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Relative cortico-subcortical shift in brain activity but preserved training-induced neural modulation in older adults during bimanual motor learning

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ABSTRACT

To study age-related differences in neural activation during motor learning, functional magnetic resonance imaging scans were acquired from 25 young (mean 21.5-year old) and 18 older adults (mean 68.6-year old) while performing a bimanual coordination task before (pretest) and after (posttest) a 2-week training intervention on the task. We studied whether task-related brain activity and training-induced brain activation changes differed between age groups, particularly with respect to the hyperactivation typically observed in older adults. Findings revealed that older adults showed lower performance levels than younger adults but similar learning capability. At the cerebral level, the task-related hyperactivation in parietofrontal areas and underactivation in subcortical areas observed in older adults were not differentially modulated by the training intervention. However, brain activity related to task planning and execution decreased from pretest to posttest in temporo-parieto-frontal areas and subcortical areas in both age groups, suggesting similar processes of enhanced activation efficiency with advanced skill level. Furthermore, older adults who displayed higher activity in prefrontal regions at pretest demonstrated larger training-induced performance gains. In conclusion, in spite of prominent age-related brain activation differences during movement planning and execution, the mechanisms of learning-related reduction of brain activation appear to be similar in both groups. Importantly, cerebral activity during early learning can differentially predict the amplitude of the training-induced performance benefit between young and older adults.

1. Introduction

Performance on motor tasks gradually decreases and often requires more mental effort and time as we age (e.g., Boisgontier et al., 2013; Seidler et al., 2010). Training interventions may help overcome such deficits, which can be witnessed across a large range of motor tasks. Whether or not motor learning is impaired in older relative to younger adults is still a topic of considerable debate (Seidler et al., 2010; Swinnen et al., 1998). Some studies report equivalent or even higher learning rates in older adults, and normal skill retention (Anshel, 1978; Voelcker-Rehage, 2008). Others have shown that learning rates are compromised in older adults (Anguera et al., 2010; Bo et al., 2011a; Raz et al., 2000; Rodrigue et al., 2005; Seidler, 2006; Voelcker-Rehage, 2008). The literature regarding bimanual skill learning in particular is similarly mixed, with age-related learning deficits observed for some tasks (Swinnen et al., 1998), but not for others (Voelcker-Rehage and Willimczik, 2006). Regardless of whether older adults show task-specific impairments relative to young adults, training-induced performance improvements are clearly evident and suggest lifelong plasticity potential (Seidler, 2007a,b; Swinnen et al., 1998).

To better understand the ability to learn new motor skills, studying the underlying brain mechanisms may reveal critical information about neuroplastic potential across the lifespan. With respect to motor performance in general, it has been demonstrated that older adults often show compensatory brain activity to support motor performance (e.g., Goble et al., 2010; Heuninckx et al., 2005, 2008; Swinnen et al., 2010; Van Impe et al., 2009; Ward, 2006; Ward and Frackowiak, 2003; Wu and Hallett, 2005) and higher-order cortical areas are often over-recruited during more complex (interlimb coordination) tasks (Goble et al., 2010; Heuninckx et al.,

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2005, 2008, 2010). Nevertheless, reduced activation in older versus young adults has also been observed in multilimb (Coxon et al., 2010, 2016; Van Impe et al., 2009) and unimanual (Anguera et al., 2010; Bo et al., 2011a,b) task studies. Despite those known age-related neural activity differences during motor performance, it remains unclear whether training-induced plasticity differs between young and older adults.

The present functional magnetic resonance imaging (fMRI) study therefore sought to address 2 primary research questions related to the effect of an extensive training intervention on the neural correlates of motor learning in older adults. First, we examined whether task-related brain activity as well as training-induced cerebral plasticity associated with practicing a new set of bimanual coordination skills over a 2-week period were affected by aging. We hypothesized that (1) older adults would demonstrate task-related cortical hyperactivation (Goble et al., 2010; Heuninckx et al., 2005, 2008) and basal ganglia hypoactivation (Coxon et al., 2010) not only during movement execution but also during planning and that (2) training would lead to reductions in cortical activation in both age groups, as previously observed in humans and primates (Beets et al., 2015; Picard et al., 2013), but to a lesser extent in older in comparison with young adults as a result of reduced learning potential associated with advanced age. Second, we examined the relationship between brain activation patterns during the early stage of learning and subsequent training-related behavioral outcomes. Specifically, we hypothesized that responses in brain regions showing age-related hyperactivation—that could be associated with better encoding but might also reflect higher degrees of online task monitoring that can not be overcome with training—would predict successful training outcome in older as compared to younger adults.

2. Materials and methods

2.1. Participants

Twenty-six younger (YA) and 25 older (OA) healthy volunteers participated in the study. All participants were naive with respect to the experimental paradigm, had normal or corrected-to-normal vision, and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Laterality scores were 93.7 ± 10.0 in OA and 87.3 ± 17.1 in YA, with a +100 score representing an extreme right-hand preference and a −100 representing an extreme left-hand preference. None of the participants had a history of neurological or psychiatric disease. Older participants were screened for cognitive impairments using the Dutch version of the Montreal Cognitive Assessment test using the cutoff score of 26 (e.g., Nasreddine et al., 2005). The included participants scored 28.6 ± 1.5 (range 27–30). One older adult did not reach the cutoff score (i.e., score equal to 24) and was therefore excluded from the analyses. Three OA were excluded due to brain atrophy/lesions as identified by a trained neuroradiologist (one with diffuse cortical atrophy, one with atrophy in the parietal lobe, and one with a small lesion in the cerebellum). Three other OA failed to comply with task instructions (they often moved in the baseline no-move conditions). As a result, we analyzed the performance of 18 OA (68.6 ± 6.0 years; 11 females). One YA was excluded from the analysis due to technical problems with the scanner at posttest. This resulted in complete prepost data of 25 YA (21.5 ± 2.3 years; 14 females). A subset of participants who completed pre and posttest also performed a behavioral retention test 6 months after posttest (16 YA, 21.6 ± 1.9 years, 11 females; 10 OA, 67.1 ± 5.0 years, 5 females). The protocol was in accordance with the 1964 Declaration of Helsinki (World Medical Association, 2008) and was approved by the local ethical committee of KU Leuven, Belgium. Participants were financially compensated for participation and provided written informed consent before the experiment.

2.2. Experimental design and setup

MRI scanning occurred before and after 5 training sessions, distributed across 2 weeks. The scanning and training sessions each lasted 90 and 60 minutes, respectively (see Fig. 1A). Prior to the first MRI scan, participants practiced the task briefly in a dummy scanner until the task was fully understood. During MRI sessions, participants lay supine in the scanner (see illustration of dummy scanner setup in Fig. 1B), 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 head movements during task performance. A nonferromagnetic 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 approximately 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.

2.3. Task

In the bimanual tracking task (BTT), a target presented on a screen has to be tracked by rotating dials with both hands simultaneously in 1 of 4 directional patterns: both hands rotated inwards (IN) or outwards (OUT) together, or in a clockwise (CW) or counterclockwise manner (CCW). The left (L) and right (R) hands controlled movements on the ordinate and abscissa, respectively. Each directional pattern was performed at 5 different relative frequency ratios: 1:1, 1:2, 1:3, 2:1, and 3:1 (L:R). For example, during the 1:2 mode, the right hand would need to move twice as fast as the left hand to match the desired movement trajectory. The combinations of rotation direction and frequency totalled 20 different coordination possibilities. Each task variant was represented by a target line with a particular slope that appeared in 1 of the 4 quadrants on the screen (Fig. 1D).

