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Reduced Neural Differentiation Between Feedback Conditions After Bimanual Coordination Training with and without Augmented Visual Feedback

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It has been established that bimanual coordination with augmented feedback (FB) versus no augmented feedback (NFB) is associated with activity in different brain regions. It is unclear however, whether this distinction remains after practice comprising both these conditions. Functional magnetic resonance imaging was used in humans to compare visual FB versus NFB conditions for a bimanual tracking task, and their differential evolution across learning. Scanning occurred before (Pre) and after 2 weeks (Post) of mixed FB and NFB training using an event-related design, allowing differentiation between the planning and execution phase of the task. Activations at the whole-brain level initially differed for FB versus NFB movements but this differentiation diminished with training for the movement execution phase. Specifically, in right dorsal premotor cortex and right dorsolateral prefrontal cortex activation increased for NFB and decreased for FB trials to converge toward the end of practice. This suggests that learning led to a decreased need to adjust the ongoing movement on the basis of FB, whereas online monitoring became more pronounced in NFB trials as discrepancies between the required and the produced motor output were detected more accurately after training, due to a generic internal reference of correctness supporting movement control under varying conditions.

Keywords: augmented visual feedback, bimanual coordination, fMRI, motor learning, neural plasticity

Introduction

Planning, initiating, and executing a motor task requires integration of internal and external sensory information. Augmented feedback (FB) refers to information provided in addition to the body's natural senses. FB contains cues that supplement information about ongoing or completed movements in addition to the normally available sensory information sources, which is often used to enhance performance and has a substantial impact on motor learning (e.g., Salmoni et al. 1984; Swinnen 1996; Schmidt and Lee 2005; Magill 2007). Several studies have explored the neural activations associated with the provision of augmented FB versus withholding it (NFB) (e.g., Debaere et al. 2003; Ogawa et al. 2006; Wenderoth et al. 2006; Heuninckx et al. 2010). Very little is known however, about how learning can alter the neural representations associated with FB. In a previous study, we used a between-groups design whereby a bimanual coordination pattern was practiced under either visual or auditory augmented FB. After training, the neural patterns associated with both types of FB became more distinct (Ronsse et al. 2010). To alleviate dependence on augmented FB, some behavioral studies have used a mix of both FB and NFB conditions within groups (e.g., Kovacs and Shea 2011; White and Diedrichsen 2013). How the neural differentiation between Feedback modes evolves when learners are exposed to both FB and NFB conditions during training is unknown. Here, our first goal was to provide insight into the evolution of the FB versus NFB neural difference as a result of learning under a training schedule comprising a mix of FB and NFB trials.

We used event-related functional magnetic resonance imaging (fMRI) to measure FB and NFB-related activations before (Pre) and after (Post) 2 weeks of training a bimanual tracking task (BTT) (Sisti et al. 2011, 2012; Gooijers et al. 2013). Based on previous behavioral studies, we hypothesized that providing FB during training improves performance, whereas its subsequent removal results in performance deterioration. This has come to be known as the guidance hypothesis of FB and suggests that the learner may become too dependent on FB (Salmoni et al. 1984; Winstein and Schmidt 1990; Swinnen 1996). Even in the absence of FB during post-training performance, the neural pattern is still tuned toward the type of augmented FB (i.e., vision vs. audition) used during training (Ronsse et al. 2010), supporting the aforementioned FB dependence. One solution to this problem is to prepare the learner for a greater variety of future contexts via exposure to both augmented and deprived FB conditions during training (Winstein and Schmidt 1990; Swinnen 1996; Kovacs and Shea 2011). We argued that, under the latter circumstances, performers build a generic representation enabling them to cope with different task contexts more successfully. Learning effects obtained within the FB condition will not only influence future behavior under FB test conditions, but will also lead to transfer of knowledge to NFB conditions, and vice versa. This would predict a pattern of neural convergence, whereby the distinction between FB- and NFB-related activations is reduced after training.

Finally, the event-related fMRI design allowed us to study the planning and execution phase separately. Planning and executing movements underlie dissociable processes whereby supplementary motor area (SMA), lateral premotor cortex, and basal ganglia show a larger involvement for planning complex movements than for executing them (Elsinger et al. 2006). The second goal of this study was to investigate whether the expected pattern of neural convergence would be prominent at the planning phase, and/or at the execution phase of the task.

Materials and Methods

Participants

Twenty-six right-handed (Oldfield 1971) healthy participants (15 female, aged 21.6 ± 2.3 years) with normal or corrected-to-normal vision participated in the experiment. Data of one female participant was incomplete, due to technical problems with the scanner at Post-test, and was not included in the analysis. All participants were naive with respect to the experimental paradigm. None of them had a history of neurological or psychiatric disease. The protocol was in accordance with the Declaration of Helsinki (1964) and was approved by the local ethical committee of KU Leuven, Belgium. Participants were financially compensated for participation and provided written informed consent prior to the experiment.

Experimental Design and Setup

Magnetic resonance imaging (MRI) scanning occurred before and after 5 training sessions, spread across 2 weeks (see Fig. 1*A*). The scanning sessions lasted 1.5 h and the training sessions lasted 1 h each. Prior to the first MRI scan, participants practiced the task briefly in a dummy scanner until the task was fully understood (~10 min).

Participants lay supine in the scanner (see illustration of dummy scanner setup in Fig. 1*B*), with the arms supported by pillows. Stimuli were displayed by means of an LCD projector (Barco 6300, 1280 × 1024 pixels), projected onto a double mirror placed in front of the eyes. Participants were instructed to produce a set of complex bimanual coordination patterns, requiring rotational movements of both hands simultaneously. A bite-bar and foam cushions were used to prevent excessive head movements during task performance. A non-ferromagnetic apparatus with 2 dials (diameter = 5 cm) for movement recording was placed over the participants' lap in a comfortable position. The dials could be adjusted to the participants' anthropometry and had an angle of approximately 45° for comfortable handling. Movements were made by turning the handle of the dials with the hands. Angular displacements were registered by means of nonferromagnetic high precision optical shaft encoders (HP, 2048 pulses per revolution, sampling frequency 100 Hz), fixed to the movement axes of both dials. This enabled registration of kinematics as well as displaying on-line visual information.

During the training sessions, participants were seated in front of a PC-screen (distance ~0.5 m). A device similar to that used during scanning was mounted on the table and included ergonomic forearm rests. Vision of the hands was occluded during all sessions.

