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BASIC NEUROSCIENCES, GENETICS AND IMMUNOLOGY - SHORT COMMUNICATION

The effects of 1 Hz rTMS over the hand area of M1 on movement kinematics of the ipsilateral hand

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Abstract 1 Hz rTMS applied over primary motor cortex (M1) reduces cortical excitability outlasting the stimulation period. Healthy right-handed subjects performed finger and hand tapping and a reach-to-grasp movement prior to (baseline) and after 1 Hz rTMS applied over (1) M1 of either the right or the left hemisphere, and (2) the vertex (control stimulation). 1 Hz rTMS applied over the left M1, but not over the vertex, improved movement kinematics of finger and hand tapping as well as grasping with the left hand. 1 Hz rTMS applied over the right M1, but not over the vertex, improved only the kinematics of hand tapping performed with the right hand. These data suggest that 1 Hz rTMS induced inhibition of ipsilateral M1 reduces transcallosal inhibition of contralateral M1 and thereby improves motor performance at the ipsilateral hand. The impact on motor performance of the ipsilateral hand is most pronounced after 1 Hz rTMS over the left M1.

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Introduction

In the healthy brain, neural activity within the motor areas of both hemispheres is functionally coupled and well balanced in terms of mutual inhibitory control (Kinsbourne 1974; Ferbert et al. 1992; Gilio et al. 2003; Fink et al. 1997; Binkofski et al. 1999). Unimanual movements are associated with increased neural activity in contralateral motor areas (Fink et al. 1997; Binkofski et al. 1999). The lateralisation of neural activity for unimanual movements is likely to be related to, at least in part, interhemispheric inhibition between motor areas exerted via transcallosal connections (Ferbert et al. 1992; Gilio et al. 2003). It has been suggested that unilateral brain dysfunction, e.g. due to stroke, may result in a release of the contralateral hemisphere from transcallosal inhibition and thereby cause an improvement of contralateral brain function (Liepert et al. 2000; Hummel and Cohen 2006). Likewise, in healthy people a temporal "virtual lesion" of the primary motor cortex (M1) induced by inhibitory repetitive transcranial magnetic stimulation (rTMS) may enhance cortical excitability in contralateral motor areas facilitating basic motor function at the ipsilateral hand (Kobayashi et al. 2004, Avanzino et al. 2008).

Here, we investigated putative changes in movement kinematics of simple and more complex manual tasks demanding temporo-spatial network interactions at the ipsilateral hand following 1 Hz rTMS applied over the hand area of M1 in either hemisphere in healthy human subjects.

Subjects and methods

Subjects

Eighteen right-handed (Crovitz and Zener 1965) healthy subjects (four females, 20–41 years, mean 27 ± 6 years) participated. The study had been approved by the Local Ethics Committee and written informed consent was obtained prior to participation.

Experimental procedure

Subjects performed index finger and hand tapping and reach-to-grasp movements with both hands prior to (=baseline condition) and after a period of 10 min 1 Hz rTMS applied over (1) the vertex (=control condition) and (2) M1 hand area. Nine subjects (two females, 20–41 years, mean 27 ± 6 years) received rTMS applied over M1 of the left hemisphere, nine subjects (two females, 20–35 years, mean 26 ± 5 years) received rTMS applied over M1 of the right hemisphere. The rTMS stimulation sessions were separated by 120 min. The sequence of rTMS application site (either vertex or M1) was counterbalanced across subjects.

Kinematic motion analysis

The experimental set-up is illustrated in Fig. 1. The movement kinematics was recorded using an ultrasonic motion analyzer as described previously in detail (Nowak et al. 2007).

Index finger tapping and hand tapping were performed as fast as possible. The following parameters were obtained (Nowak et al. 2007): (1) movement frequency (in Hz) and (2) peak movement amplitude (in mm). During the reach-to-grasp task, subjects reached for a cylindrical object (diameter: 9 cm, width: 4 cm, weight: 350 g), grasped it between the tips of the index finger and thumb, lifted it and held it for 3 s before placing it back. Ten such movements were performed by each subject with each hand as fast and as accurate as possible. The following parameters were obtained (Nowak et al. 2007): (1) peak of vertical wrist position (in mm), (2) peak of vertical wrist velocity (in mm/s), (3) peak grasp aperture (in mm) and (4) peak velocity of grasp aperture (in mm/s). All parameters were averaged across all trials performed by each participant.