Two principal task phases were discerned. During the "planning phase", which lasted 2 seconds, the blue target line was presented together with a visual cue to indicate the upcoming condition. In this phase, participants were instructed to identify the upcoming trial, but to refrain from performing any movement. During the "execution phase", a white target dot moved over the blue target line from a start position (center of the screen) to a desired end location at a constant speed (duration = 9 seconds). The intertrial interval was 3 seconds. The tasks were trained under 2 conditions with equal number of trials: without (no feedback condition [NFB]) and with (feedback condition [FB]) augmented online visual feedback of the integrated movement patterns. In 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, whereas only the blue target line was presented in the

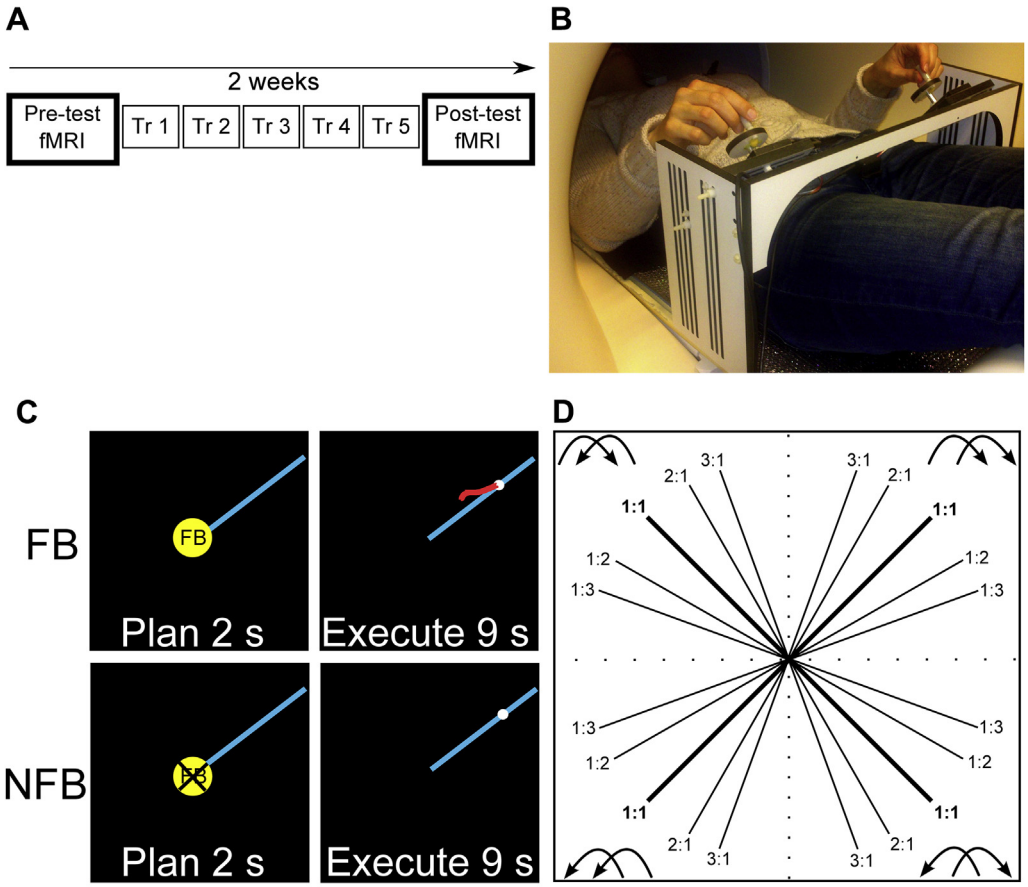

Fig. 1. Study design. (A) Training protocol. Pretest and posttest were interleaved by 2 weeks in which 5 training sessions took place. (B) Example setup in the dummy scanner. The MRI compatible device was mounted on the participants' lap, which was used for both the dummy session and both pretest and post-scanning sessions. (C) Task. During the first 2 seconds, the blue target line was shown together with a cue indicating whether FB would be received or not (cross in 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 2 seconds, 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). (D) All possible bimanual directional combinations (n = 4) and frequency ratios (n = 5) (schematic drawing). Abbreviation: fMRI, functional magnetic resonance imaging; FB, feedback condition; NFB, no feedback condition. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

NFB condition. The goal in both conditions was to match the white dot representing the participant's position as close as possible to the moving target dot.

Control trials were included for the previously described conditions to serve as the baseline measure for fMRI analyses (see Section 2.7 below). In those trials, equivalent visual feedback was presented to the participants, which were instructed not to perform any movement. In the no-move trials with FB, participants were presented with a video of a previous performance of the same relative frequency ratio.

2.4. Task procedure

2.4.1. Scan sessions

The design of the event-related scan sessions was identical at pretest and posttest. 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" (i.e., control) 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 response. For both move and no-move trials, augmented visual FB was present for half of 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 differently 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. 1C), and the order was semi-randomized. In the no-move FB trials, a random replay of the participant's performance obtained during training was shown at posttest; at pretest, a performance replay of one of the experimenters was shown. For each condition, the required frequency ratio was randomly distributed such that 1/3 of trials required a 1:1 ratio, 1/3 required a 1:2 or 2:1 ratio, and 1/3 required a 1:3 or 3:1 ratio (Fig. 1D). Thus, there were for instance 24 move FB trials with 8 trials for each frequency ratio level.

2.4.2. Training sessions

For each of the 5 training days, 10 blocks of 20 move trials (duration = 11 seconds, intertrial interval = 3 seconds) were performed, with augmented visual FB presented in half of the trials (trial order fully randomized). Information feedback was given directly after each NFB trial to enhance learning in this condition. This was done by showing the entire actually produced trajectory in red on top of the blue target line that was required, for a total duration of 1 second after execution of the task. All other aspects of the training trials were identical to those of the scanning sessions.

2.4.3. Retention session

The retention test was carried out 6 months after posttest and consisted of 6 runs with 24 trials each, using the exact same protocol as in pretest and posttest (mixed FB and NFB). Imaging data were not acquired in this session. Before the retention test started, a warm-up of NFB trials (NFB to prevent learning from visual feedback) was used in order for participants to refamiliarize themselves with the task and setup.

2.5. Kinematic analyses

Data were recorded and analyzed with Labview software (version 8.5, 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. Specifically, for each trial, the target error was measured as the Euclidean 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 (i.e., lower error scores). Outlier move trials ($z > 3$) and trials in which only an unimanual movement was made were discarded from the analysis (YA: pretest = 3.3% of all trials, posttest = 1.2%; OA: pretest = 5.5%, posttest =3.5%). No-move trials were discarded when 1 or both hands moved for at least 1 movement cycle (YA: pretest = 1.3%, posttest = 0%; OA: pretest = 0.9%, posttest = 6.6%).

2.6. Behavioral statistical analyses

Statistical analyses of behavioral data were performed on average target error using Statistica (version 10, StatSoft, Inc, Tulsa, OK, USA) and Matlab R2015b. Four different statistical models were used to evaluate different features of performance and learning. Data acquired during the scanning sessions were analyzed with an age (old, young) × time (pretest, posttest) × feedback (FB, NFB) repeated measures analysis of variance (ANOVA). Short-term learning was evaluated by comparing first and last quarter of the scanning sessions with an age (old, young) × time (early and late pretest, early and late posttest) × feedback (FB,NFB) repeated measures ANOVA. Data acquired during the training sessions were analyzed with an age (old, young) × time (5 training sessions) × feedback (FB, NFB) repeated measures ANOVA. We also evaluated performance normalized to the first training day (i.e., divided by initial performance) to evaluate improvement regardless of absolute baseline performance levels. Training and scanning sessions were analyzed separately because the context of task performance was different (scan runs also consisted of no-move trials, whereas these were absent during the training sessions). To ensure sufficient task complexity, 5 different frequency ratios and 4 different movement directions were trained. However, we did not consider these factors in our statistical analyses to reduce analysis and interpretation complexity. Data acquired during the retention test were analyzed with an age (old, young) × time (posttest, retention) × feedback (FB, NFB) repeated measures ANOVA on performance of the 6 mixed FB/NFB retention blocks. The level of significance was set at $p < 0.05$ in all analyses. Significant effects were further explored using Tukey's honest significant difference test to correct for multiple comparisons.

