Long-term progressive motor skill training enhances corticospinal excitability for the ipsilateral hemisphere and motor performance of the untrained hand

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Abstract

It is well-established that unilateral motor practice may cause increased performance in the opposite non-trained hand. Here, we test the hypothesis that progressively increasing task difficulty during long-term skill training with the dominant right hand increase performance and corticomotor excitability of the left non-trained hand. Subjects practiced a visuomotor tracking task engaging right digit V for 6 weeks with either progressively increasing task difficulty (PT) or no progression (NPT). Corticospinal excitability was evaluated from the resting motor threshold (rMT) and recruitment curve parameters following application of transcranial magnetic stimulation (TMS) to the iM1 hotspot of the left abductor digiti minimi muscle (ADM).

PT led to significant improvements in left hand motor performance immediately after 6 weeks of training (63±18%,P<0.001) and 8 days later (76±14%,P<0.001). Additionally, PT led to larger improvements compared to NPT (19±15%,P=0.024 and 27±15%,P=0.016). Following the initial training session, corticospinal excitability increased across all subjects. After 6 weeks of training and 8 days later, only PT was accompanied by increased corticospinal excitability evidenced by a left and upward shift in the recruitment curves i.e. decreased rMT (P=0.002) and I50 (P=0.032) and increased MEP_{max} (P=0.012). Eight days after training similar effects were observed, but 14 months later motor performance and corticospinal excitability were similar between groups. We suggest that progressively adjusted demands for timing and accuracy promote motor skill learning and drive the iM1-corticospinal excitability resulting in enhanced performance of the non-trained hand. The results underline the importance of increasing task difficulty progressively and individually in skill learning and rehabilitation training.

Introduction

Motor memories encoded through repeated practice often result in performance increases when performing similar tasks or the same task with other limbs. An example of the latter is the process whereby training of a skill involving one limb gives rise to enhancements in the performance of a non-trained limb. This process, commonly referred to as *interlimb transfer* or *cross-education,* has been demonstrated across different types of motor learning including reaching in novel dynamics (1), ballistic movements (2), the serial reaction time task (3-5) and more complex tasks such as the peg-board task (6). Importantly a putative role of interlimb transfer has been demonstrated in rehabilitation (e.g. (7)).

Although the effect of unimanual practice on contralateral performance has been studied extensively throughout the last three decades (1-6, 8-12), the underlying neural mechanisms remain a matter of debate. In essence two complementary conceptual frameworks account for the mechanisms. The *shared access* model entails that during unilateral motor practice, motor engrams or models are formed and these may be utilized bilaterally by neural circuitries involved in controlling movements of both limbs (13, 14). Based on this notion, performance of the non-trained hand is expected to increase predominantly in the early stages of skill acquisition, which requires a significant cognitive involvement and is also expected to vary with the complexity of the motor task (15, 16). Evidence from reaching studies in non-human primates and able-bodied subjects does indeed suggest this (17, 18).

The *cross-activation* model is derived from the finding that unilateral motor practice is accompanied by increased excitability of cortical motor areas in both the contralateral (e.g. (19, 20), and the ipsilateral hemisphere as well as changes in interhemispheric inhibition (2, 9, 16). The tenet is that during unilateral practice, activation of homologous motor networks leads to adaptations in both hemispheres, contributing to improved motor performance also for the non-trained limb (2, 3, 9, 21-23). Since cross-activation of the ipsilateral primary motor cortex (M1) is closely related to the intensity of the unilateral contraction (4), the increased performance of the non-trained hand is predicted to relate to the neural drive required to perform the motor task (16).

In line with both the shared access and cross activation models, we hypothesized that incrementally challenging motor practice enhances performance of the non-trained hand. The rationale for this hypothesis is that progressively increasing task difficulty requires sustained attention in order to accommodate the increasing demands for speed and accuracy, hereby forcing the subject to continuously optimize the employed motor control strategies and hence the corticospinal output. We have recently found that increasing task difficulty progressively leads to enhanced motor performance and pronounced changes in contralateral corticospinal excitability compared to training with a fixed task difficulty (Christiansen et al. in review). We speculated that progressive motor skill training would also be accompanied by enhanced bilateral performance and incremental changes in corticospinal excitability to the non-trained hand. To address this possibility, we tested the hypothesis that 6 weeks of progressive or

fixed-level of training of a right hand visuomotor accuracy task would improve skill acquisition and long-term retention of motor performance of the non-trained left hand. Changes in excitability of the non-trained hemisphere were assessed with the use of Transcranial Magnetic Stimulation (TMS).