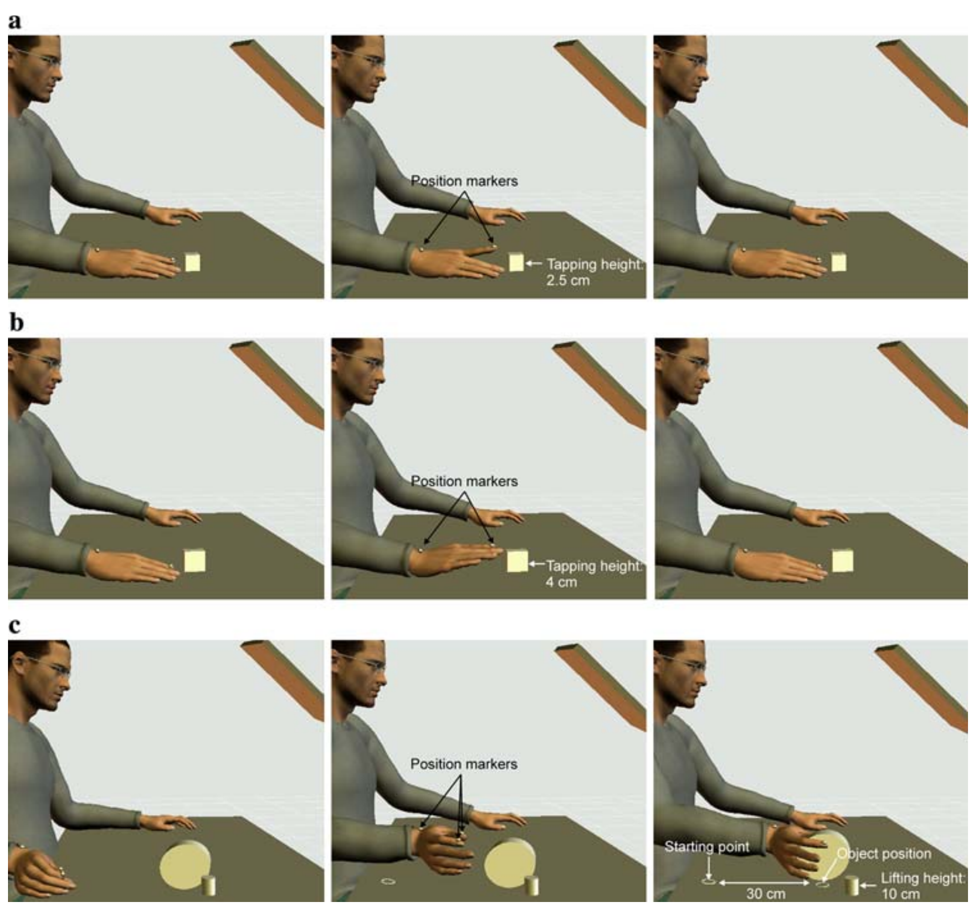

Fig. 1 Recording of the **a** index finger tapping, **b** hand tapping and **c** reach-to-grasp movements. Movement kinematics during each task was recorded using a three-dimensional motion analysis system based on ultrasound-emitting position markers. For the index finger tapping and hand tapping tasks, the position markers were fixed to the distal segments of the index finger and to the styloid process of the radius. For the reach-to-grasp task, position markers were fixed to the distal segments of the index finger and thumb and to the styloid process of the radius

