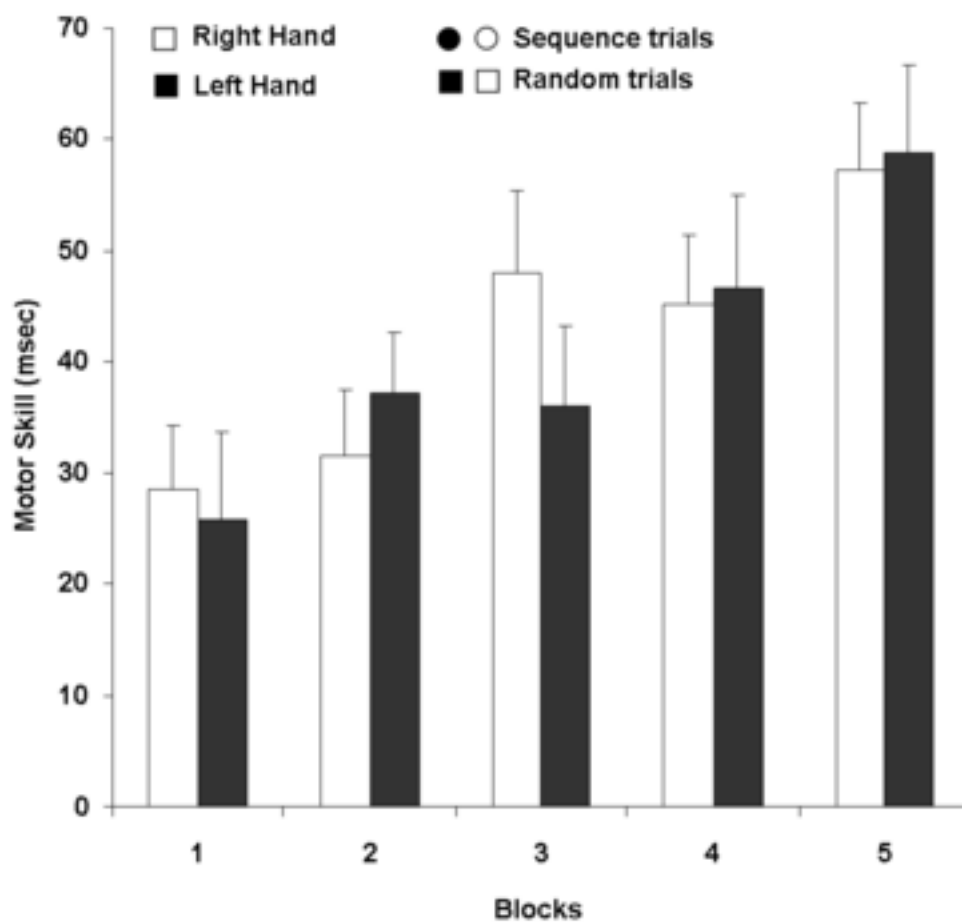
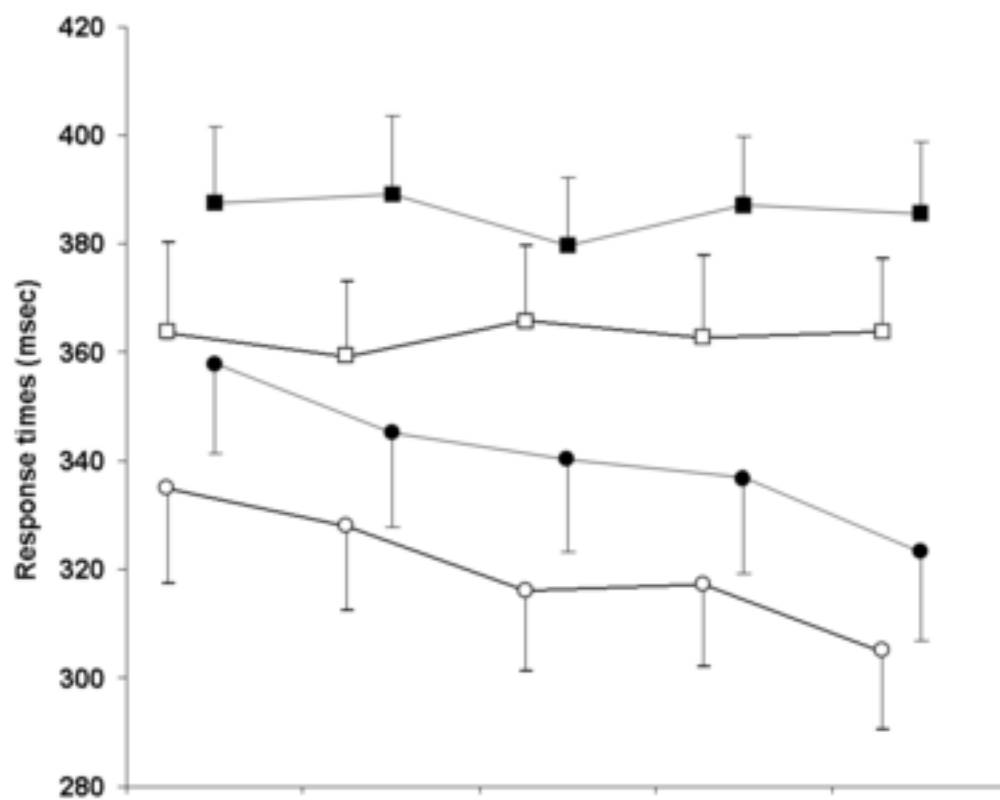