2.7. 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 3-dimensional high-resolution T1-weighted image was obtained first (MPRAGE, repetition time [TR]/echo time [TE] = 2300/2.98 ms, 1 × 1 × 1.1 mm voxels, field-of-view [FOV] = 240 × 256, 160 sagittal slices) and lasted 8 minutes. Then, a field map was acquired to address local distortions. T2-weighted functional images were obtained for each of the 6 runs of task practice (116 scans per run) with a descending gradient Echo-planar imaging (EPI) sequence (TR/TE = 3000/30 ms, flip angle = 90°, 50 oblique axial slices, slice thickness = 2.8 mm, interslice gap = 0.028 mm, inplane 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 5.0) (Smith, 2004; Woolrich et al., 2009) in conjunction with the parallel command-line tool (Tange, 2011). Before entering data into the model, the Brain Extraction Tool was applied leaving only relevant brain voxels in the T1 and the field map images. A high-pass filter cutoff of 200 seconds 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. For each run (1-6) and each session (pretest and posttest), regressors of the conditions of interest (move FB, move NFB, no-move FB, and no-move NFB) and their first temporal derivatives were defined for the planning (2 seconds) and execution (9 seconds) phases. 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, although both were included in the same first level statistical model (but not higher levels). 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 T1 image (6 DoF linear transformation) and subsequently to the Montreal Neurological Institute (MNI) template using FNIRT (12 DoF affine transformation and additional nonlinear warping). The estimated linear motion parameters were added as regressors of no interest to the first level model. For both age groups, motion outliers were calculated using the *fsl_motion_outliers* command with the dvars metric using the default threshold (the 75th percentile + 1.5 times the interquartile range) and were added as an additional confound explanatory variable in FEAT to disregard volumes with motion artifacts. As no effect of FB was observed across sessions and groups (see Section 3.1), FB and NFB conditions were grouped together such as the linear contrast of interest reported in this article consists in (move vs. no move) irrespective of the FB condition during the planning and execution phases separately, within, across, and between sessions.

In the 2nd level analysis, a fixed effects model was used to collapse across the 6 runs within each session (pretest and posttest) for each participant. These contrasts were then entered in a third-level analysis in which an ANOVA model was used to explore within, across, and between group effects.

A gray matter covariate, created with *feat_gm_prepare*, was added as a voxel-dependent explanatory variable of all higher level analyses in FEAT, with the exception of the regression analysis (see paragraph below), to account for inter-individual and inter-group differences of gray matter. This ensured that activation differences between groups were task-related and not attributable to structural differences, such as gray matter atrophy (Oakes et al., 2007). These effects were calculated using the random-effects model of FSL (FLAME 1). Only gray matter voxels were included (average of all individual subjects using a threshold of 0.3). 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 was 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 (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) 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.

Finally, to assess the relationship between task-related brain activity during early learning and subsequent training-induced learning outcome, we performed whole-brain regression analyses at the third level between individual within-subject contrast images at pretest (move vs. no move, irrespective of FB condition for the planning and execution phases separately) and relative changes in performance from pretest to posttest, controlling for initial error scores. A final ANOVA compared this regression between age groups. Statistical parameters were identical as described previously, except that no gray matter covariate was used in this model.

3. Results

3.1. Behavioral results

3.1.1. Learning effect between pretest and postscan sessions

To assess overall motor performance improvement, a 2 × 2 × 2 (age × time × feedback) repeated measures ANOVA was conducted for average target error during the scan sessions (Fig. 2A). The main effects of age [$F(1, 41) = 50.4$, $p < 0.0001$], time [$F(1, 41) = 142.5$, $p < 0.0001$], and feedback [$F(1, 41) = 1124$, $p < 0.0001$] were significant indicating that error was higher in OA than YA, in NFB versus FB trials and that performance improved (error decreased)

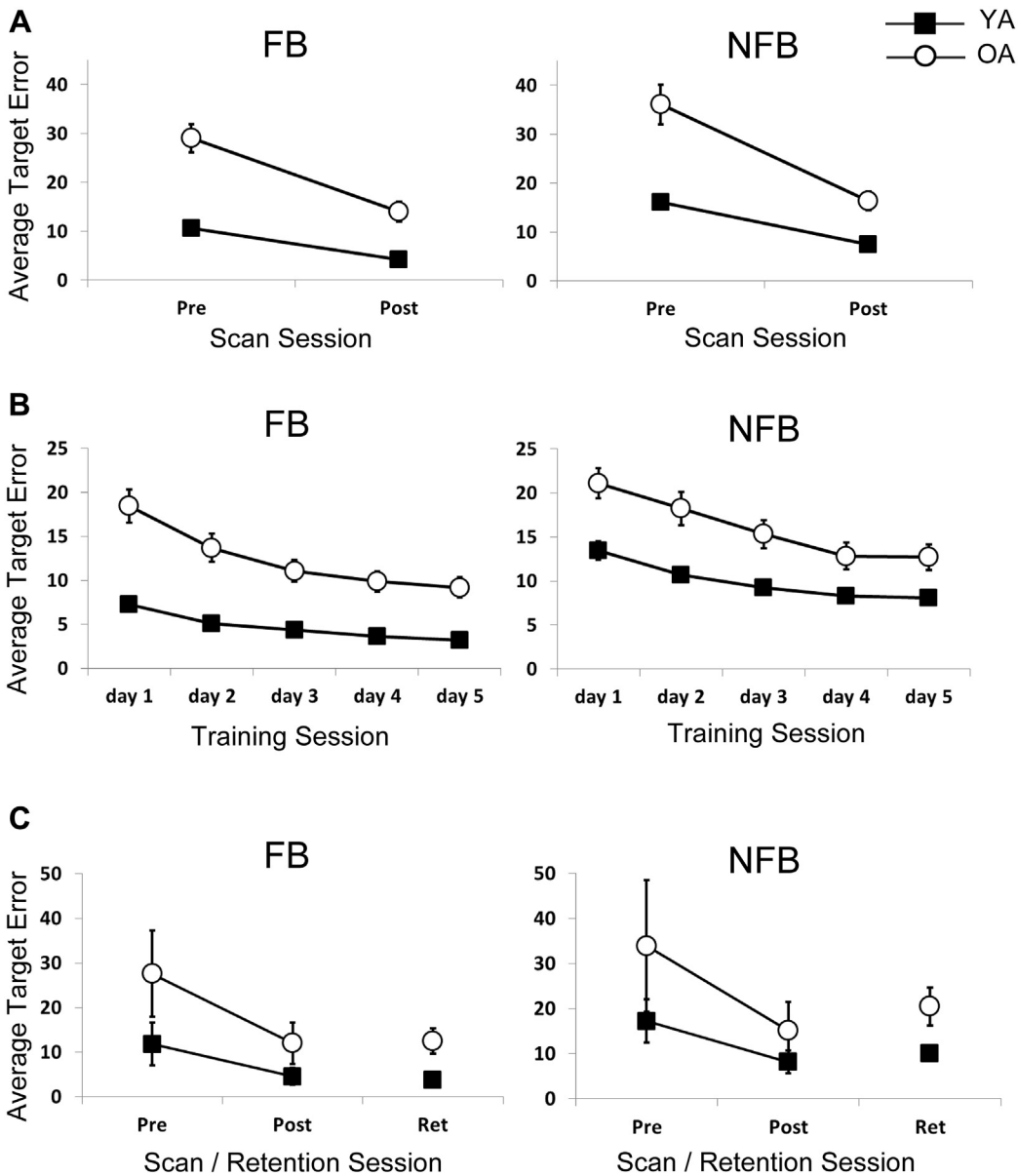

Fig. 2. Behavioral results. Average target error for young (YA) and older adults (OA). (A) Average target error during pretest and post-scanning sessions for both FB (left panel) and NFB (right panel) modes. (B) Average target error across training sessions for both FB (left panel) and NFB (right panel) modes. (C) Average target error across scan and retention sessions for the subset of participants who completed the scan sessions ($N_{YA} = 25$; $N_{OA} = 16$) plus retention test (Ret, $N_{YA} = 16$; $N_{OA} = 10$). All error bars show standard error.