Repetitive transcranial magnetic stimulation

rTMS was performed using a 70-mm figure-of-eight coil and a Magstim Rapid stimulator (Magstim Company, Dyfed, UK). The coil was placed tangentially over M1 at the optimal site where stimulation at a slightly suprathreshold intensity elicited the largest motor evoked potential in the contralateral first dorsal interosseus muscle (FDI). The resting motor threshold was defined as the lowest stimulator output that elicited motor evoked potentials with peak-to-peak amplitude of at least 50 μV in the contralateral FDI in at least five of ten trials. rTMS was applied at a rate of 1 Hz, 100% resting motor threshold over 10 min. This stimulation protocol has been shown to reduce cortical excitability at least for 10 min (Maeda et al. 2000; Chen et al. 1997). Control stimulation was applied positioning the coil over the vertex using the identical rTMS frequency and intensity parameters. Positioning the coil over the vertex resulted in stimulation of an area posterior to the supplementary motor area.

Statistical analysis

Repeated measures ANOVAs were calculated for each kinematic parameter with the factors "stimulation site" [levels: (1) rTMS applied over M1 of the left and (2) rTMS applied over M1 of the right hemisphere], "hand" [levels: (1) right and (2) left hand] and "intervention" [levels: (1) baseline, (2) vertex and (3) M1]. Post hoc pair-wise comparisons between conditions were performed using *t* tests. A *P* value of 0.05 was considered significant after Bonferroni correction for multiple comparisons.

Results

Figure 2 summarizes mean and standard deviations of the frequencies of index finger and hand tapping, and peak velocities of grasp aperture during reach-to-grasp tasks performed with both hands at each condition. Compared to baseline the average increase (±standard deviation) in tapping frequency induced by 1 Hz rTMS over M1 of the left hemisphere was 7.3% (±6.9%) for finger tapping and 8.1% (±10%) for hand tapping performed with the ipsilateral (left) hand. 1 Hz rTMS over the right M1 caused an average increase in tapping frequency of 8.4% (±16.7%) for finger tapping and 11.5% (±13%) for hand tapping performed with the ipsilateral (right) hand. Compared to baseline the average velocity of grasp aperture (± SD) increased by 32% (±27.3%) for reach-to-grasp movements performed with the left hand after 1 Hz rTMS over the left M1. 1 Hz rTMS over the right M1 increased the velocity of grasp aperture by 22.5% (±41.9%) in comparison to baseline for reach-to-grasp movements with the right hand.

Index finger and hand tapping tasks

ANOVA revealed significant effects of the factors "hand" (index finger tapping: $F_{1,8} = 16.1$, $P < 0.01$; hand tapping: $F_{1,8} = 16.4$, $P < 0.01$) and "intervention" (index finger tapping: $F_{1,8} = 6.6$, $P < 0.01$; hand tapping: $F_{1,8} = 4.7$, $P < 0.05$) on the frequencies of index finger and hand tapping. The factor "stimulation site" did not reach significance. For index finger and hand tapping, only the interaction "stimulation site" × "intervention" × "hand" (index finger tapping: $F_{1,8} = 5.0$, $P < 0.05$; hand tapping: $F_{1,8} = 4.7$, $P < 0.05$) had a significant influence on tapping frequency, implying that the increase in tapping frequency was most pronounced at the left hand after rTMS applied over the left M1 ($P < 0.01$ for each comparison). Note that there was no significant effect of either factor or their interactions on tapping amplitudes which indicates that the rTMS induced increase in tapping frequency is a true behavioural improvement, and did not result from a reduction in tapping amplitude in the other conditions.

Reach-to-grasp task

Hand transport component of the task was not influenced by rTMS as evident from a lack of significant effects of either factor or their interactions on wrist position and wrist velocity. In contrast, rTMS influenced the kinematics of the grasp component as suggested by a significant effect of "intervention" ($F_{1,8} = 4.2$, $P < 0.05$) on the velocities of grasp aperture, meaning that rTMS applied over M1 increased movement speed at the ipsilateral hand. A significant interaction "stimulation site" × "hand" × "intervention" ($F_{1,8} = 10.8$, $P < 0.01$) implied that the increase in speed of grasp aperture was most pronounced for the left hand after rTMS applied over M1 of the left hemisphere ($P < 0.01$ for each comparison).

