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Reduced Modulation of Task-Related Connectivity Mediates Age-Related Declines in Bimanual Performance

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Abstract

Aging is accompanied by marked changes in motor behavior and its neural correlates. At the behavioral level, age-related declines in motor performance manifest, for example, as a reduced capacity to inhibit interference between hands during bimanual movements, particularly when task complexity increases. At the neural level, aging is associated with reduced differentiation between distinct functional systems. Functional connectivity (FC) dedifferentiation is characterized by more homogeneous connectivity patterns across various tasks or task conditions, reflecting a reduced ability of the aging adult to modulate brain activity according to changing task demands. It is currently unknown, however, how whole-brain dedifferentiation interacts with increasing task complexity. In the present study, we investigated age- and task-related FC in a group of 96 human adults across a wide age range (19.9–74.5 years of age) during the performance of a bimanual coordination task of varying complexity. Our findings indicated stronger task complexity-related differentiation between visuomotor- and nonvisuomotor-related networks, though modulation capability decreased with increasing age. Decreased FC modulation mediated larger complexity-related increases in between-hand interference, reflective of worse bimanual coordination. Thus, the ability to maintain high motor performance levels in older adults is related to the capability to properly segregate and modulate functional networks.

Key words: aging, bimanual coordination, functional connectivity

Introduction

Multiple aspects of motor behavior are negatively impacted by aging (Seidler et al. 2010; Krehbiel et al. 2017) in a task complexity-related manner (Serrien et al. 2000; Yan 2000; Bangert et al. 2010). In the specific case of continuous bimanual coordination, an increase in between-hand interference (BHI) toward preferred coordination modes has been observed in older

adults when attempting to execute relatively more complex movement patterns (Swinnen et al. 1998; Wishart et al. 2000). Such deficits in the ability to decouple limbs during coordination tasks are likely the result of multiple factors, including age-related changes in interregional communication at the brain level, that is, functional connectivity (FC) (Bernard et al. 2013; Heitger et al. 2013; Solesio-Jofre et al. 2014, 2018).

Previous research has revealed that older age is associated with widespread changes in communication among brain networks, especially in the absence of task execution, that is, resting state (Damoiseaux et al. 2008; Ferreira and Busatto 2013; Baldassarre and Corbetta 2015; Spreng et al. 2016; Damoiseaux 2017). More specifically, increasing age has been associated with stronger FC between distinct functional networks, as well as reduced within-network connectivity, with negative behavioral implications across multiple domains (Baldassarre and Corbetta 2015; La et al. 2015; Ferreira et al. 2016; King et al. 2018). Evidence indicates that these age-related FC differences are observable not only at rest but also persist during the execution of motor and cognitive tasks (Madden et al. 2010; Sambataro et al. 2010; Heitger et al. 2013; Geerligs et al. 2014a). In the context of bimanual coordination, aging has been linked to increased task-related FC among various brain regions (Heitger et al. 2013; Monteiro et al. 2019).

In addition to long-term changes as a result of aging, network topology reorganization takes place at shorter time scales as well (i.e., in response to task demands). This ability to flexibly modulate FC has been associated with better measures of cognitive performance in young adults (Braun et al. 2015; Vatanserver et al. 2015). Although older adults appear to retain the ability to modulate network connections between rest and the execution of cognitive (working memory and selective attention) tasks, they exhibit an impairment in FC modulatory ability in response to increased task difficulty levels (Geerligs et al. 2014b).

Altogether, there is compelling evidence indicating that older age is marked by progressively less distinctive functional systems (i.e., more dedifferentiation; Goh 2011; Koen and Rugg 2019). From a network perspective, it is important to note that such dedifferentiation encompasses both less segregation among distinct networks and less connectivity modulation across different task conditions. The relevance of modulating whole-brain FC in response to task complexity demands has been shown for cognitive but not for (bimanual) motor tasks. In the present study, we aim to address this gap in the literature by investigating whole-brain FC across a wide age span during the execution of bimanual coordination tasks of varying complexity levels. Our primary hypothesis is that older adults will show less FC changes as a function of increasing task complexity. Furthermore, we hypothesize that greater impairments in task-related FC modulation will be associated with larger age-related declines in bimanual performance in the more complex relative to simpler task variants.