from pretest to posttest. The age × time interaction [$F(1, 41) = 21.2$, $p = 0.0004$] revealed a stronger improvement in OA compared to YA from pretest to posttest. The time × feedback interaction [$F(1, 41) = 25.8$, $p < 0.0001$] revealed a stronger improvement in the NFB compared to the FB condition over time. The age × feedback [$F(1, 41) = 0.15$, $p = 0.7$] and age × time × feedback interactions [$F(1, 41) = 2.9$, $p = 0.9$] were not significant, which suggested that the NFB disadvantage did not differ between groups and over time.

3.1.2. Learning effect within session

As performance improves more quickly in the early stages of learning, a 2 × 4 × 2 (age × time × feedback) repeated measures ANOVA was conducted for the average target error scores obtained during the first and last halves of pretest and posttest scanning sessions (PRE1, PRE2, POST1, and POST2). The main effect time [$F(1, 3) = 139.05$, $p < 0.001$] denoted a significant performance improvement across sessions. Post hoc tests indicated that improvement was significant already from early to late pretest ($p < 0.001$). No significant improvement was detected from early to late posttest ($p = 0.29$). The remaining effects reflect what is reported in Section 3.1.1.

Furthermore, we examined whether performance improvement was correlated with initial performance. Error scores were correlated within pretest (PRE1 × PRE2, r = 0.92, $p < 0.001$, $n = 43$) and between pretest and posttest (PRE2 × POST2, r = 0.7, $p < 0.001$, $n = 43$). Overall improvement was negatively associated with initial performance error (PRE2 X Pre-to-Post Improvement, r = −0.81, $p < 0.001$, $n = 43$). Overall improvement relative to initial error was also negatively associated with initial performance, although not so strongly (PRE2 x Pre-to-Post relative improvement, r = −0.36, $p < 0.001$). In summary, participants with initially high error scores displayed larger gains but ultimately performed at a comparatively lower skill level.

3.1.3. Learning effect over training sessions

To assess incremental training-induced motor performance changes, a 2 × 5 × 2 (age × time × feedback) repeated measures ANOVA was conducted for the average target error scores obtained across training days (Fig. 2B). The main effect of age [$F(1, 42) = 33.7$, $p < 0.0001$] indicated a higher average target error for OA. The main effect of time [$F(4, 168) = 132.5$, $p < 0.0001$] indicated a significant improvement across the 5 training days. Post hoc tests revealed significant improvements day by day (all $p < 0.01$), except for day 4–5 ($p = 0.8$), suggesting that a performance plateau was reached at day 4. The main effect of feedback pointed to significantly higher error scores in NFB as compared to FB trials [$F(1, 42) = 193.3$; $p < 0.0001$]. The age × time interaction [$F(4, 168) = 13.6$, $p < 0.0001$] again revealed that the overall improvement in performance was larger in OA than that in YA. The time × feedback [$F(4, 168) = 3.4$, $p = 0.011$] interaction suggested a stronger improvement in NFB trials, and the age × feedback [$F(4, 168) = 6.8$, $p < 0.0001$] interaction showed that OA had a bigger differential score between FB and NFB trials; thus, OA performed disproportionately less accurately on the NFB condition. The age × time × feedback interaction was significant [$F(4, 168) = 5.1$, $p = 0.0006$], revealing that performance change was strongest for YA in NFB trials, whereas OA showed the relatively strongest improvements in FB trials (see Fig. 2B).

To assess motor performance improvement relative to the first training session, a 2 × 4 × 2 (age × time × feedback) repeated measures ANOVA was conducted for the average target error scores relative to the first training session. There was no main effect of age [$F(1,42) = 0.2$, $p = 0.63$] nor age × time interaction [$F(3,126) = 0.2$, $p = 0.87$]. The age × feedback interaction was significant [$F(1, 42) = 6.7$, $p = 0.01$], indicating a larger session-to-session improvement for OA in NFB trials. The main effect of feedback [$F(1,42) = 16.3$, $p < 0.001$] denotes a larger improvement for the FB trials. Nonetheless, the interaction time × feedback was not significant [$F(3, 126) = 0.4$, $p = 0.72$].

In summary, both age groups displayed significant improvement in task performance. Absolute error reduction was greater in older adults, but no significant group difference was found for the normalized performance measure. This indicates that the larger performance improvement observed in the nonnormalized data might stem from initial lower performance levels seen in older adults (i.e., greater gains possible).

3.1.4. Retention 6 months after training

To assess retention, an age (old, young) × time (post, ret) × feedback (FB, NFB) repeated measures ANOVA was run on average target error for the 6-block mixed FB/NFB retention blocks for participants who completed the retention test only (Fig. 2C). The main effects of age [$F(1, 24) = 40.5$, $p < 0.0001$], feedback [$F(1, 24) = 127.3$, $p < 0.0001$], and time [$F(1, 24) = 6.6$, $p = 0.017$] indicated higher error scores for OA compared to YA, for NFB compared to FB trials, and an error increase from posttest to retention. The age × time interaction was not significant [$F(1, 24) = 3.0$, $p = 0.095$], suggesting that skill loss from posttest to retention was similar for both age groups. The age × feedback interaction was not significant [$F(1, 24) = 0.36$, $p = 0.55$], whereas the time × feedback interaction [$F(1, 24) = 51.5$, $p < 0.0001$] showed that the increase in error from posttest to retention was higher in the NFB condition compared to the FB condition. Post hoc t-tests revealed that FB trials did not differ between posttest and retention ($p = 0.8$), whereas error was higher in NFB trials during retention as compared to posttest ($p = 0.0002$). Finally, there was a trend toward significance for the age × time × feedback interaction [$F(1, 24) = 3.8$, $p = 0.063$], suggesting that the FB condition was retained well in both age groups but OA encountered more difficulty with the NFB condition after the 6-month retention interval.

Altogether, both age groups improved performance after training, and error scores were generally higher in NFB conditions, although there was no age difference in this feedback effect. Older adults obtained a larger error reduction, although initial error was significantly larger in comparison to young adults. Error reduction rates relative to initial performance, however, were similar in both age groups.

3.2. Imaging results

3.2.1. Age-related activation differences do not change with training

One of our principal questions was whether age-related differences in brain activity typically seen in older as compared to younger adults while executing a motor task would be differentially modulated by practice. During the execution phase at pretest, we identified hyperactivation in frontal, parietal, occipital, and temporal areas in older adults (Fig. 3, Table 1). Conversely, cerebellar and subcortical areas showed hypoactivation in older in comparison with younger adults (Fig. 3, Table 1). Those results largely agree with current literature.

Despite the widespread age-related differences in brain activity during pretest, the age × time model (using both FB/NFB conditions) did not demonstrate any interaction, neither with respect to the planning nor the execution phase of the task. Thus, although brain activation differed quite dramatically during pretest, no age-related differences in modulation could be found. This suggests that OA did not show more brain activity decreases than YA, in spite of their prominent cortical hyperactivity.