Task

The goal of the BTT was to track a target presented on a screen by rotating dials with both hands simultaneously in one of 4 directional patterns: both hands rotated inwards (IN) or outwards (OUT) together, or in a clockwise (CW) or counter-clockwise manner (CCW) (Sisti et al. 2011, 2012; Gooijers et al. 2013). The left (L) and right (R) hands controlled movements on the ordinate and abscissa, respectively. To increase complexity of the task, each direction was performed at 5 different relative frequency ratios: 1:1, 1:2, 1:3, 2:1, and 3:1 (L:R) (Fig. 1*C*). A 1:2 ratio indicates that the right hand is required to rotate twice as fast as the left hand. A blue target line was always oriented from the origin (center of the screen) with different orientations across the 4 quadrants of the screen (upper-right, upper-left, lower-left, and lower-right) to indicate the required movement pattern. The required frequency ratio could be inferred from the slope of the projected target line on the screen: 45° targets followed a 1:1 ratio, while steeper lines (>45°) required the left hand to rotate faster and less steep lines (<45°) required the right hand to rotate faster. During the "planning phase", which lasted 2000 ms, the target line was presented together with a visual cue to indicate the upcoming condition (see Task Procedure section). During the "execution phase", a white target dot moved over the target line from start (center of the screen) toward the end of the blue line at a constant speed (duration = 9000 ms). The beginning and end of the execution phase were marked with an auditory cue (126 ms, begin: 525 Hz, end: 442 Hz). Between trials, there was a 3000 ms inter-trial interval (ITI).

BTT is a complex task that requires intensive practice to successfully integrate the 2 separate limb movements into one common spatiotemporal pattern. Learning such a task involves breaking away from the natural tendency to move both limbs in phase with the same velocity (i.e., a 1:1 frequency ratio) (Swinnen et al. 1997; Swinnen 2002). These new patterns were trained and performed under 2 conditions: without (NFB) and with (FB) augmented online visual FB of the integrated movement patterns. This type of augmented FB can be used efficiently for on-line movement guidance and error correction processes (Lee et al. 1995; Swinnen et al. 1997). During both conditions, the blue target line was shown, with the white dot indicating the pace (see previous paragraph). During the FB condition, concurrent visual FB was provided by means of a red cursor displaying the actual tracking trajectory based on the contribution of both limbs. The goal in both conditions was to match the target trajectory as closely as possible, indicated by the white dot moving along the line. Perfect performance would be reached in case the positions of the participant's red cursor and the white target dot were exactly matching.

Task Procedure

The event-related scan sessions at pre- and post-test were identical. Each session consisted of 144 trials, divided equally across 6 runs. There were 96 "move" trials in which bimanual tracking was actively performed. The remaining trials were "no-move" trials, containing the same visual information as the "move" trials but required no movement. They provided the baseline measure of the blood oxygen level dependent (BOLD) response. For both move and no-move, augmented visual FB was present for half the trials. This resulted in 4 conditions: move FB, move NFB, no-move FB, and no-move NFB. The move and no-move conditions were cued with a different colored dot appearing at the center of the screen and containing either a cross for NFB or no cross for FB during the planning phase of each trial (Fig. 1*D*) and the order was semirandomized. The no-move FB trials consisted of a random replay of the participant's performance obtained during training. For each condition, the required frequency ratio was randomly distributed such that one-third of trials required a 1:1 ratio, one-third required a 1:2 or 2:1 ratio, and one-third required a 1:3 or 3:1 ratio.

For each of the 5 training days, 10 blocks of 20 move trials (duration = 11 s, ITI = 3 s) were performed, with augmented visual FB presented in half the trials (trial order fully randomized). Knowledge of results was given directly after each NFB trial in order to enhance learning in this condition. This was done by showing the entire produced line in red next to the blue target line that was required, for 1 s. All other aspects of the training were identical to the scanning sessions.

Kinematic Analyses

Data were recorded and analyzed with Labview (8.5) software (National Instruments, Austin, TX, USA). The x and y positions of the target dot and the participants' cursor were sampled at 100 Hz. Offline analysis was carried out using Matlab R2011b and Microsoft Excel 2007. Accuracy was measured by calculating the average target error. That is, for each trial, the target error was measured as the Euclidian distance between the target and the cursor position at each point in time and then averaged. For this measure, better performance is reflected by lower values. Outlier move trials ($z > 3$) were discarded from the analysis (3.3 and 1.2% of all trials in Pre- and Post-tests, respectively). No-move trials were discarded when one or both hands moved for at least 3 movement cycles (1.3% Pretest and 0% Post-test).

Statistical Analyses

Statistical analyses were performed using Statistica 10 (StatSoft, Inc. Tulsa, OK, USA). A repeated-measures analysis of variance (ANOVA) was run (Time × Feedback Condition × Frequency Ratio) for average target error on the scanning (2 × 2 × 5), and training (5 × 2 × 5) data. Training and scanning sessions were analyzed separately, as the