Materials & Methods

We obtained measures of motor performance and applied transcranial magnetic stimulation (TMS) to assess the effect of two different long-term unimanual training protocols on performance and changes in corticospinal excitability for the non-trained hand. Two groups of subjects each participated in 6 weeks of visuomotor training with either maintained, non-progressive (NPT) or progressively increased task difficulty (PT). Training consisted of a visuomotor accuracy task. The effect of training on corticospinal excitability was assessed through TMS by comparing recruitment or stimulus-response curve parameters before and after the initial training session and after 6 weeks of training with retention tests following 8 days and 14 months of detraining.

Participants

Twenty-four adult men aged 21-29 years, (24±4, mean ± s.d.) were randomly allocated into the two different training groups. All participants had a moderate to high level of daily physical activity and had no known medical condition that could interfere with motor skill learning involving the hands. Subjects were paired based on initial right hand performance in the task. Each member of the pair was then randomly assigned to one of the two groups in order to ensure comparable baseline performance in the two groups. For details on the performance test, see below. For each subject, all experimental sessions were conducted at the same time of the day in order to minimize intra-individual day-to-day differences in motor performance and in corticospinal excitability (24) . Participants were instructed not to engage in physical training of any kind prior to testing sessions and to eat, sleep and drink similarly before the tests. Nevertheless, one subject had to be excluded from the longitudinal comparisons in the study because he showed significant fatigue during the 6-week test due to prior strenuous exercise. Twenty-three subjects were right handed according to the Edinburgh Handedness Inventory (25) and one had no hand preference.

Prior to their participation in the study, written informed consent was obtained from all participants. The experiments were approved by the local ethics committee of the capital region of Denmark (KF01-131/03) and all experimental procedures were carried out in accordance with the Helsinki Declaration (1964).

(Insert figure 1 here)

Design

The two groups of subjects trained 18 times over a period of 6 weeks with their right (dominant) hand. Training sessions were distributed 3 times per week and when possible, separated by 48 hours. Each training session consisted of 7 4-minute bouts of activity interspaced with 2-minute rest periods. Baseline electrophysiological and motor performance tests took place at the beginning of the week, either Monday or Tuesday. Electrophysiological and behavioural testing was repeated following 6 weeks of training and again after 8 days without training. Fourteen months after the end of the 6-week training period all available participants were subjected to a second delayed retention test. At least 3 days prior to the baseline test all subjects were accustomed to the lab setting and experimental procedures involving TMS. During baseline tests, the electrophysiological measurements were collected both before training and again immediately after the first training session. At post-test following the 6-week intervention and during the retention tests electrophysiological measurements were only obtained once. An overview of the study design is presented in figure 1.

The first training session took place at the baseline test day and was similar for the two groups. After the first training one group kept on training at the baseline level (non-progressive training, NPT), while the other group trained at a task level, which was progressively adjusted to correspond to their capability in the motor task (progressive training, PT). For details on the progression, see below.

The Visuomotor task

The training task consisted of a visuomotor game called "*BreakOut*", a spin-off from a classic arcade game (see figure 2). Subjects were able to move a small paddle presented at the bottom of a monitor using a custom made board containing a trackball, which was controlled by adduction and abduction of the fifth digit. The paddle was moved left-right by moving the trackball from side to side with the finger in order to make a ball bounce between the paddle and a collection of bricks with the purpose of shooting down bricks and avoid losing the ball in case it did not hit the paddle. Losing three balls caused the game to start over

with the original amount of bricks restored. Performance was quantified as the average number of bricks shot down per ball and this score was multiplied by a factor 1.x, with x being the number of screens/rounds cleared without losing the ball. For the subjects in the PT group, the speed of the ball, size of the paddle and number of bricks were adjusted in order to increase the difficulty of the game in accordance with a previously established progression routine. The idea is, that a decrease in paddle size increases the demands for movement accuracy, an increase in the speed of the ball increases the demands for movement velocity and the increases in the amount of bricks counteracts the decrease in trial time otherwise caused by the increase in ball speed.