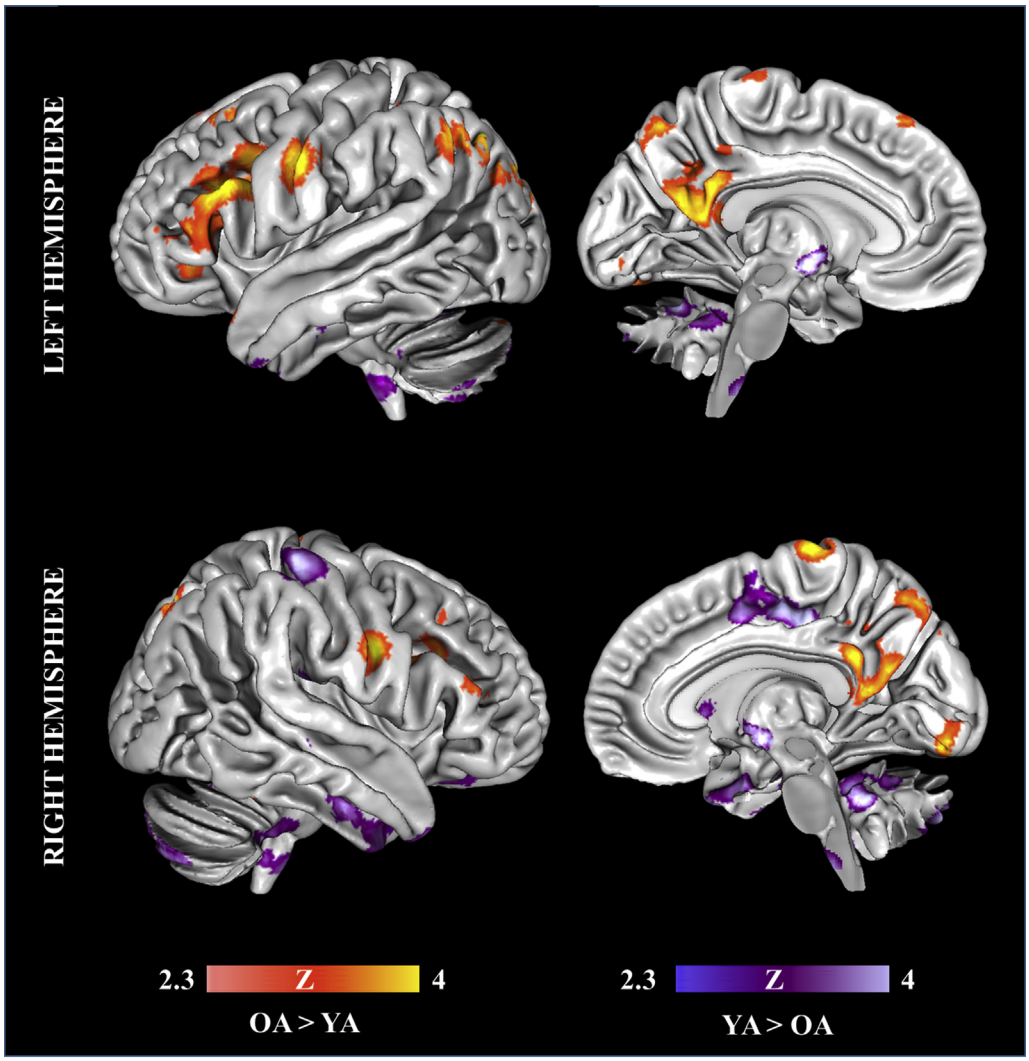

Fig. 3. Age-related differences in brain activity during task execution at pretesttest. Clusterwise-corrected activations with threshold Z ≥2.3; $p < 0.05$.

3.2.2. Effect of age on brain activity during movement planning and execution

As we found no age-related difference in training-induced modulation, we evaluated the main effects of age on general neural activation present during motor performance during training (i.e., average over pretest and posttest sessions). Furthermore, trials were also averaged over FB and NFB trials as there was no age × time × feedback behavioral effect. Large overall differences in brain activity were found during both planning and execution phases (Fig. 4, Table 2). In the planning phase, parietal, frontal, and occipito-temporal areas were more activated in OA compared to YA. On the other hand, several subcortical areas were more active in YA

Table 1
Age-related activation differences at pretest during task execution (irrespective of FB condition) corrected for gray matter intensity

Brain region	Cluster size (# voxels)	Peak activation coordinates (x, y, z)			Z-value	*p*-value
Old > young						
L IFG, also L MFG	11,859	−42	18	24	4.35	<0.00001
R precentral G, also, R postcentral G	2828	60	−2	28	4.05	<0.00001
R lingual G	1169	6	−84	−10	3.67	<0.00001
R precentral G	1028	6	−28	74	3.89	<0.00001
R LOC	606	36	−74	48	3.58	<0.001
L ITG	374	−42	−50	−8	3.34	<0.01
L hippocampus	272	−30	−18	−12	3.47	<0.05
Young > old						
Cerebellum R crus II,	5592	8	−86	−42	4.55	<0.00001
Bil. thalamus, also R putamen, bil. caudate	4975	0	−6	−6	4.58	<0.00001
R precentral G, also posterior cingulate, R pre-SMA	1803	14	−24	42	4.19	<0.00001
L temporal pole	1355	−46	12	−42	3.74	<0.00001
R postcentral G, also R anterior SMG	920	50	−30	60	3.94	<0.00001

Key: bil., bilateral; G, gyrus; ITG, inferior temporal gyrus; L, left; LOC, lateral occipital cortex; R, right; SMG, supramarginal gyrus.

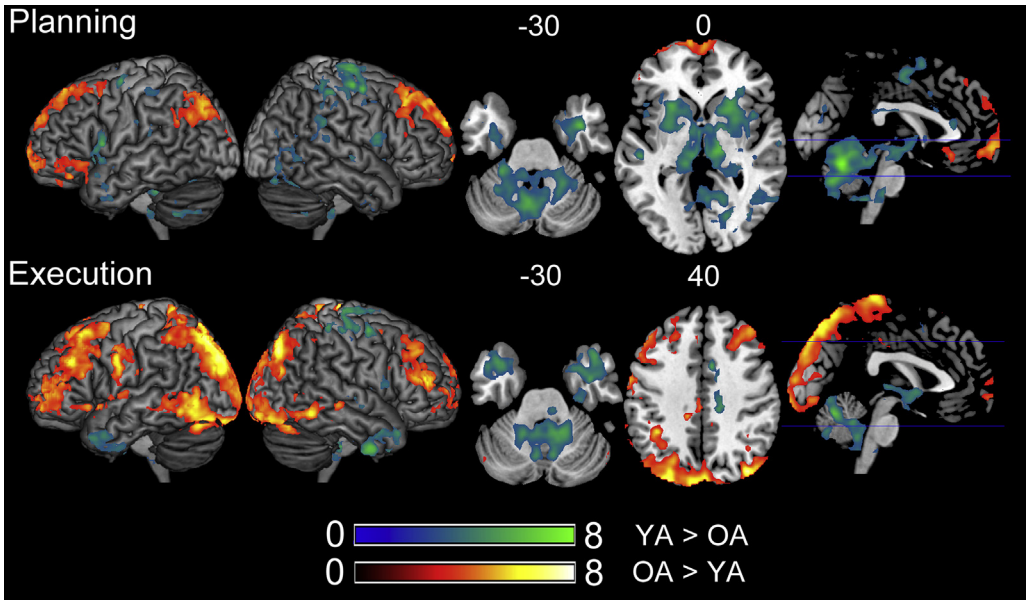

Fig. 4. Areas showing a main effect of age across pretest and posttest sessions and across FB conditions for planning and executing the bimanual tracking task. Activation maps were overlaid on the ch2better template using MRIcron (www.sph.sc.edu/comd/rorden/mricron/), neurological orientation. OA >YA in red-yellow; YA >OA in blue-green. Bottom: legend for intensity of fMRI images. Activations are significant using a clusterwise threshold $Z > 2.3$; $p < 0.05$. Abbreviation: fMRI, functional magnetic resonance imaging. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