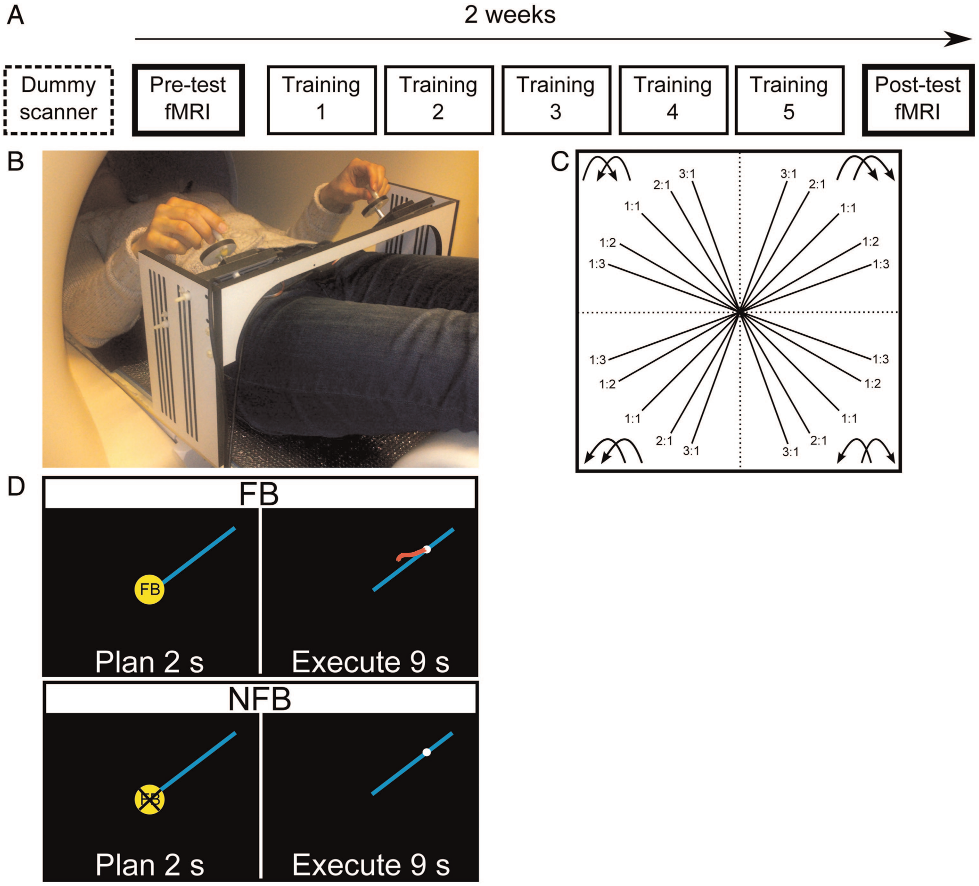

Figure 1. (*A*)Training protocol. Pre- and Post-test were interleaved by 2 weeks in which 5 training sessions took place. (*B*) Example setup in the dummy scanner. The MRI compatible device was mounted on the participants' lap which was used for both the dummy session and both Pre- and Postscanning sessions. (*C*)All possible bimanual directional combinations and frequency ratios ($n = 5$) (schematic drawing). (*D*)Task. During the first 2 s, the blue target line was shown together with a cue indicating whether FB would be received or not (cross in the case of NFB). The cue was either yellow or pink, indicating whether it was a "move" or a "no move" trial (color counterbalanced across participants). After 2000 ms, the cue disappeared and the white target dot started moving starting from the center of the screen along the line with constant speed, which had to be traced (red cursor visible for FB; not visible for NFB).

context of task performance was different. Movement direction (IN, OUT, CW, and CCW) was fully counterbalanced in the design and of no interest for the present analyses (but see Gooijers et al. 2013). The level of significance was set at $P < 0.05$. Significant effects were further explored using Tukey's HSD test to correct for multiple comparisons.

Scan Acquisition and Imaging Analysis

A Siemens 3-T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with a 12-channel head coil was used. For anatomical details, a 3D high-resolution T_1-weighted image was obtained first (magnetization prepared rapid gradient echo, time repetition/time echo = 2300/2.98 ms, 1 × 1 × 1.1 mm voxels, field of view (FOV) = 240 × 256, 160 sagittal slices), lasting 8 min. Then a field map was acquired to address local distortions. The 6 task-fMRI runs each consisted of 116 descending gradient echo planar images (EPI) for T_2-weighted functional images (TR/TE = 3000/30 ms, flip angle = 90°, 50 oblique axial slices, slice thickness = 2.8 mm, inter-slice gap = 0.028 mm, in-plane resolution = 2.5 × 2.5 mm, 80 × 80 matrix). The first 3 volumes from each run were deleted to ensure steady-state magnetization at the start of the task.

The imaging data for each run were analyzed using the FMRIB Software Library (FSL 4.1) (Smith 2004; Woolrich et al. 2009). Prior to entering data into the model, the brain extraction tool (BET) was applied leaving only relevant brain voxels in the T_1 and the field map images. A high-pass filter cutoff of 200 s and MCFLIRT motion correction was used to realign EPI's to the middle volume of each run and the field map was used for B0 unwarping. Slice timing correction was applied along with spatial smoothing using a full-width-half-maximum of 5 mm. Regressors of the conditions of interest (move FB, move NFB, no-move FB, and no-move NFB) and their temporal derivatives were defined for the planning (2 s) and execution (9 s) phase of each condition. All event-related fMRI analyses were conducted on these trial phases separately. Because the onsets of planning and execution were always separated with a fixed interval and were therefore not independent, we refrained to make direct comparisons between them. Discarded trials based on behavioral performance (see kinematic analysis above) formed separate regressors of no interest in the model. EPI's were coregistered to the T_1 image (6 degrees of freedom (DoF) linear transformation) and subsequently to the Montreal Neurological Institute (MNI) template using FNIRT (12 DoF affine transformation and additional nonlinear warping).

In the second-level analysis, a fixed effects model was used to collapse across the 6 runs for each participant. The main effect of Time (Pre and Post), Feedback Condition (FB and NFB), and the Time × Feedback Condition interaction were analyzed on the group level, using the random-effects model of FSL (FLAME 1). Note that Frequency ratio was included to enhance complexity of the task for learning across days, but as this variable was not of interest for our primary question, we collapsed these trials for the fMRI analyses. To focus on differences in activation, as opposed to deactivation, main effects and interactions were masked inclusively by contrasting each condition to its respective baseline at $Z > 0$. This was done in order to control for the different types of visual information in both conditions (i.e., each condition therefore had its own baseline). Furthermore, only grey matter voxels were included (average of all individual subjects using a threshold of 0.3). The main effect of Feedback Condition was tested by directly comparing FB and NFB trials (collapsed over the Pre- and Post-test) independently for the planning and execution phases. The main effect of Time was calculated by comparing Pre- versus Post-test collapsed over FB and NFB trials. To test whether training resulted in a more similar (convergence) or distinct (divergence) pattern of activation in the FB and NFB conditions, a conjunction analysis was performed to determine the number of voxels responding to both FB and NFB conditions (FB ∩ NFB) in each participant. A repeated-measures ANOVA (Statistica 10) was used to test the percentage of common activation (FB ∩ NFB) in Pre- and Post-test. To identify the neural loci of diverging or converging activity, the Time (Pre and Post) × Feedback Condition (FB and NFB) interaction was calculated. For cluster peaks, percent signal change (PSC) for each Feedback and Time condition was calculated relative to baseline. All fMRI analyses were done using Gaussian Random Field Theory at the cluster level using $Z > 2.3$ and a cluster probability threshold of $P < 0.05$. The activation peak of each cluster will be reported together with local maxima if the cluster spans multiple regions. Labeling of areas was based on the "Juelich histological cyto-architectonic atlas" toolbox in FSL (Eickhoff et al. 2005, 2006, 2007). When no label was found, the "Harvard-Oxford Cortical Structural Atlas" toolbox, and for subcortical structures, the "Harvard-Oxford Subcortical Structural Atlas" toolbox (Frazier et al. 2005; Desikan et al. 2006; Makris et al. 2006; Goldstein et al. 2007) were used. The "Cerebellar Atlas in MNI152 space after normalization with FNIRT" toolbox (Diedrichsen et al. 2009) was used for identifying cerebellar structures. The Human Motor Area Template from Mayka et al. (2006) was used to identify sensorimotor regions.

As performance differs between the levels of Feedback and Time conditions, control analyses were performed in order to assess which effects would be driven by brain–behavior correlations. Whole-brain analyses of covariance were carried out by adding the demeaned average target error (collapsed across frequency ratios but for each Feedback condition) as a covariate for all FB conditions and Time points in separate models for the planning and execution phase.

Results

Kinematic Data

Scan Sessions

To assess motor performance during the scan sessions, a 2 × 2 × 5 (Time × Feedback Condition × Frequency Ratio) repeated-measures ANOVA was conducted for average target error. There was a strong learning effect from Pre- to Post-test, reflected by the main effect of Time [$F_{1,\ 24} = 103.5$, $P = 0.001$], whereby average target error dropped sharply (Fig. 2*A*).