In order to progress from one game level to the next, the screen had to be cleared three times during the same training session. In each training session the subject started out by training at the task difficulty, which was reached during the previous training.

Subjects received standardized information about the game and the performance score and were asked to do their best at all times. During training (and testing) the subject was seated in a comfortable chair with both hands on a panel placed on top of a table. The subject was positioned so that the shoulder was slightly flexed and abducted and the elbow joint was flexed to an angle of 90 degrees. The hands and forearms were secured with Velcro™ straps to maintain the standard hand position. The forearm was kept flat on the panel by two straps; one distal to the elbow joint and the other approximately 2 cm proximal to the wrist. The hand was held in a pronated position by two straps, one distal to the wrist and the other crossing the back of the hand. Digits 1 to 4 were similarly fixed to the panel by two straps. The trackball was built into the panel and positioned below the fifth digit. The subjects manipulated the trackball and thereby the position of the game-paddle by abducting and adducting the finger. The left and right arm was placed in the same (mirrored) position. The hands and arms were positioned in an identical position during electrophysiological and behavioural testing procedures, but during training (right hand only) the left (non-training) hand was free to restart the game by pressing the space bar on a keyboard. The experimental setup is illustrated in Figure 2.

(Insert figure 2 here)

Left hand motor performance

During the testing sessions at baseline, after 6 weeks of right hand training and at the delayed retention tests left hand 'BreakOut' performance was tested during a 4 min bout in which a screen contained 80

bricks. The task level for left hand motor performance testing was the same in all testing sessions and corresponded to the baseline level for both groups. Motor performance was quantified as the average number of bricks shot down with per ball during the 4 min. period and this score was multiplied by a factor 1.x with x being the number of screens/rounds cleared without losing the ball i.e. a bonus for completing trials successfully.

Recording and stimulation procedures

Electromyographic (EMG) recordings from the ADM muscle were obtained with bipolar surface EMG electrodes (0.5 cm diameter of electrodes; 2 cm distance between electrodes; Blue Sensor, Ambu Inc., USA) over the belly of the muscles. A ground electrode was placed proximal to the wrist. The EMG signals were amplified (x2000), using NeuroLog EMG amplifiers (Digitimer Ltd., UK) , filtered (band-pass, 5 Hz to 1 kHz) sampled at 2 kHz, and stored on a PC for off-line analysis (CED 1401+ with Signal 3.09 software, Cambridge Electronic Design Ltd., UK). Electromyographic activity during training was recorded with Spike 2 (CED, Cambridge UK) and stored for off-line analysis.

Magnetic stimuli were delivered to the right hemisphere primary motor cortex (M1) by a Magstim Rapid[2] stimulator (Magstim Company Ltd., Whitland, UK) via a custommade 90 mm figure-of-eight coil (batwing design, Magstim Company Ltd., Whitland, UK) with the capability to deliver a magnetic field of 2 T. All TMS measurements were obtained while the subject was at rest. At the beginning of each experimental session, the optimal position (hotspot) of the coil for eliciting motor evoked potentials (MEPs) in the ADM muscle was established through a mini mapping procedure round a grid covering the primary motor cortex (M1). During assessment of the resting motor threshold (MT) and during generation of the TMS recruitment curves the coil was placed with the centre oriented parallel to the scalp over the hot-spot of the ADM representation with the handle of the coil pointing backward at an angle of 45 degrees to the sagittal and horizontal axis (see figure 2). The MT was defined as the minimum intensity required to elicit a peak-to-peak MEP amplitude larger than 2 x s.d. of average background activity in 3 out of 5 trials (this amplitude was in all sessions below 50 μV). A TMS recruitment curve was obtained by delivering 60 stimulations at stimulus intensities ranging from 80-180% of MT in the baseline test in a random-intensity sequence with an inter-stimulus interval of 3 seconds (26). For each stimulation, the peak-to-peak amplitude of the Motor

Evoked Potential (MEP) was quantified based on the raw EMG. Trials in which pre-stimulation EMG amplitudes exceeded mean background + 2 s.d. were discarded and additional stimulations were added.

During all experiments involving TMS frameless stereotaxy (Brainsight 2, Rogue Research, Montreal, Canada) was used to identify the coordinates of the M1 hotspot and to monitor the position and orientation of the coil relative to the subjects' head.