Discussion

We found that rTMS applied over the left M1, but not over the vertex, in healthy right-handed subjects improved the frequency of index finger and hand tapping as well as the velocity of grasp aperture during a reach-to-grasp movement performed with the left hand. A period of 1 Hz rTMS applied over the right M1, compared to vertex stimulation, improved only the frequency of hand tapping with the right hand. Our data suggest that rTMS induced suppression of excitability of M1 can be used to increase excitability of the contralateral motor cortex, which fits well with current concept of interhemispheric competition within the motor system.

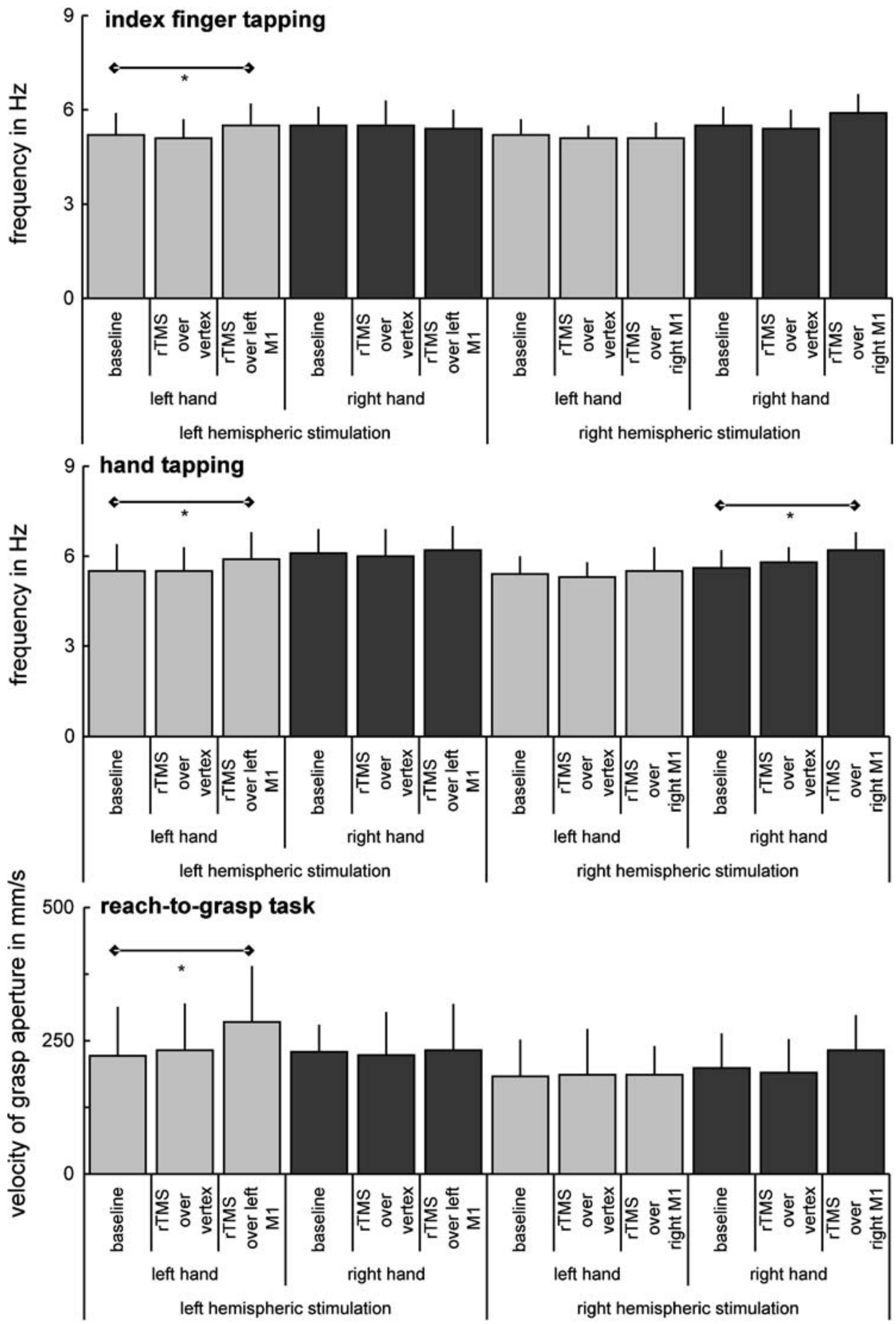

Fig. 2 Average group data (+1 standard deviation) of index finger tapping frequency, hand tapping frequency and peak velocity of grasp aperture during the reach-to-grasp task illustrated for each hand and intervention. Significant differences in performance after rTMS over M1 compared to baseline are given (Student's *t* test; $P < 0.01$). Note that subjects within the groups of left and right hemispheric stimulation differed

Consistent with our findings it has recently been shown that suppression of cortical excitability of M1 by means of 1 Hz rTMS can fasten the execution of a serial button pressing task with the ipsilateral hand in healthy humans (Kobayashi et al. 2004). Importantly, the behavioural changes at the ipsilateral hand after rTMS applied over M1 were accompanied by an enhancement of intracortical facilitation in the M1 contralateral to the site of stimulation (Kobayashi et al. 2004). 1 Hz rTMS applied over right M1 was also found to modify several kinematic parameters of a sequential finger opposition task performed with the ipsilateral hand (Avanzino et al. 2008). Taken together, these and our findings strongly support the suggestion that disinhibition of the contralateral motor cortex is based on rTMS-induced suppression of inhibitory transcallosal pathways originating from the motor cortex (Kobayashi et al. 2004; Liepert et al. 2000; Hummel and Cohen 2006). The precise neuronal mechanisms driving this transcallosal inhibition among the primary motor cortex remain to be identified (Hummel and Cohen 2006; Talelli and Rothwell 2006; Netz et al. 1995). Interestingly, we observed a stronger effect on motor performance of the ipsilateral hand after 1 Hz rTMS over the left M1, compared to 1 Hz rTMS over the right M1. This observation, we hypothesize, may reflect stronger interhemispheric influences exerted from the dominant (left) hemisphere. More research is necessary to shade some more light onto this issue.