compared to OA: one cluster of cerebellum vermis VI extending to thalamus and putamen (Fig. 4, Table 2). In the execution phase, larger clusters of parietal, frontal, and occipitotemporal areas were more activated in OA compared to YA, including left and right inferior parietal lobule (IPL), left superior parietal lobule and precuneus, and left and right middle frontal gyrus (MFG) and left ventral premotor cortex (PMv). The areas showing more activation in YA than in OA were located in 4 smaller clusters with peaks in cerebellum vermis VI, left caudate, right posterior cingulate, and right dorsal premotor cortex (PMd). Within these clusters, other regions were also active, including cerebellum vermis V and VIIa, right inferior temporal lobe (ITL), bilateral insula, right caudate, bilateral putamen, right pre-supplementary motor area (pre-SMA), right anterior cingulate cortex (ACC), and right primary sensorimotor cortex (see Table 2).

A control analysis in which performance was matched (pretest data set of YA and posttest data set of OA) (see Supplementary Material) confirmed that these group differences were not due to performance differences between age groups.

3.2.3. *Training-related brain activity decreases during the planning and execution phase*

Results revealed brain activation decreases as a function of time (main effect of time including data sets of both YA and OA, FB and NFB conditions). No increases as a function of time were observed. In the planning phase, posttest activity levels were lower in 4 clusters compared to pretest. The cluster peaks showing this effect were located in left MFG (part of the lateral prefrontal cortex), right ITL, left (and right) caudate, and right insular cortex (Table 3). In the execution phase, activity in 5 clusters decreased as a function of training. The peaks were located in (1) left middle temporal lobe; (2) right superior frontal gyrus (SFG); (3) right thalamus; (4) left ITL; and (5) left pre-SMA (Table 3).

3.2.4. *Distinct brain activity at pretest associated with performance gains in young and older adults*

We evaluated whether the age-related difference in neural activity seen at pretest would relate to performance gain. To this end,

Table 2
Locations of main cluster activation peaks (MNI-coordinates) and Z-scores for areas showing a main effect of age across pretest and posttest sessions and across FB conditions, corrected for gray matter intensity

Brain region	Cluster size (# voxels)	Peak activation coordinates (x, y, z)			Z-value	*p*-value
Old > young						
Planning						
R DMPFC, also L DMPFC, R MFG, L orbitofrontal cortex, L VMPFC	9344	10	66	28	6.51	<0.00001
L lateral parietal cortex	1678	−48	−76	38	6.33	<0.001
Execution						
L IPL, also R IPL, L SPL, L precuneus	22,188	−26	−78	48	7.74	<0.00001
L MFG, also L PMv, R MFG	9944	−48	36	32	6.92	<0.00001
Young > old						
Planning						
Cerebellum vermis VI, also bil. thalamus, bil. putamen, R pre-SMA, left cerebellum lobe VIIIa	45,515	0	−62	−20	8.15	<0.00001
Execution						
Cerebellum vermis VI, also V, VIIa, R ITL, R insula	16,316	0	−64	−20	6.34	<0.00001
L caudate, also R caudate, bil. putamen, L anterior insula	1211	−8	14	14	5.02	<0.01
Posterior cingulate, also R pre-SMA	1205	14	−24	42	5.8	<0.01
R PMd, also R S1, RM1	1063	42	−4	56	5.87	<0.05

Key: bil., bilateral; ITL, inferior temporal lobe; L, left; R, right; VMPFC, ventromedial prefrontal cortex.

Table 3
Locations of main cluster activation peaks (MNI-coordinates) and Z-scores for areas showing a main effect of time across FB conditions and across groups

Brain region	Cluster size (# voxels)	Peak activation coordinates (x, y, z)			Z-value	*p*-value
Pre > post						
Planning						
L MFG, also L PMv, R MFG	22,293	−42	50	4	5.4	<0.00001
R ITL (temporooccipital), also R IPL, L SPL	6410	46	−42	−22	5.25	<0.00001
L caudate, also R caudate	1690	−10	18	2	4.72	<0.00001
R insula, also R temporal pole, R OFC	581	40	2	−16	4.54	<0.05
Execution						
L MTL, also R IPL, cerebellum crus II, R ITL (temporooccipital), R fusiform gyrus	29,922	−46	−42	−2	5.58	<0.00001
R SFG, also R PMd, R MFG	1252	20	12	60	4.48	<0.001
R thalamus, also L thalamus, bil pallidum	938	6	−26	14	4.15	<0.01
L ITL (pole)	906	−46	−4	−44	5.41	<0.01
L pre-SMA, also L PMd, L pre-PMd	883	−10	10	60	4.65	<0.01

Key: bil., bilateral; ITL, inferior temporal lobe; L, left; OFC, orbitofrontal cortex; PMd, dorsal premotor cortex; R, right.

we performed whole-brain regression analyses between task-related brain activity at pretest (irrespective of feedback condition) during planning and execution, separately, and changes in performance from pretest to posttest. Our results show that activity in distinct brain regions is associated with performance improvement in each age group. More specifically, we observed that more prominent anterior (frontal) activity in older adults in contrast to more posterior (occipitoparietal) and cerebellar regions in younger adults was associated with performance improvement from pretest to posttest (Fig. 5, Table 4).

During the planning phase, activity in left parietal and occipital regions—left IPL, postcentral gyrus, MTG, and middle occipital gyrus—was correlated with larger performance gains in younger adults. This activation cluster was found to be significant both in the within and between groups model (Table 4). Lower performance improvement in YA was found to be correlated with higher activity in parts of the cerebellum (right lobules I-IV, V and left I-IV, V, and VI), right insula, and Heschl's gyrus (Table 4). No significant correlation between performance improvement and blood oxygen level–dependent activations was found for older adults during the planning phase.

During the execution phase, higher performance improvement was associated with a strongly lateralized and frontal activation pattern in old adults. Such positive correlation was found—and significantly higher in comparison with younger adults—for activity in the left MFG, inferior frontal gyrus (IFG), anterior cingulate gyrus, bilateral SFG, and frontal pole (Fig. 5, Table 4). In younger adults, higher improvement was associated with markedly more activity in posterior and subcortical regions, including right precuneus, left posterior cingulate gyrus, and cerebellar right crus I and right lobule VI (Table 4). This correlation was significantly higher in YA in relation to OA. Furthermore, bilateral activity in the thalamus and hippocampus was found to correlate more strongly with performance improvement in YA when compared to OA.

Those results indicate that overall performance gains are associated with neural activity in distinct brain regions in each age group. This association is already present, and strongly lateralized, during the planning phase only in young adults. Importantly, performance gains are predicted by mainly frontal regions activated during the execution phase in older adults. Conversely, performance gains in younger adults are correlated with higher activity in more posterior and cerebellar structures during this phase.