Before generation of TMS recruitment curves at each test, maximal compound muscle action potentials of ADM (maximal M-waves or M_{max}) were elicited by bipolar electrical stimulation of the left arm ulnar nerve using a constant current electrical stimulator (DS7A, Digitimer, UK). The intensity of the 1ms stimulation was increased from a subliminal current until there was no further increase in the peak-to-peak amplitude of the M-wave with increasing intensity. The purpose of this procedure was to normalize all MEP amplitudes obtained for each subject on each test day to the corresponding M_{max}. This allowed comparison across different test sessions.

Data analysis and statistics

Statistical analysis was performed on the data using Matlab (R2011a, The Mathworks Inc.) and Sigmaplot 12.5 software (Systat Software Inc. USA).

Left hand motor performance scores were entered into a two-way repeated measures analysis of variance (ANOVA) with GROUP (PT, NPT) and TIME (baseline, 6 weeks, 8d retention and 14 mo retention) as factors. Post hoc pairwise multiple comparisons were performed as Bonferroni t-tests. Since one subject was excluded at the 6 week test, 23 subjects were included in this analysis.

MEP amplitudes were normalized to the individual M_{max} amplitude recorded just prior to testing on that day to allow comparison between test days and stimulation intensity was normalized to MT in the baseline test. The recruitment curves were constructed by modelling the relation between stimulus intensities and MEPs with a Boltzmann-like sigmoid equation as described by Barsi et al.(27). The equation relating the magnitude of the MEP to the stimulus intensity (*I*) is:

$$MEP(I) = MEP_{min} + \frac{MEP_{max} - MEP_{min}}{1 + e^{\frac{I_{50}-I}{S}}}$$

Where MEP_{min} is the baseline (ideally 0 but inevitably reflecting non-systematic low-level background noise), MEP_{max} is the maximum plateau value, I_{50} is the stimulus intensity at the inflection point where a MEP amplitude of 50% of MEP_{max} is obtained, and S is the slope at the inflection point. The inverse of the slope parameter (1/S) is directly proportional to the maximum steepness of the function. These parameters can be interpreted as estimates of parameters, which together with the motor threshold describe the MEP recruitment curve by the maximum elicited response (MEP_{max}), and the transition between them (S, I_{50}) in relation to stimulus intensity (I) (26). The parameters were estimated by fitting this equation to the stimulus-response data with a standard Marquardt–Levenberg non-linear least squares algorithm (Matlab curve fitting toolbox).

In order to investigate changes in corticospinal excitability during and following the training protocol and detraining, the electrophysiological parameters MT, MEP_{max}, I50 and slope were entered into statistical analyses. Short-term effects of skill training were tested by entering the parameter estimates of MEP_{max}, I50 and slope obtained before and after the first right hand training session into paired t-tests. If data were not normally distributed, the test was Wilcoxon signed rank test. Data for 24 subjects were included in this analysis. In order to test long term effects of motor skill learning the MT, MEP_{max}, I50, slope and M_{max} were entered into a two-way repeated measures ANOVA with GROUP and TIME (baseline, 6 weeks, 8d retention) as factors. Since only 14 out of the original 24 subjects were able to participate in the delayed retention test 14 months following training, the data for these subjects were analysed in a separate two-way repeated-measures ANOVA with GROUP $\times$ TIME (baseline, 6 weeks, 8d and 14mo retention) as factors. All posthoc pairwise comparisons were performed as Bonferroni t-tests.

Potential relations between changes in motor performance and changes in measures of corticospinal excitability were tested using Pearson Product Moment correlation tests both within and across intervention groups. All values are reported as mean ± s.e.m. unless stated otherwise. In all tests, statistical significance was assumed if $p < 0.05$.