Transcallosal inhibition is essential to prevent undesirable mirror movements that arise from activity in the opposite hemisphere (Danek et al. 1992). Accordingly, an alternative explanation may be that rTMS induced inhibition of cortical excitability is associated with a decrease in homologous mirror activity during ipsilateral hand movements, and thus allows the contralateral motor cortex to operate more effectively without the need to suppress mirror movements. Recently, we observed that mirror movements are most pronounced for voluntary movements of the left hand compared to the right hand in right handed subjects (Uttner et al. 2007). This suggests that suppression of cortical excitability of left M1 should be more effective to enhance motor performance at the ipsilateral hand than suppression of cortical excitability of right M1. Our interpretation is speculative, however, and more data are needed to draw definitive conclusions as to why 1 Hz rTMS over the left (dominant) M1 is more effective than 1 Hz rTMS over the right (non-dominant) M1 to improve motor performance at the ipsilateral hand.

The reach-to-grasp task incorporates two movement components, which are closely linked in time and space (Jeannerod 1984). A reach component transports the hand towards an object to be grasped and relies on coordinated activity within proximal muscles of the arm and shoulder. A grasp component refers to the progressive opening and closure of the fingers in anticipation of the mechanical object properties. The grasp component relies on more distal muscle groups of the lower arm and hand. 1 Hz rTMS over the hand area of M1 did impact on the grasp, but not on the reach component, of the reach-to-grasp task. This observation may reflect the somatotopic representation of proximal and distal muscle segments of the arm and hand within M1 as well as somatotopic transcallosal connections in between the M1 homologues of both hemispheres. Inhibitory rTMS was directed to the area of M1 eliciting motor responses in the contralateral first interosseus dorsalis muscle. Thus, the inhibitory effects on cortical excitability were probably most pronounced within the hand area of M1, but less effective in the area representing more proximal muscles of the arm and shoulder. The observation that reduction of cortical excitability within the hand area of the left M1 influences ipsilateral motor performance of distal muscles of the arm and hand, while performance of more proximal muscles remained unchanged, argues for a somatotopic enhancement in cortical functioning within the homologous hand area of the right M1.