Furthermore, a main effect of Feedback Condition was observed [$F_{1,\ 24} = 170.3$, $P = 0.001$] (i.e., higher error in the NFB as compared with the FB condition), together with a main effect of Frequency Ratio [$F_{4,\ 96} = 37.5$, $P < 0.001$]. Average target error was higher in difficult (non-1:1) as compared with the easier (1:1) frequency ratios. *T*-tests revealed that all frequency ratios differed from each other significantly [all $P < 0.05$], except for the 1:3 with the 3:1 and 2:1 conditions, and the 2:1 with the 3:1 condition [all $P > 0.7$].

The Time × Feedback Condition interaction [$F_{1,\ 24} = 14.8$, $P < 0.001$] and the Time × Frequency Ratio interaction [$F_{4,\ 96} = 12.8$, $P < 0.001$] were significant but can be explained in light of the 3-way interaction. The significant 3-way interaction of Time × Feedback Condition × Frequency Ratio [$F_{4,\ 96} = 4.1$, $P = 0.005$] implied that the combined effect of Feedback Condition and Frequency Ratio was reduced after training. Learning therefore not only resulted in performance improvement, but also in better handling of the more difficult task conditions (Fig. 2*A*).

Training Sessions

A 5 × 2 × 5 (Time × Feedback Condition × Frequency Ratio) repeated-measures ANOVA was conducted for the average target error scores obtained across training days (Fig. 2*B*). The main effect of Time was significant [$F_{4,\ 100} = 52.9$, $P < 0.001$], suggesting a strong practice effect. Post hoc *t*-tests revealed that Sessions 1 and 2 significantly differed from each other as well as from all other sessions [all $P < 0.05$]. Session 3 was only different from Session 5 [$P = 0.018$] but not from Session 4 [$P = 0.18$]. The difference between Session 4 and 5 did not reach significance [$P = 0.89$]. This suggests that the practice effect was strongest at the first few training sessions and a plateau effect was reached toward the final 2 sessions.

As expected, average target error was lower in the FB compared with the NFB condition [$F_{1,\ 25} = 17.3$, $P < 0.001$]. The main effect of Frequency Ratio revealed greater error rates for the non-1:1 as compared with the 1:1 frequency ratio(s) [$F_{4,\ 100} = 30.6$, $P < 0.001$]. Post hoc *t*-tests revealed that the 1:1 frequency ratio differed from all other frequency ratios [all $P < 0.001$]. The non-1:1 frequency ratios did not differ from each other [all $P > 0.1$].

The significant Time × Feedback Condition interaction [$F_{4,\ 100} = 4.5$, $P = 0.002$] reflected a greater decrease in average target error for the NFB condition across sessions compared with the FB condition, resulting in a smaller effect of Feedback Condition as training progressed. The significant Feedback Condition × Frequency Ratio interaction [$F_{4,\ 100} = 14.2$, $P < 0.001$] suggested that the performance differences among the different frequency ratios were larger in the NFB as compared with the FB condition. The Time × Feedback Condition × Frequency Ratio and the Time × Frequency Ratio interactions did not reach significance [$P = 0.91$ and $P = 0.2$, respectively].

Imaging Data

The results are reported separately for the planning and execution phase of the BTT. Here, the main effects of Feedback Condition and Time on neural activity are reported, and finally their interaction.

Main Effect of Feedback Condition

The main effect of Feedback Condition assessed neural activation differences between FB and NFB movement conditions.

Areas Showing Higher Activation in NFB Than in FB Condition. Two clusters were more active for NFB than FB in the *planning phase* (Table 1). NFB movements resulted in more activity in bilateral pre-SMA and bilateral dorsal premotor cortex (PMd), including the pre-PMd.

Five clusters were more active for NFB than for FB in the *execution phase* (Table 1). The active clusters were located in left lingual gyrus, bilateral primary somatosensory cortex (S1) and left secondary somatosensory cortex (S2), and bilateral cerebellar lobe VI.

Areas Showing Higher Activation in FB Than in NFB Condition. Seven clusters were more active for the *planning phase* of FB compared with NFB trials (Table 1). They consisted of left parieto-occipital part, posterior cingulate, bilateral primary motor cortex (M1), left S1, and several cerebellar subareas in both hemispheres.

For the *execution phase*, 7 main clusters were obtained which were more active for FB than for NFB trials (Table 1).

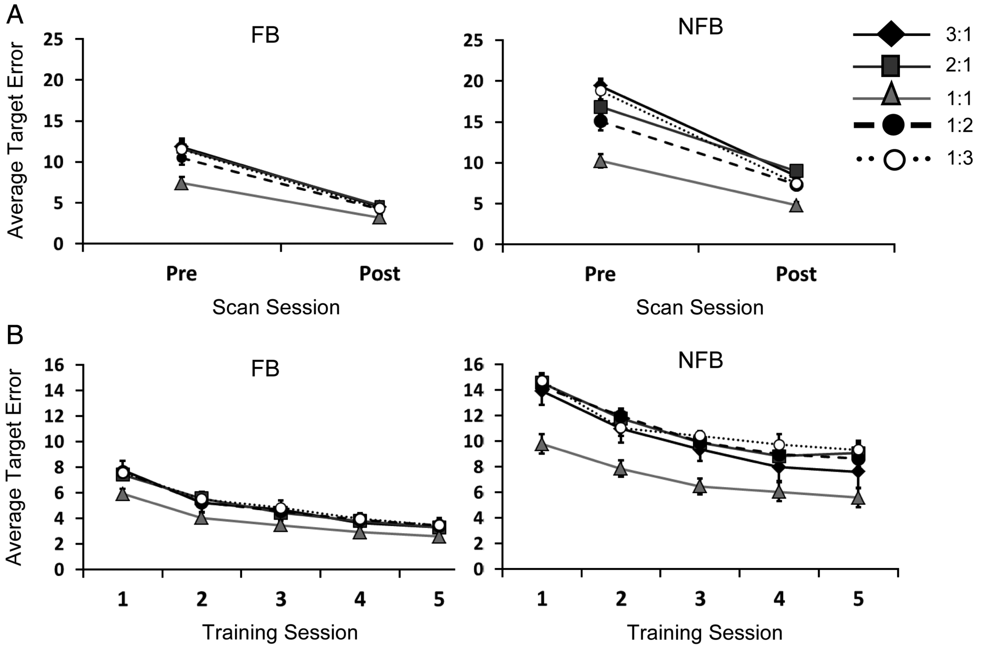

Figure 2. Behavioral results. Average target error is plotted for all frequency ratios (see legend in the upper-right corner). (*A*)Average target error during Pre and Postscanning sessions for both FB (left panel) and NFB (right panel) modes. (*B*)Average target error across training sessions for both FB (left panel) and NFB (right panel) modes. All error bars show standard error (SE).