Results

Left hand motor performance

For both groups, the motor performance improved significantly for the right hand following 6 weeks of motor practice (Christiansen et al. submitted). For the left hand, the motor performance scores are listed

in Table 1 and performance normalized to baseline is presented in figure 3. The 2-way RM ANOVA on motor performance normalized to baseline demonstrated a significant effect of GROUP ($F_{(1,68)}$=5.25, P=0.032), TIME ($F_{(2,68)}$=14.32, P<0.001) and a significant GROUP × TIME interaction ($F_{(2,68)}$=3.56, P=0.03). Within the PT group there was a 63±18% increase in motor performance from baseline to post test (t=4.5, P<0.001) and a 76±14% increase to the 8-day retention test (t=5.41, P<0.001) (see figure 3). For the NPT group there was a no significant increase in motor performance following 6 weeks of training (19±15%, t=1.3 P=0.6) nor at the 8-day retention test (27±15, t=1.82, P=0.22). After 6 weeks of training, the PT group performed significantly better than the NPT group (t=2.46, P=0.017) and this was also the case at the 8-day retention test (t=2.74, P=0.008).

(Insert table 1 here)

Since it was only possible to test retention after 14 months in 14 subjects (7 in each group), a separate 2-way RM was performed including these subjects and adding the time point 14mo. This analysis demonstrated a significant effect of GROUP ($F_{(1,55)}$=7.64, P=0.017, TIME ($F_{(3,55)}$=5.6, P=0.003) and a GROUP × TIME interaction ($F_{(3,55)}$=6.36, P=0.001). While the PT group performed better than the NPT group after 6 weeks of training and at 8d retention tests, motor performance in the PT group decreased from these time points to the 14mo test (t=3.1, P=0.026)(t=3.25, P=0.015). Although mean motor performance at 14mo was 33±12% and 23±21% higher than at baseline for the PT and NPT groups respectively, posthoc tests revealed that there was no difference between baseline and 14mo motor performance across groups (t=1.98, P=0.33).

Insert figure 3 here)

In conclusion the PT group had significantly larger gains in left hand motor performance compared to the NPT group following 6 weeks of training with the right hand. Motor performance at the 8d retention test was also significantly better for the PT group. 14 months after training there was no longer significant retention effects and no differences between groups.

Electrophysiological measurements

For all subjects, TMS stimulus-response curves were obtained in the baseline test before and after the first training session in order to elucidate short-term effects. Since the first training session was identical

for the two intervention groups, all subjects were included in the analysis of short-term effects of right hand training. All MEP amplitudes were normalized to the corresponding M_{max}. There were no differences in M_{max} amplitudes between GROUPs $F_{(1,68)}=1.49$, P=0.24 nor an effect of TIME $F_{(2,68)}=1.14$, P=0.33 or a GROUP × TIME interaction $F_{(2,68)}=0.4$, P=0.67.

Short-term effects

Parameter estimates from the obtained TMS stimulus-response curves were compared before and after the first training session for all 24 subjects. The mean values for MEP_{max}, I50 and the slope parameter are listed in Table 2. Following the first training session MEP_{max} increased (z=-2.09, P=0.038) and I50 decreased (z=2.06, P=0.041) while there was no significant change in the slope parameter (t=1.22, P=0.12). The results indicate that a single session of right hand visuomotor skill training did increase corticospinal excitability for the right hemisphere (left hand).

(Insert table 2 here)

Long-term effects

In order to assess long-term effects of motor skill learning TMS stimulus-response curve parameters were also compared between baseline (pre), following 6 weeks of motor skill training and at the retention test after 8 days. For the Motor threshold (rMT) the two-way RM ANOVA revealed a significant main effect of TIME ($F_{(2,68)}=10.33$, P<0.001). Post hoc pairwise comparisons were performed as Bonferroni t-tests. Within the PT group there was a significant decrease in MT from baseline to the post test at 6 weeks (t=3.32, P=0.002) and to the 8-day retention test (t=3.52, P=0.001)(see table 3 and figure 4A). For the NPT group, there was a tendency towards a decrease in rMT from baseline to the post test (t=1.95, P=0.058) and a decrease from baseline to the 8-day retention test (t=2.35, P=0.024).

(Insert figure 4 here)

For MEP_{max} there was a significant GROUP × TIME interaction ($F_{(2,68)}=3.68$, P=0.03). Post hoc pairwise comparisons were performed as Bonferroni t-tests. Within the PT group there was a significant increase in MEP_{max} from baseline to post test (t=3.05, P=0.012) and to the 8-day retention test (t=3.05, P=0.012)(see table 3 and figure 4B). For the NPT group there was a no significant increase in MEP_{max} following 6 weeks of training nor at the 8-day retention test.