Figure2

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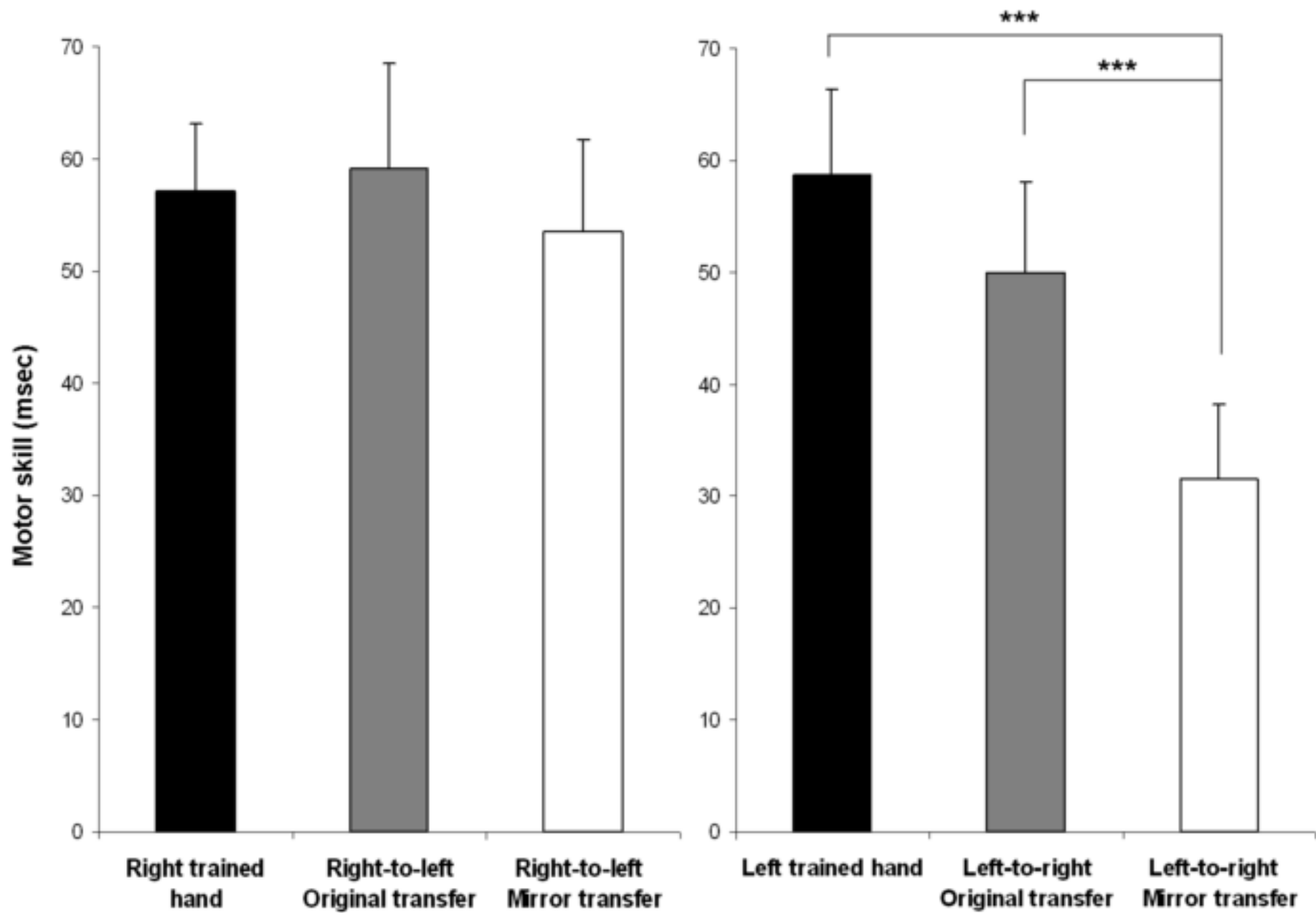


Figure3

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