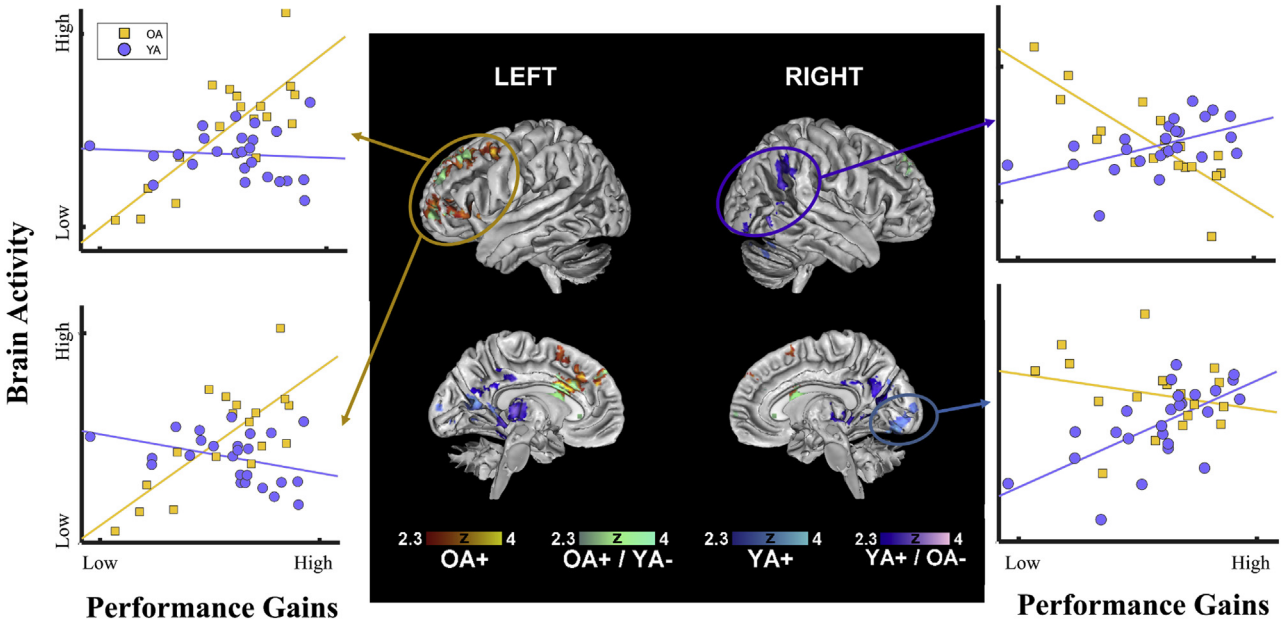

Fig. 5. Activation map at pretest during execution irrespective of the FB condition showing regions positively correlated with long-term performance improvement (i.e., from pretest to posttest). In older adults, activity in anterior frontal regions predicted between-session performance improvement and more so than in young adults. The side plots depict the correlation between mean activation within each cluster at pretest and performance gains from pretest to posttest.

Table 4
Locations of main cluster activation peaks (MNI-coordinates) and Z-scores for areas where activity at pretest (irrespective of FB condition) is correlated with performance improvement from pretest to posttest

Brain regions	Cluster size (# voxels)	Peak activation coordinates (x, y, z)			Z-value	*p*-value
Planning						
OA+						
N.S.	-	-	-	-	-	-
OA−						
N.S.	-	-	-	-	-	-
YA+						
L IPL. also	895	−39	−33	27	6.05	<0.0001
L insula L postcentral G						
L MTG L mid occ G						
YA−						
Cerebellum lobule right I-IV also	341	9	−45	−9	6.32	<0.05
Right V						
Left I-IV, V and VI						
R Insula also	334	36	−15	6	5.48	<0.05
R Heschl's G						
OA+/YA−						
N.S.	-	-	-	-	-	-
YA+/OA−						
L IPL also	398	−39	−33	27	5.88	<0.005
L insula. L postcentral G						
L lat occ cortex. also	328	−51	−81	12	5.01	<0.05
L mid occ G. L MTG						
Execution						
OA+						
L cingulate G (ant) also	2113	−9	12	27	4.88	<0.0001
L MFG. bil. frontal pole.						
bil. SFG.						
L IFG						
OA−						
R IPL. also	605	51	−36	36	4.42	<0.001
R SMG. R ang G.						
R postcentral G						
YA+						
R precuneus. also	377	18	−57	12	3.91	<0.05
bil. lingual G.						
Cuneus. L cingulate G (post.)						
R occ fusiform G. also	336	27	−75	−15	3.79	<0.05
Cerebellar right crus I. right VI						
YA−						
N.S.	-	-	-	-	-	-
OA+/YA−						
R cingulate G (ant.). also	1882	−9	9	27	4.25	<0.0001
R MFG. bil. SFG.						
Bil. frontal pole						
YA+/OA−						
Bil. thalamus. also	520	9	−33	3	3.49	<0.005
Bil. hippocampus						
R SMG. also	413	69	−51	12	3.7	<0.05
R angular G. R inf occ cortex.						
R MTG						
R Cingulate G (post) also	335	6	−63	15	3.49	<0.05
R intracalcarine cortex,						
R precuneus,						
R temporal occ cortex						

Key: bil., bilateral; L, left; N.S., non significant; R, right.

4. Discussion

We addressed whether changes in brain activity associated with learning a new set of bimanual coordination skills are affected by aging. We also investigated whether brain activity in the early stages of training could predict subsequent training-induced performance gains. Across a 2-week period, performance on the bimanual task set improved significantly in both groups. There were, nonetheless, widespread differences in both the behavioral and the neural correlates associated with these effects.

Performance improvement was higher in older adults, although this is likely due to lower performance levels overall. Retention was largely unaffected by age, although we did find a trend-level indication that older adults present more difficulty in the absence of augmented feedback after the 6-month period. Regarding functional activations, we found a dominant pattern of task-related cortical hyperactivation and subcortical hypoactivation in older as compared to young adults during task planning as well as execution. Surprisingly, training-induced decreases in brain activity did not differ between the 2 age groups. However, the degree of prefrontal recruitment in older adults during initial training on the task was identified as an important marker of subsequent training-induced performance gains. Overall, the findings suggest that skill improvement and the associated reduction in brain activation is preserved in older adults. In addition, cerebral activity during early learning can

differentially predict the amplitude of the training-induced performance benefit between young and older adults.

4.1. Behavioral findings

There is a long-standing debate in the literature about whether older adults show impairments in motor learning (see Section 1). In the case of learning a new set of bimanual tasks, as used in the present study, older adults performed overall at a lower level when compared to young adults but were able to reduce the performance gap with training. Whether performance gain was different between age groups was dependent on the type of measure used. Absolute error improvement was larger in OA, in part due to the fact that OA performed with lower accuracy already at pretest, leaving more room for improvement. When error was normalized in relation to early pretest, performance gains did not differ between groups. Regardless of measure, our findings indicate that, although motor performance deteriorates with age, training-induced improvement is maintained for this complex set of tasks.

Older adults appeared to show similar skill persistence as younger adults across a 6-month period. This result differs from previous studies showing age-related differences in motor skill retention (Rodrigue et al., 2005; Wishart et al., 2002). This discrepancy must be interpreted with care however, as there was a nonsignificant trend for older adults to exhibit lower skill retention, especially in the absence of augmented visual feedback. This may indicate that older adults show reduced consolidation over long retention intervals. The relatively small sample size with respect to the retention data prevents us to make bald statements about this. Nonetheless, bimanual coordination training in older adults may be worthwhile for preserving and even regaining basic motor functions.

4.2. Neural activation differences between age groups

Hyperactivation in older adults was found in prefrontal and parietal cortex during actual performance of the BTT, consistent with previous research on interlimb coordination (Goble et al., 2010; Heuninckx et al., 2005, 2008). A new finding was that this hyperactivity already emerged during the movement planning phase. During planning, dorsomedial and ventromedial prefrontal, middle frontal, and orbitofrontal cortex as well as lateral parietal cortex were more active in older adults than in young adults, pointing to a strong prefrontal activation pattern. It is noteworthy that some of these areas (dorsomedial prefrontal cortex and lateral parietal cortex) are closely associated with the default mode network (Raichle et al., 2001), which younger adults typically deactivate during task performance compared to baseline conditions. The finding that older adults activated this region more than young adults could point to an inability to deactivate the default mode network during task planning, in line with previous reports of similar neural activity patterns in older adults during cognitive tasks compared to fixation (Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007, 2014; Sambataro et al., 2010).