For I50 there was a significant main effect of GROUP ($F_{(1,68)}$=4.69, P=0.04). Post hoc pairwise comparisons revealed a significant decrease in I50 from baseline to the post test at 6 weeks within the PT group (t=2.2, P=0.032))(see table 3 and figure 4C). There were no changes in I50 in the NPT group. There were no significant changes in the slope parameter for either of the groups.

(Insert figure 5 here)

At the long-term retention test 14 months after the end of the training period, 14 subjects (7 from each intervention group) were tested. A separate two-way repeated measure ANOVA including these subjects revealed no differences between groups at this time point and no differences compared to baseline (see table 3 and figure 4).

The results indicate that following 6 weeks of right hand visuomotor skill training, subjects who practice with a progressively adjusted task difficulty demonstrate pronounced changes in corticospinal excitability for the right hemisphere (left hand) compared to subjects who practice without progression in task difficulty. This difference was also evident at the retention test 8 days after the training period whereas there were no differences in corticospinal excitability at the retention test 14 months after the intervention. In order to illustrate the effects of motor skill training on the TMS stimulus-response curves figure 5 depicts global fits for the TMS stimulus-response data obtained for the two intervention groups at all time points.

(Insert table 3 here)

No significant correlations were found between the observed changes in motor performance and measures of corticospinal excitability either within or across groups.

Discussion

In agreement with the hypothesis, the main finding of this study is that 6 weeks of progressive visuomotor training enhances performance with the non-trained hand. Whereas the initial motor training session at the baseline level was accompanied by an increase in corticospinal excitability assed from the right hemisphere to the left ADM across all subjects, only the progressive training protocol was accompanied by pronounced changes corticospinal excitability following long-term motor skill training. These findings

suggest that the improved performance of the non-trained hand depends on the sustained challenging nature of the progressive practice protocol. In accordance with the theoretical framework, plastic changes in the M1 and corticospinal pathway are likely involved.

Why does progressive training with the right hand promote left hand motor performance?

The purpose of the progressive adjustments of task difficulty was to continuously adjust the imposed demands for movement accuracy and speed to the current skill level of each individual subject. By doing so, the task would impose demands on attention, cognitive and sensorimotor processing and thus be challenging throughout the intervention period leading to a less effector specific and consequently a more flexible representation(17, 28, 29). In support of this, previous studies indicate that the capacity to execute a complex skill with a non-trained limb reflects the abstract representation of external visuospatial coordinates (10, 11, 30), which is likely represented in higher order circuits (31). It has been suggested that novel motor skills are acquired through encoding in two distinct parallel systems (32). This model is in accordance with the intrinsic and extrinsic coordinate coding systems model, in which intrinsic coordinates are encoded as joint representations (1), muscle kinetics (33) and the orientation of the limbs in relation to the body (34). In contrast, extrinsic coordinates are coded as Cartesian coordinates of the surrounding space in relation to the body (e.g. (35)). Rapid encoding of visuospatial coordinates as required in the BreakOut game is an abstract representation, which is effector non-specific. This process is thought to be dominant in the early stages of learning, whereas a slow evolving encoding of motor coordinates has been suggested to be dominant after extended practice. This model was supported by Nakahara et al (36), who found it more likely than a simple encoding model using computer modelling. A possible generalization of the model across tasks is supported by the later findings by Trempe & Proteau (37, 38)(2008, 2010), Berniker and Kording (39, 40) (2008, 2011) using adaptation paradigms, very different from the sequential tasks used by Panzer and colleges(10, 41) (2009, 2011). The mechanisms underlying the difference in effector specificity and consequently the increase in performance of non-trained limbs may therefore depend on dominance of the two systems during encoding.

Role of iM1

In the present study, the results not only demonstrated behavioural differences between progressive and non-progressive training, but also changes in iM1 and corticospinal excitability following training. After

the initial training session corticospinal excitability increased across all subjects, and following long-term training changes were pronounced in the PT group compared to the NPT group. Thus, the results demonstrate that right hand motor skill training has implication for the iM1.