Table 1

Locations of main cluster activation peaks (MNI-coordinates) and *Z*-scores for areas showing a main effect of Feedback Condition

Brain region	Peak activation coordinates (*x*, *y*, and *z*)			*Z*-value	*P*-value
NFB > FB					
Planning					
R pre-SMA, also L pre-SMA, R PMd	6	14	44	4.82	<0.00001
L PMd	−24	−4	50	4.47	0.00046
Execution					
L lingual gyrus	−28	−58	−2	5.45	0.00607
S2	−56	−38	10	4.29	0.037
R S1	28	−24	72	4.87	0.00014
L S1	−52	−18	44	4.51	0.00239
R CER lobe VI, also L CER lobe VI	10	−74	−12	7.05	<0.00001
FB > NFB					
Planning					
L parieto-occipital part	−2	−86	38	5.58	<0.00001
Posterior cingulate	0	−34	40	3.66	0.0489
R M1	22	−26	52	4.16	0.00152
L M1, also L S1	−32	−24	56	3.42	0.0392
L CER lobe VI	−26	−70	−20	5.57	0.00064
R CER lobe VI	38	−56	−26	4.59	0.0108
L CER lobe VIIIa, also VIIIb	−22	−58	−62	4.22	0.0143
Execution					
R hMT/V5+, also R V3v and R LOC	46	−64	−10	9.34	<0.00001
L V3v, also L V2 and L hMT/V5+	−32	−94	−10	8.89	<0.00001
R PMd, also R PMv	26	−8	46	7.92	<0.00001
L PMd	−22	−10	58	7.53	<0.00001
L PMv	−52	4	32	5.03	0.0395
R MFG	32	38	22	5.26	0.00053
R anterior insula	32	18	4	4.87	0.0229

Table 2

Locations of main cluster activation peaks (MNI-coordinates) and *Z*-scores for areas showing a main effect of Time

Brain region	Peak activation coordinates (*x*, *y*, and *z*)			*Z*-value	*P*-value
Pre > Post					
Planning					
L PMd, also R S1, L M1, L pre-PMd	−16	−6	64	6.48	<0.00001
R MFG, also L MFG	44	46	8	4.91	0.00265
Execution					
L S1, also L M1, L SPL	−18	−40	62	6.66	<0.00001
L S2	−54	−20	6	6.07	0.00688
R STL, also R S2	60	−14	0	5.66	0.0107
R M1, also R S1, R SMG	20	−26	68	4.85	0.00019
R CER lobe VI, also L CER CR1, CER vermis VI, L ITL, R CER VIIIb	38	−46	−30	5.48	<0.00001

The activation peaks were located in bilateral hMT/V5+, bilateral extrastriate visual cortex V3v, left prestriate visual cortex V2 and right lateral occipital complex (LOC), bilateral dorsal and ventral premotor cortices (PMd and PMv), right middle frontal gyrus (MFG) (part of the dorsolateral prefrontal cortex [DLPFC]) and right anterior insula.

Main Effect of Time

To assess the effects of learning on brain activity, scans of Pre- and Post-test were compared. We only found activation decreases, but no increases as a function of time.

Areas Showing Activation Decreases as a Function of Training. Activity decreased in 2 clusters as a function of training in the *planning phase*. A Pre > Post effect was observed in left PMd, right S1 and left M1, and bilateral MFG (part of DLPFC) (Table 2).

Also in the *execution phase*, activity in a number of areas decreased as a function of training. Five clusters were found (Table 2) involving left SPL, right supramarginal gyrus (SMG), bilateral S1 and bilateral S2 (including part of superior temporal lobe), bilateral M1, and right cerebellar lobe VI together with left cerebellum crus 1, left vermis VI, left inferior temporal lobe (ITL) and right cerebellum VIIIb.

Evolution of Neural Differentiation Between Feedback Conditions as a Function of Training

A whole-brain conjunction analysis was carried out to determine whether the activity pattern diverged into distinct neural patterns depending on Feedback Condition, or whether they converged toward more similar neural patterns. The more voxels that are shared between both Feedback conditions as shown by conjunction, the more similar the neural pattern between conditions is. The common activation for FB and NFB conditions with respect to the total number of active voxels was calculated per participant. Figure 3*A* shows that the overlap in activation of both Feedback conditions slightly increased from Pre- to Post-test for planning the task, whereas this overlap increased to great extent for executing the task. Indeed, the mean percentage of voxels showing FB ∩ NFB activity compared with the total number of activated voxels showed a trend of Pre- to Post-test increase during the *planning phase* [$F_{1,\ 24} = 4.18$, $P = 0.052$]. For *executing* the task, this percentage increased considerably from Pre- to Post-test [$F_{1,\ 24} = 95.9$, $P < 0.0001$] (Fig. 3*B*). Note that this increase in common activation is only a relative number compared with the total amount of activation; the total amount of activated voxels actually decreased from Pre- to Post-test in both planning and execution (see Table 3 for absolute number of voxels).

The Time × Feedback Condition interactions indicate where the 2 FB conditions showed a differential evolution in brain activation as a function of training.

In the *execution phase*, a $\mathrm{Pre}_{\mathrm{FB>NFB}} > \mathrm{Post}_{\mathrm{FB>NFB}}$ effect was observed in right PMd and right MFG (part of DLPFC) (Table 4, Fig. 4*B*). The right PMd activation cluster also extended into the left PMd, bilateral pre-SMA and SMA (verified using the Human Motor Area Template from Mayka et al. 2006), a small part of the right pre-PMd and the right anterior cingulate cortex (ACC) (Fig. 4*B*). In these areas, a clear converging pattern was seen (Fig. 4*B*) whereby activations, as measured by PSC, started out higher for the FB condition than in the NFB condition, and evolved toward similar levels at Post-test.

A $\mathrm{Post}_{\mathrm{FB>NFB}} > \mathrm{Pre}_{\mathrm{FB>NFB}}$ effect was found in left cerebellar lobe V for *planning*, and in left S1 for *execution* (Table 4). The activations did not show a typical converging or diverging pattern, as both conditions had different starting and ending points whereby activity in NFB was higher than in FB at Pre-test, and evolved toward higher activity in FB compared with NFB at Post-test (Fig. 4*A*).

Correlation Between BOLD Response and Behavior

A whole-brain analysis of covariance for both Feedback and Time conditions was carried out to investigate correlations between BOLD response and average target error. Only positive correlations were found between activity and average target error. In other words, a higher BOLD response was associated with higher error. For the *planning* phase, the correlation was located in left temporal fusiform cortex and right LOC (Table 5). For the *execution* phase, peak clusters were located in right precuneus and left superior frontal sulcus (Table 5).