Materials and Methods

Participants

A cohort of right-handed (Oldfield 1971) adults aged between 19 and 80 years was recruited from Leuven and the surrounding region to take part in the study. Participants had normal or corrected-to-normal vision, reported no known psychological, psychiatric, or neurological disorders, were not taking psychoactive medication and did not present any magnetic resonance imaging (MRI) contraindication. Out of the 106 participants who met the aforementioned criteria, 10 were excluded from the analyses: 2 participants voluntarily withdrew from the study, 1 participant reported a change in medication status, 1 presented a brain lesion, 2 participants did not reach the cut-off score (>24) on the Montreal Cognitive Assessment (MoCA;

Table 1 Age group division

	Age groups			
	YA	MA1	MA2	OA
N	24	24	24	24
N Male	14	11	14	15
Mean age	25.2	43.8	58.3	69.8
STD	4.5	4.04	5.02	2.59
Minimum	19.9	36.8	51.5	66.0
Maximum	34.5	51.3	65.5	74.4

Included participants (N=96) were subdivided into 4 groups according to age (specified in years) (YA = young adults, MA1 = young middle-aged adults, MA2 = older middle-aged adults, and OA = older adults).

Nasreddine et al. 2005), and the remaining 4 were excluded due to technical issues during data acquisition leading to an incorrect number of task blocks being performed. Thus, the final analyses were performed on 96 participants (ages 20–74 years; 54 males). Prior to analyses, the final group of participants was split into 4 age groups of equal size (Table 1).

The experiment was approved by the local ethical committee of KU Leuven (study number: S51615), and all participants provided written informed consent prior to their participation in the study and were compensated afterward.

Experimental Protocol and Task

The full experimental protocol consisted of 3 sessions. In the first session, participants practiced the bimanual coordination task and performed screening tests to assess eligibility. The screening protocol included the MoCA, health status questionnaire, and MRI contraindications. Initial task practice consisted of 8 blocks of the motor task (see below for a description of the task) while lying supine inside a mock scanner. The purpose of the initial practice blocks was to minimize the effects of early skill acquisition on task performance and FC analyses. In the second session, a series of scans in the absence of task execution were acquired. Those scans included a high-resolution T1-weighted structural image, resting-state functional MRI (fMRI), and multiple magnetic resonance spectroscopy (MRS) images. Analyses from resting-state and MRS scans are reported by King et al. (2018) and Levin et al. (2019), respectively. In the third session, 8 active and 1 passive blocks of fMRI scans (each of 6 min in length, see Imaging Acquisition and Processing for details) of the visuomotor bimanual tracking task (BTT) were acquired. Assessment of task performance differed from previous reports to emphasize mutual interference effects (King et al. 2018; Levin et al. 2019). All MRI scans were obtained at the University Hospital of KU Leuven.

Participants were instructed to perform 8 blocks of a BTT similar to that previously used in our research group (Sisti et al. 2011; Gooijers et al. 2013; Serbruyns et al. 2013; Solesio-Jofre et al. 2014; Monteiro et al. 2017). The goal of the task was to track a moving target along a predetermined trajectory projected on a screen as closely as possible. A custom-made nonferromagnetic device was placed above the participant's lap. The device consisted of a support surface with 2 dials (5 cm diameter), which could be rotated to control the movement of a cursor on a computer screen. Clockwise (CW) movements of the left-hand dial moved the cursor upward and counterclockwise (CCW) rotations moved