Importantly, rTMS applied over M1 developed no detrimental effects on movement kinematics of the contralateral hand, regardless of the task performed. One can speculate that this fact might be attributed either to higher susceptibility for neurons containing transcallosal information or to putative multiplication of the rTMS effect in the ipsilateral hemisphere by changing the balance of excitability between other motor areas, e.g. supplementary motor or premotor areas, resulting in an additive effect in reducing the inhibitory drive towards M1 of the contralateral hemisphere (Grefkes et al. 2008).

In conclusion, we have shown that low frequency rTMS applied over the left (dominant) M1 in right-handed subjects has the potential to impact on motor performance of the ipsilateral (left) hand. 1 Hz rTMS applied over the right M1 did not cause a similar change in motor performance of the (dominant) right hand. The reasons for the differential effect of 1 Hz rTMS on non dominant and dominant hand function are still to be discovered. Detailed kinematic assessment using 3D motion analysis may help to elucidate what aspects of movement respond best to rTMS treatment, and provide possible targets for rehabilitation.

References

Avanzino L, Brove M, Trompetto C, Tacchino A, Ogliastro C, Abbruzzese G (2008) 1-Hz ripetitive TMS over ipsilateral motor cortex influences the performance of sequential finger movements of different complexity. Eur J NeuroSci 27:1285–1291

Binkofski F, Buccino G, Stephan KM, Rizzolatti G, Seitz RJ, Freund HJ (1999) A parieto-premotor network for object manipulation: evidence from neuroimaging. Exp Brain Res 128:210–213

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48:1398–1403

Crovitz HF, Zener K (1965) A group for assessing hand and eye dominance. Am J Psychol 75:271–276

Danek A, Heye B, Schroedter R (1992) Cortically evoked responses in patients with Xp223-linked Kallmann's syndrome and in female gene carriers. Ann Neurol 31:299–304

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. J Physiol 453:525–546

Fink GR, Frackowiak R, Pietrzyk U, Passingham RE (1997) Multiple nonprimary motor areas in the human cortex. J Neurophysiol 77:2164–2174

Gilio F, Rizzo V, Siebner HR, Rothwell JC (2003) Effects on the right motor hand-area excitability produced by low-frequency rTMS over human contralateral homologous cortex. J Physiol 551:563–573

Grefkes C, Nowak DA, Eickhoff SB, Dafotakis M, Küst J, Karbe H, Fink GR (2008) Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. Ann Neurol 63:236–246

Hummel FC, Cohen LG (2006) Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke. Lancet Neurol 5:708–712

Jeannerod M (1984) The timing of natural prehension movements. J Mot Behav 16:235–254

Kinsbourne M (1974) Mechanisms of hemispheric interaction in man. In: Kinsbourne M, Smith WL (eds) Hemispheric disconnection and cerebral function Springfield. Thomas, IL, pp 260–285

Kobayashi M, Hutchinson S, Theoret H, Schlaug G, Pascal-Leone A (2004) Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. Neurology 62:91–98

Liepert J, Hamzei F, Weiller C (2000) Motor cortex disinhibition of the unaffected hemisphere after acute stroke. Muscle Nerve 23:1761–1763

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A (2000) Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 111:800–805

Netz J, Ziemann U, Homberg V (1995) Hemispheric asymmetry of transcallosal inhibition in man. Exp Brain Res 104:527–533

Nowak DA, Grefkes C, Dafotakis M, Küst J, Karbe H, Fink GR (2007) Dexterity is impaired at both hands following unilateral subcortical middle cerebral artery stroke. Eur J NeuroSci 25:3173–3184

Talelli P, Rothwell JC (2006) Does brain stimulation after stroke has a future? Curr Opin Neurol 19:543–550

Uttner I, Kraft E, Nowak DA, Müller F, Philipp J, Zierdt A, Hermsdörfer J (2007) Mirror movements and the role of handedness: isometric grip force changes. Motor Control 11:16–28