Discussion

The goal of this study was to provide insight into the evolution of the FB versus NFB brain activation differences as a result of training a bimanual tracking task under mixed FB and NFB conditions. Major performance improvements across training days in both Feedback conditions were observed. The Feedback-related neural activation differences decreased with practice on the whole-brain level which was particularly evident in right DLPFC, bilateral PMd, bilateral (pre-)SMA, right pre-PMd, and ACC, showing a converging interaction effect. Accordingly, our data support the neural convergence hypothesis: activations associated with each Feedback Condition became more similar with practice. Below, we will describe and interpret the findings in more detail, starting with behavior and the neural convergence hypothesis, followed by the main effects of Feedback Condition and Time.

Behavioral Changes as a Result of Training

Kinematics revealed a typical performance curve with major improvements during the first training days. From Day 4 on, a performance plateau was reached. Training also led to better coping with the more difficult task variants, i.e., performing asymmetric frequency ratios, particularly under NFB conditions.

Reduction in Neural Differentiation Between Feedback Conditions as a Function of Training

The whole-brain conjunction analysis revealed that the neural differentiation between Feedback conditions was reduced as a function of training but this effect was primarily observed during the execution phase of the task. All participants practiced under both Feedback conditions, forcing them to cope with different task contexts. Behavioral research suggests that training with augmented FB exclusively, leads to a dependency on FB and performance deterioration when FB is removed (Salmoni et al. 1984; Winstein and Schmidt 1990; Swinnen 1996), whereas training using solely NFB trials limits learning. Therefore, mixed FB and NFB is the best training strategy to cope with different task contexts (Winstein and Schmidt 1990; Kovacs and Shea 2011). Our findings differ from Ronsse et al. (2010), where brain activation evolved toward more distinct patterns when separate groups exclusively received either visual or auditory FB during training without being exposed to NFB trials. Clearly, the different groups became tuned to the specific sources of available information with practice. In contrast, for the mixed FB/NFB context employed here, transfer of learning occurred between both conditions. This led to decreased neural differentiation between both performance modes, underlining the importance of the trained task-context.

The obtained significant interaction effect implied that the neural convergence effect in our study, observed during the *execution* phase, was particularly evident in right PMd cluster (including neighboring areas as mentioned above) and right DLPFC, where activation was higher during FB trials at Pre-test and reduced at Post-test, while the opposite effect was observed during NFB trials. As a consequence, more similar activation levels were reached by the end of practice. These areas are critically implicated in controlling movements online, by (strategically) monitoring the possible responses for action (DLPFC, BA 46) (Frackowiak et al. 2004), updating the motor plan for movement redirection (PMd) (Rushworth et al. 2003), performing movements without augmented FB (SMA)

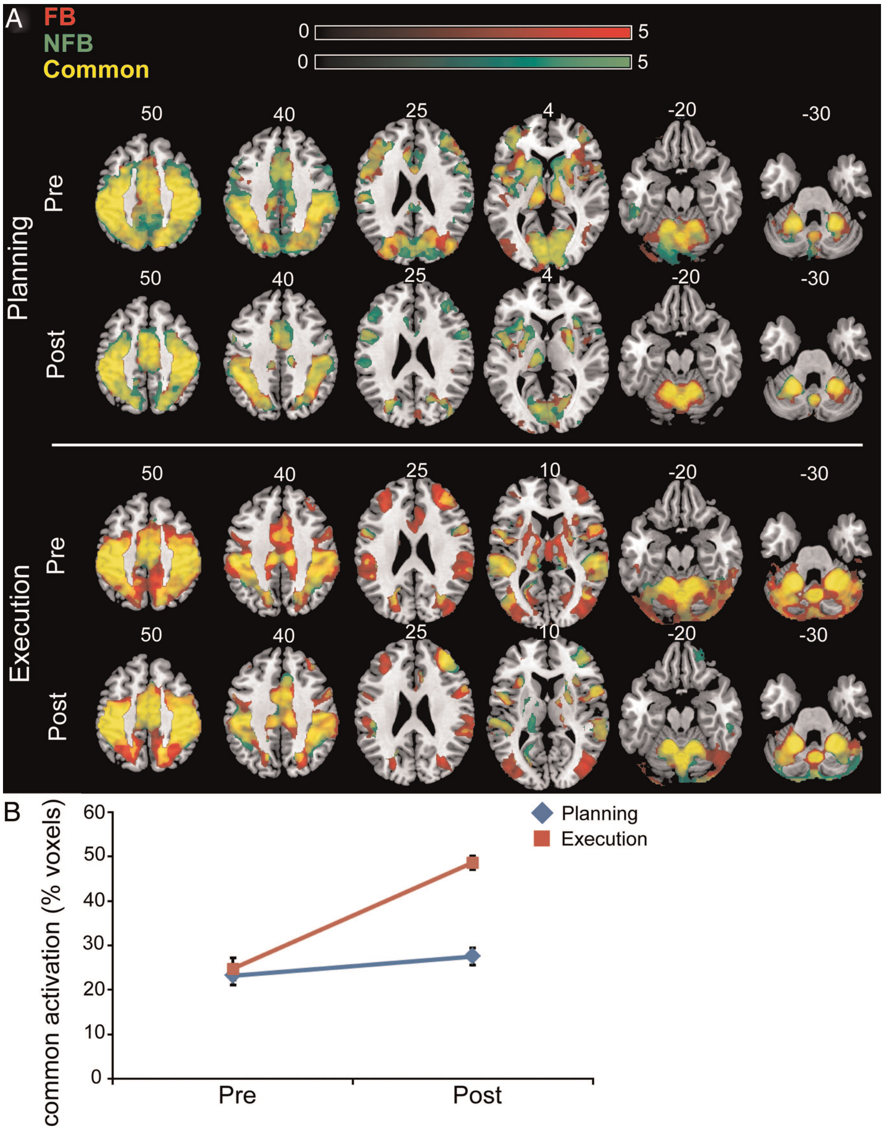

Figure 3. Conjunction analysis. Activation maps were overlaid on the ch2better template using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/), neurological orientation. (*A*) Visualization of areas active during the FB (red) condition, the NFB (green) condition, and for both conditions (yellow), during Pre- and Post-test and with respect to planning (top) and execution (bottom) phases of the task. Activations are significant, using a clusterwise threshold $Z > 2.3$, $P < 0.05$. Numbers above slices are the *z*-coordinates of the presented slices in MNI space. (*B*)Percentage of voxels showing common activation in relation to the total number of significant voxels activated by either FB and/or NFB for both Pre- and Post-test.