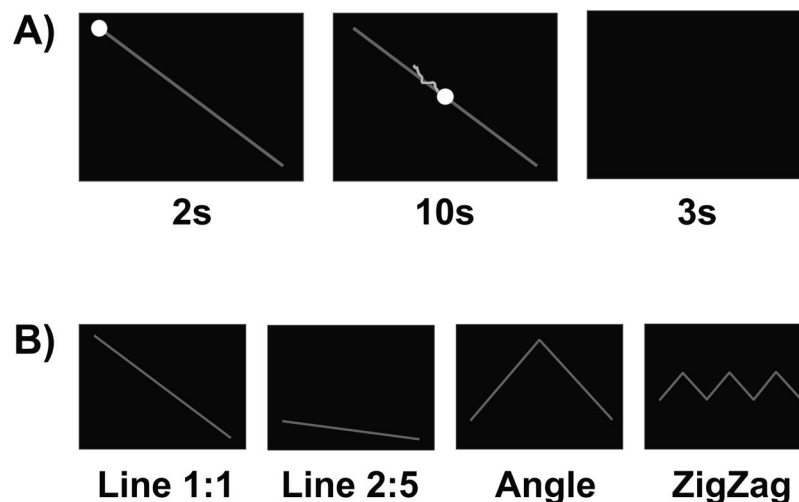


Figure 1. BTT time course and complexity variants. (A) Each BTT block lasted 15 s was divided into 3 phases (planning: 2 s, execution: 10 s and inter-trial interval: 3 s). (B) Movement trajectories followed 1 of 4 task conditions of varying complexity.

the cursor downward. Analogously, CW and CCW of the right-hand dial moved the cursor toward the right and left sides of the screen, respectively. Angular displacements of the dials were recorded with nonferromagnetic high precision optical shaft encoders (HP, 2048 pulses per revolution, 100 samples per second). All task blocks were performed while lying supine inside a mock (session 1) or real (session 3) MRI scanner.

Each BTT trial started with the target trajectory and target dot presentation (Fig. 1A). This information remained on screen for 2 s, during which no movement was required. Subsequently, the target dot started moving automatically along the target line at a constant speed for a total duration of 10 s. During this time, participants were instructed to rotate the left and right dials simultaneously in order to track the target dot as accurately as possible. Online visual feedback of the performed trajectory was provided in the form of a red line depicting the current and past positions (cursor positions corresponding to the preceding second). Once the 10-s period ended, the screen turned black for 3 s, after which the next trial would begin (i.e., 3-s intertrial interval).

BTT trials were divided into 4 conditions referring to patterns of differing relative complexity (Fig. 1B). In the simplest condition (Line 1:1), participants moved the dials at constant and matching speed (either both dials CW or CCW; 6 trials per block). In the second condition (Line 2:5; not analyzed in this study, see next paragraph), the hands needed to rotate continuously, but at differing speeds. Specifically, for every 2 rotations performed by the left hand, the right hand needed to perform 5 rotations (or vice versa (5, 2); 6 trials per block, balanced across hands). The third (Angle) and fourth (ZigZag) movement patterns required reverting rotation direction during the trial. In the Angle condition, both hands moved at constant and matching speed, but the left hand switched rotation direction from CW to CCW in the middle of the trial while the other hand continued (or vice versa; 6 trials per block, balanced across directions). In the Zigzag conditions, both hands again moved at constant and matching speed; however, one of the hands performed 4 rotation switches during the trial (6 trials per block, balanced across hands). Therefore, while the first 2 task conditions required continuous rotational movements without a switch in direction, the last 2 task conditions required continuation of one hand movement while the other hand had

to perform 1 (Angle) or 4 switches in the rotation direction (ZigZag).

In this study, we were interested in age-related differences in BHI during the execution of the BTT. From a motor perspective, successful performance in the BTT task depends on the execution of each hand's required movement parameters (e.g., rotational frequency) as part of a unified goal. In the case of hand movement decoupling, left-hand and right-hand tracking error scores are expected to be minimally associated. Especially in cases where only one hand performs a relatively more complex maneuver as compared to the other, error covariance can be interpreted as indicative of BHI.

By adding rotational switches performed with one hand without changing the interhand rotational frequency relationship, BHI can be interpreted as a function of a single parameter (i.e., number of switches). Performance changes from condition Line 1:1 to condition Line 2:5, however, likely reflect both the increased complexity in frequency relationship and rotational speed. Consequently, we did not include Line 2:5 in our analyses [an outcome of task condition Line 2:5 is reported by King et al. (2018)].

A total of 192 BTT trials were performed (48 per condition) and divided into 8 blocks of equal length. Conditions were pseudorandomized within task blocks but were the same across participants. The six trials of each condition within a task block were always grouped together. Between blocks 4 and 5, a passive/rest BTT block took place where an exemplar performance was presented on the screen, but no actual movement was executed. Imaging data from this block were not analyzed here.