Results from studies in healthy subjects and neurological patients suggest bilateral, but distinct motor cortical activation during unilateral motor activity (42). A recent imaging study found increased iM1 activation with the demand for precision during a pointing task suggesting that the involvement of iM1 relates to task difficulty (43). Also, a lesion to the iM1 caused by cerebral infarction impairs fine motor control of the hand (44), whereas temporarily disrupting iM1 with rTMS in able-bodied subjects can impair execution of complex piano sequences (45) and alter timing of muscle recruitment probably through transcallosal influences (46, 47). This interpretation is supported by the sparse ipsilateral corticospinal connections seen in non-human primates (48). The involvement of iM1 in unilateral motor control is supported by the finding of increased corticospinal excitability and decreased intracortical inhibition during execution of a goal-oriented precise movement with the ipsilateral hand compared to a control situation with comparable muscle activity (49). Together these results suggest that fine goal-oriented motor control is partly dependent on and can be influenced by activity in the ipsilateral primary motor cortex. In many studies, however, it is not possible to assess the extent to which iM1 influences or is influenced by the unilateral motor activity. This is also the case for the present study, although the observed changes in iM1 corticospinal excitability could be consistent with the cross-activation model, since we also recently found cM1 excitability to be increased following this type of training (unpublished observation). It is however difficult to speculate on cross-activation, since all measurements were obtained at rest.

Changes in corticospinal excitability

Similar to the present study, changes in performance of the non-trained hand have previously been demonstrated to coincide with increases in iM1 excitability following unimanual training of a ballistic task (2) and to be susceptible to interference induced by rTMS over the iM1 following training (23). Despite contrasting results demonstrating decreased ipsilateral excitability following ballistic training (50), the majority of findings support a role for the ipsilateral M1 in both unilateral motor control and bilateral increases in performance. Our results support this role and suggest that increasing the before mentioned demands to motor preparation and output increases performance in the non-trained hand along with

increased corticospinal excitability. This is in line with earlier studies suggesting more ipsilateral activation during execution of complex tasks (51).

The coinciding, but uncorrelated increases in corticospinal excitability of iM1 and performance of the non-trained hand suggest that the change in balance between excitatory and inhibitory activity in the corticospinal pathway reflects a change in inputs to iM1 not directly related to the amount of learning. Higher cortical areas with denser interhemisperic connections such as the SMA (3) is likely to be involved in the performance increments as illustrated by the lack of bilateral performance gains, when SMA activity is disrupted prior to each trial during acquisition of the Serial Reaction time Task (4). Our results support a "bilateral access" model as proposed by Imamizu & Shimojo (52), which suggests that structures or networks with access to both hemispheres are responsible for the bilateral performance gains. Rather than a linear relationship, the present results point towards a more complex interaction between motor performance and changes in corticospinal excitability.

Perspectives

For many patients, bilateral performance gains accompanying unilateral training effects may have important clinical implications. During limb immobilization training of the contralateral limb has been demonstrated to attenuate the atrophy, strength loss and decline in range of motion through cross-education effects (53-55). Maladaptive plastic changes in the CNS accompanying immobilization have been demonstrated for both the upper (56) and lower extremities (57, 58). These can be counteracted through training of the non-immobilized contralateral limb (53). This has been demonstrated (59) following both distal radial fractures and ACL reconstruction(60). In neurorehabilitation training, bilateral recovery has also been demonstrated in patients with hemiplegia e.g.stroke patients following unimanual training of both upper (61) and lower (7) extremities. The idea is that transfer of training effects from the least affected limb to the more affected limb can promote recovery of motor functions of the latter and re-establish bilateral symmetry in the central nervous system (for review see(62)) and it is thus clinically important to promote these effects.

Conclusions

We have demonstrated that long-term right hand visuomotor skill learning with progressively increased task difficulty enhances left hand motor skill compared to training without progression i.e. at a fixed task difficulty. Whereas initial skill practice at the baseline level was accompanied by increased corticospinal excitability for the non-trained (right) hemisphere across all subjects, progressive training was accompanied by pronounced long-term changes in iM1 and corticospinal excitability compared to non-progressive training. Both the behavioural effects and the electrophysiological differences between groups were also evident at the retention test 8 days after the training period, but 14 months after the intervention there were no differences between groups. The enhanced left hand performance and accompanying changes in corticospinal excitability suggest that changes in the ipsilateral motor cortex and corticospinal pathway contribute to the improved performance of the non-trained hand. The findings may have important clinical implications for rehabilitation training and add to previous studies suggesting that unilateral training with the least affected limb can contribute to functional gains in neurological patients who are unable to train with the more affected side.

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