Table 3
Absolute mean number of voxels activated by FB and NFB (common # voxels) versus total number of voxels activated (total # voxels)

	Pretest				Post-test			
	Common # voxels	SD	Total #voxels	SD	Common # voxels	SD	Total #voxels	SD
Planning	8954.8	8544.9	34912.8	22022.2	8368.2	7456.4	27360.4	19877.0
Execution	14822.2	12225.6	58507.4	30936.6	28174. 6	15336.6	56636.0	27069.0

SD, = standard deviation; #, number of.

Table 4
Locations of main cluster activation peaks (MNI-coordinates) and Z-scores for areas showing an interaction between Feedback Condition and Time

Brain region	Peak activation coordinates (*x*, *y*, and *z*)			*Z*-value	*P*-value
Pre (FB > NFB) > Post (FB > NFB)					
Execution					
R PMd, also bilateral (pre-)SMA, R pre-PMd, R ACC	18	−4	60	4.13	<0.00001
R MFG	36	46	28	4.74	<0.00001
Post (FB > NFB) > Pre (FB > NFB)					
Planning					
L CER lobe V	0	−58	−12	3.41	0.00063
Execution					
L S1	−46	−18	48	3.73	0.026

(Debaere et al. 2003; Ogawa et al. 2006; Wenderoth et al. 2006; Heuninckx et al. 2010), higher-order visuomotor processing (pre-PMd) (Picard and Strick 2001), and performance monitoring and/or error detection (ACC) (Bush et al. 2000). The SMA is also important for bimanual coordination (Serrien et al. 2002; Toyokura et al. 2002; Swinnen and Wenderoth 2004; Puttemans et al. 2005). These processes were already evident at Pre-test during the FB condition because the discrepancy between the participants' and the target cursor (external

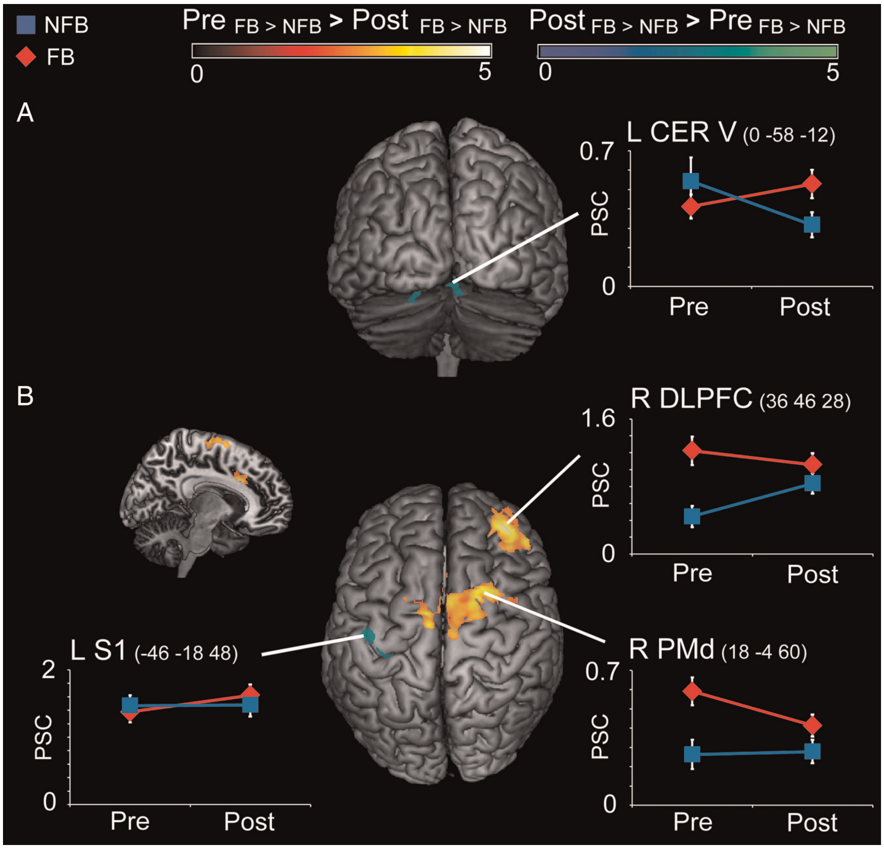

Figure 4. Areas showing a significant Time × Feedback Condition interaction. Activation maps were overlaid on the ch2better template using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/), neurological orientation. Upper-left: legend for symbols used in line graphs which depict PSC. Upper right: color map for voxel Z-values in fMRI images. Graphs depict PSC in peak activation sites and their MNI coordinates (x, y, and z). (*A*)Planning the BTT. (*B*) Executing the BTT. Activations are significant, using a clusterwise threshold $Z > 2.3$, $P < 0.05$.

Table 5

Locations of main cluster activation peaks (MNI-coordinates) and Z-scores for areas showing a positive correlation between BOLD response and average target error

Brain region	Peak activation coordinates (*x*, *y*, and *z*)			*Z*-value	*P*-value
Planning					
L temporal fusiform cortex, also L ITL, L MTL	−38	−26	−32	4.37	0.00099
R LOC, also R V2, V3v	44	−66	−6	3.75	0.0012
Execution					
R precuneus, also L precuneus, L angular gyrus	2	−70	42	4.78	<0.00001
L superior frontal sulcus, also L MFG	−22	34	36	5.03	0.00017

reference of correctness) could be directly inferred from the PC screen. During the NFB condition, these processes (and their associated activations) were less prominent at Pre-test in the absence of augmented FB. However, practice enabled participants to construct an internal reference of correctness (or somatosensory-based model) that allowed them to monitor performance with increasing success at Post-test under NFB conditions. The increased DLPFC-PMd activation during the NFB condition from Pre- to Post-test is consistent with this viewpoint. This differential evolution of brain activation between both Feedback conditions provides new insights into FB-dependent learning and suggests fundamental differences in the neural control of movement as a function of provision of augmented FB sources.

Not surprisingly, the first level activations (see also Fig. 3) revealed a strong bilateral activation pattern, which would be expected for bimanual movement production. However, the interaction of Feedback Condition and Time primarily revealed right-lateralized activations. The right hemisphere has been implicated in various aspects of motor performance (Kawashima et al. 1993, 1998; Li et al. 1996; Volkmann et al. 1998; Cramer et al. 1999; Nirkko et al. 2001; Solodkin et al. 2001; Kobayashi et al. 2003; Serrien et al. 2006; Gut et al. 2007; Van Impe et al. 2009; Callaert et al. 2011), and particularly when increased attention is required to deal with error-detection/correction or when resolving discrepancies between motor intention, proprioception and visual FB (Fink et al. 1999; Serrien et al. 2006). These processes were very prominent during the early stage of FB-assisted practice and became less prominent at later stages. The converse effect was observed under NFB conditions because it required sufficient practice to build the somatosensory model.