During the movement execution phase, hyperactivation in parietal (bilateral IPL as well as left superior parietal lobule and precuneus) and prefrontal areas (left and right MFG, including dorsolateral prefrontal cortex) is most likely due to older adults having to allocate more neural resources for online control of action compared to young adults. Hyperactivation in medial and lateral parietal regions as well as prefrontal regions has been observed during performance of interlimb coordination tasks in previous studies (Goble et al., 2010; Heuninckx et al., 2005). Particularly, the left hemisphere regions are implied in motor attention (Jueptner et al., 1997; Rushworth et al., 1997; 2001a,b; Toni and Passingham, 1999; Toni et al., 2001). The peak coordinates are also close to the areas observed in the central executive network (Curtis and D'Esposito, 2003; Seeley et al., 2007). The results showed a similar overall pattern of brain activity differences between both age groups when data sets with similar performance levels were compared (see Supplementary Material), suggesting that the age-related differences in neural activity were not driven by performance differences. This extends previous evidence for increased cognitive control of movement in OA.

Interestingly, older adults also showed substantial hypoactivation of primarily subcortical structures (bilateral cerebellar regions, thalamus, and putamen) and pre-SMA during the task planning phase. This is a less documented finding although previous work, that has predominantly focused on actual task performance (not learning), has reported similar observations (Coxon et al., 2010; Goble et al., 2010; Heuninckx et al., 2005, 2008). This may suggest that age-related motor deficits during execution can partly be accounted for by processes occurring prior to movement initiation, i.e., at the stage of movement planning (Amrhein et al., 1991).

During the task execution phase, the same regions as mentioned during the planning phase, plus bilateral caudate, right PMd and pre-SMA, and right primary sensorimotor cortex were less activated in older adults. Although age-related activation increases have received prominent attention in the medical imaging literature on motor function, reduced brain activity in some of these regions, among others, has also been observed in previous studies (Coxon et al., 2010; Hutchinson et al., 2002; Logan et al., 2002; Riecker et al., 2006; Van Impe et al., 2009; Wu and Hallett, 2005). Although hypoactivation of putamen in older adults is in contrast with some previous studies (Mattay et al., 2002; Ward et al., 2008), it is in line with Van Impe et al. (2009). As we corrected for gray matter intensity voxelwise, it is unlikely that this deficit arose from age-related neuronal loss. Alternative possibilities are that it may indirectly reflect the consequences of reduced D1- and D2-like receptors (Bäckman et al., 2000; Rinne et al., 1993; Wang et al., 1998) and dopamine transporters (Volkow et al., 1998) in the striatum (Van Impe et al., 2009) but this requires further investigation. Reduced dopaminergic function in the basal ganglia may have played a role in failing to upregulate activity in motor-related structures, although this would need to be directly investigated for further confirmation. In sum, whereas young adults appeared to rely more on the basic motor network to plan and perform the task, older adults apparently needed backup recruitment from parietal and (pre)frontal areas to complete the task (Heuninckx et al., 2005, 2008).

4.3. No effect of training on age-related neural activation differences

Our assumption that the age-related activation differences (hyperactivity and hypoactivity) would diminish with training, leading to activation patterns which were more similar between both groups, was not upheld as no significant age $\times$ time interaction effect was observed. This suggests that these age-related alterations in brain activation are profound and not easily overcome. The main effect of time underscored a decreased need for recruitment of neural resources in both age groups. With respect to the planning phase, activity decreases were observed across the broader cortical territory from frontal to parietal and occipitotemporal areas. With respect to the movement execution phase, decreases in activation were prominent in primarily left (pre)motor areas (including pre-SMA and pre-PMD), right superior and mid-frontal gyrus,

temporal and parietal areas. In addition, activation decreases were also observed in bilateral pallidum and thalamus as well as cerebellar crus II. Overall, this suggests increased economy of brain activity with increasing motor skill level. Moreover, the reductions in prefrontal areas (MFG, SFG) and those at the verge between frontal and motor structures (pre-SMA, pre-PMd) as well as cerebellar crus II (with connections to prefrontal areas) point to reduced cognitive demands as a result of training.

4.4. Frontal brain activity associated with higher performance gains

Some studies have shown evidence that hyperactivation is related to compensatory mechanisms, implying that those older adults showing increased brain activation also show higher performance levels (Cipolotti et al., 2015; Goble et al., 2010; Heuninckx et al., 2008; Seidler et al., 2010). As such, the hyperactivation is meaningful. Interestingly, whole-brain regression analyses revealed that responses in some of the brain regions showing age-related hyperactivity at early stages of practice (mainly frontal areas) were correlated with performance gains induced by subsequent training. Specifically, activity in multiple frontal areas, including left MFG and bilateral SFG and frontal pole, during execution was predictive of performance gain in older adults, that is, older adults showing higher activation in these areas at pretest also exhibited more learning gains. By contrast, performance gains were associated with more posterior (right occipitoparietal regions, including right angular gyrus) and cerebellar regions in younger adults, already during the planning phase of the movement.

Our results showed a strong age-related hyperactivation of the left dorsolateral prefrontal cortex during the execution phase of the BTT, which largely agrees with current interlimb coordination literature (Goble et al., 2010; Heuninckx et al., 2005, 2008). Although this area is known to be involved in learning across all ages (e.g., Debaere et al., 2004; Rémy et al., 2008; Ronsse et al., 2011; Sakai et al., 1998; Toni et al., 2001, 2002), we found a positive correlation between activity in this region and performance improvement only in older adults. Further evidence for the functional relevance of prefrontal areas during motor control in older adults has been previously demonstrated using cognitive-motor dual-task paradigms (Fraser et al., 2010; Schaefer and Schumacher, 2011). In such paradigms, performance decrease has been shown to be more pronounced in older as compared to young adults, suggesting competing recruitment of brain regions responsible for cognition, which include prefrontal areas. In conjunction with our results, this suggests that activation of prefrontal areas in older adults has functional relevance, both for motor performance and learning.

One consideration must be taken into account when interpreting those results. On the one hand, as performance gains from pretest to posttest were strongly associated with both initial performance and within pretest improvement, further investigation is required to determine the nature of the correlations shown here. However, as initial performance and improvement were negatively correlated, it seems unlikely that the reported brain activity is associated with baseline performance (i.e., those who show this pattern of activation perform better), but rather with performance improvement, both in the initial and later learning stages.

5. Conclusions

During acquisition of a set of bimanual tasks, older adults showed lower performance levels than young adults but comparable performance gains from training. Besides convincing evidence for hyperactivation as well as hypoactivation, our imaging results showed, for the first time, that these age-related activation differences could already be observed during the planning phase of the task, suggesting that different neural mechanisms are already active in older adults prior to movement initiation. Furthermore, the brain activation decreases observed after the training intervention were similar in both age groups, suggesting comparable processes of reduced cognitive resources and increased economy of brain activity as a result of skill improvement. Nevertheless, the typical hyperactivity in older adults did not disappear with training, suggesting the pervasiveness of this mechanism. Finally, prefrontal hyperactivation in older adults was correlated with larger training-induced performance gains, suggesting a compensatory mechanism for neuroplasticity in aging.

Disclosure statement

All authors declare that there are no actual or potential conflicts of interest. Participants were informed about the experimental procedures and provided written informed consent. The study was approved by the local Ethics Committee of KU Leuven and was performed in accordance with the 1964 Declaration of Helsinki.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2017.06.004.

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