At first sight, the pattern of neural convergence that emerged with practice in our study appears inconsistent with recent work showing that neural representations for sequencing movements became more specialized after 4 days of training, leading to a faster and more accurate execution of the learned movements (Wiestler and Diedrichsen 2013). Increased specialization of neural activations with training was also prominent in Ronsse et al. (2010) in which 2 groups obtained a different modality of augmented FB (visual vs.

auditory). Overall, this suggests that the decrease in neural differentiation (increased convergence) in our present study must have been a direct consequence of the practice schedule in which mixed FB conditions were provided.

Main Effects of Feedback Condition and Time

Brain Areas More Activated During NFB Than FB Movements

Whereas pre-SMA activity dominated the planning phase of the NFB condition, the somatosensory cortices were involved in the execution phase of the NFB condition, suggesting that planning NFB movements relied more on cognitive-motor planning processes, whereas executing NFB was more reliant on somatosensory input in the absence of visual FB on the screen.

Pre-SMA, showing higher activations for *planning* NFB compared with FB movements, is closely connected to the prefrontal cortex and is involved in retrieving visuo-motor associations (Picard and Strick 2001). Posterior pre-SMA (involved here) shows up when making open decisions between alternative actions (Haggard 2008; Zhang et al. 2012). Furthermore, bilateral PMd, which is responsible for generating action plans (e.g., Halsband and Passingham 1985; Grafton et al. 1998), is more active for planning NFB compared with FB movements. This suggests that decision-making processes related to action selection were more prominent for planning NFB trials to overcome the lack of visual guidance during the execution phase.

Executing the bimanual task resulted in greater activity for NFB in bilateral primary and left secondary somatosensory areas. Somatosensory input was the main sensory source in the absence of augmented visual FB. S1 processes somatosensory inputs, and S2 performs higher-order functions including sensorimotor integration (Mima et al. 1998; Burton et al. 1999; Chen et al. 2008) and has been linked to NFB movements before (Woolley et al. 2010). Furthermore, cerebellar lobe VI was activated, of which the peak coordinates have been associated with working memory tasks (Stoodley and Schmahmann 2009). Left lingual gyrus has been implicated in locating objects (Committeri et al. 2004). This may suggest that spatial working memory was important to keep track of the produced coordination patterns under NFB conditions.

Brain Areas More Activated During FB Than NFB Movements

Planning FB movements involved the parieto-occipital pathway, as part of the dorsal stream (Kravitz et al. 2011), posterior cingulate, primary visual areas and parts of the cerebellum. Posterior cingulate is especially responsive to processing visual FB as it is linked to sensory and oculomotor processes (Olson and Musil 1992). The cerebellum has been linked to visual FB-assisted movements before (e.g., Stein 1986; Grafton et al. 1992; Stein and Glickstein 1992; van Donkelaar and Lee 1994; Jeuptner et al. 1996; Ellerman et al. 1998; Inoue et al. 1998; Jueptner and Weiller 1998; van Donkelaar et al. 1999, 2000; Vaillancourt et al. 2003; Ogawa et al. 2006; Heuninckx et al. 2010). More specifically, the (bilateral) cerebellar lobes VI have been associated with FB compared with NFB movements in bimanual coordination (e.g., Debaere et al. 2003) and cerebellar lobes (left) VIIIa and VIIIb are involved in motor performance (Stoodley and Schmahmann 2009), particularly when tasks are complex (Swinnen et al. 2010). This may extend to motor planning, too. Cerebellum may indeed be important for motor planning (Cui et al. 2000), suggesting that the brain prepares for the upcoming online visual FB during the planning phase. Finally, bilateral M1, also involved in response planning (Richter et al. 1997; Zang et al. 2003; Cross et al. 2007; Cohen et al. 2009) was more active in FB than in NFB conditions. Anticipating a FB-guided movement may therefore lead to direct visuo-motor readiness (i.e., just move and see), whereas one may plan a NFB movement more cognitively (i.e., first think, then move), as also confirmed above by the increased pre-SMA and PMd activity for planning NFB movements.

Executing FB trials evoked activity in hMT/V5+, important for motion processing (Born and Bradley 2005; Zanto et al. 2011), which has been associated with (bimanual) movements guided by online visual FB before (e.g., Debaere et al. 2003; Remy et al. 2008; Heuninckx et al. 2010; Ronsse et al. 2010). Also DLPFC was more activated, which is implicated in top-down anticipatory control of visuomotor processing (Liang et al. 2002) and visually-guided action (Ogawa et al. 2006). Furthermore, the activity in bilateral pre-motor areas may reflect adjustments of the ongoing movement (Rushworth et al. 2003). In addition, in line with Heuninckx et al. (2010), anterior insula was more active, reflecting the binding of visual (external) and tactile (internal) information (Amedi et al. 2005). Visuo-somatosensory integration was apparently crucial for performing visually guided action.

Brain Areas Showing Training-related Decreases in Activation

Across both Feedback conditions, training-related decreases in activity (no increases) were found. In line with other motor learning studies (e.g., Debaere et al. 2004; Remy et al. 2008; Ronsse et al. 2010; Dayan and Cohen 2011), activity in DLPFC decreased as a function of training. Here, this effect was observed solely in the *planning phase* of the task. Training also resulted in activity decreases in left PMd (partly in pre-PMd), left M1, and right S1, suggesting a decreased need for sensorimotor preparation in order to plan the task. This finding is not in line with Cross et al. (2007), who found an increase, instead of a decrease, in activity of sensorimotor areas during the planning phase. However, their study differed from ours in the type of task (sequence task) and the reported effect was the product of a Time by Group interaction.

Sensorimotor processing requirements decreased or became more efficient with training in the *execution phase* of BTT, as reflected by the reduced bilateral S1, S2, and M1 activity and of motor-related sub-areas of the cerebellum, which are mainly involved in sensory-motor tasks (right VI, left CR1, vermis VI, and right VIIIb). Additionally, a decrease in parietal activity was observed, which may reflect diminished need for or more efficient spatiotemporal integration of the limbs to produce a common bimanual action (Wenderoth et al. 2004).

Conclusion

A training procedure mixing FB and NFB trials leads to a more generic neural activation pattern that is less dependent on the specific Feedback context at hand. The observed changes in neural activation suggest the development of a more generic internal model, based on the somatosensory modality, which liberates the learner from strong guidance provided by augmented visual FB. This will promote performance success under different environmental contexts. Because the goal of training in work-related, recreational or rehabilitation contexts is ultimately to enable learners to perform their daily routines in the absence of augmented FB sources that may have been used during training, additionally exposing them to nonaugmented FB conditions during training may facilitate such transfer to real-life contexts.

Authors' Contributions

Designed research: I.A.M.B., J.G., J.P.C., S.P.S. Performed research: I.A.M.B., J.G. Analyzed data: I.A.M.B., J.G., J.P.C. Wrote the paper: I.A.M.B., J.G., M.P.B., L.P., J.P.C., G.W., S.P.S.

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Notes

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