Virtual cursor trajectories (from target and participants) derived from left- and right-hand dial components were processed offline using Matlab R2015b (The Mathworks). The main behavioral outcome used was the amount of deviation of each hand's movement relative to the target trajectory. More specifically, we quantified the rate in which tracking error increased or decreased in both hands at the same time, referred here as BHI. BHI was estimated by calculating the mutual information (MI) between error changes over time from each hand relative to the target trajectory (Fig. 2). Conceptually, MI measures the amount of information one variable contains about another variable. An MI value of 0 would indicate that

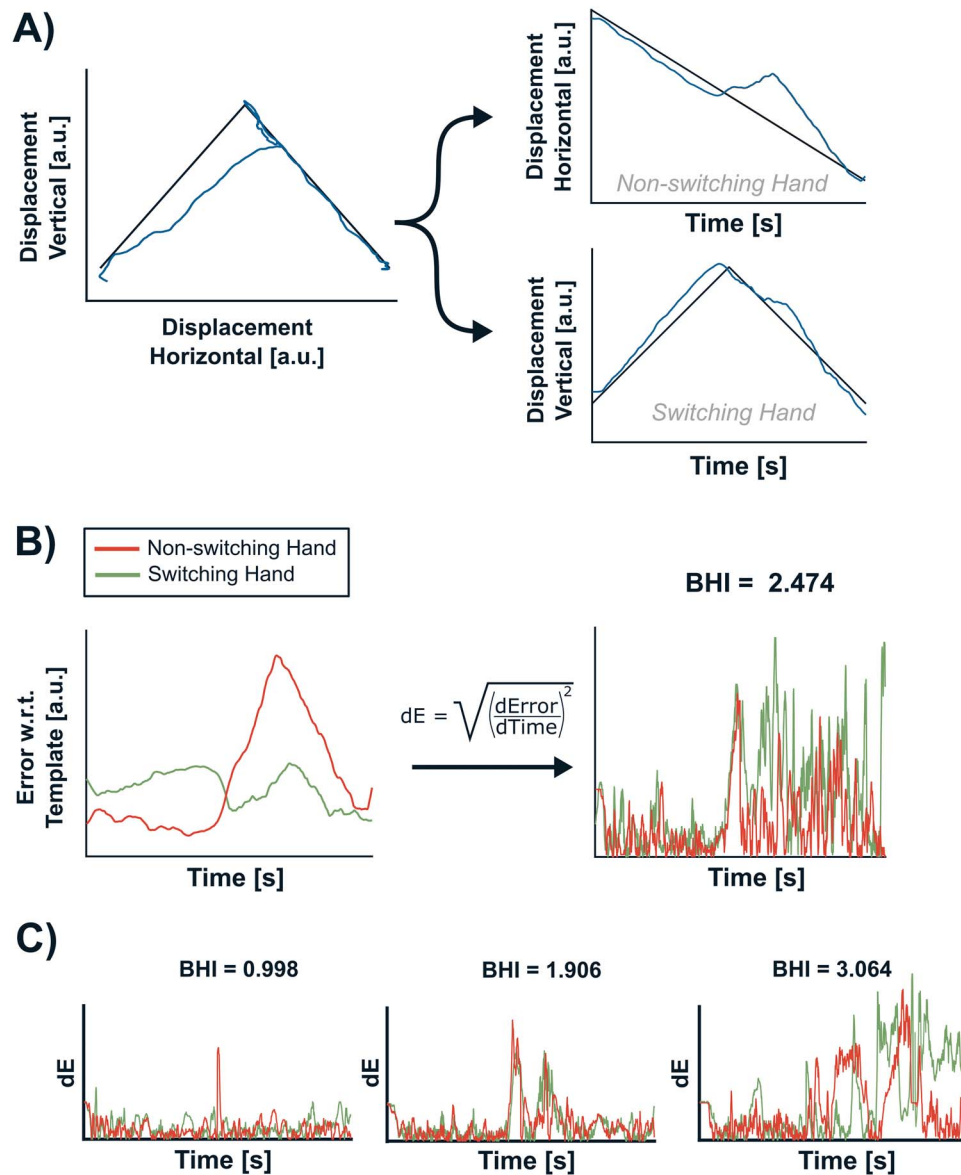


Figure 2. Decomposition of a single trial in its hand components (A), calculation of error rate with respect to target over time (B), and exemplary performance errors and their associated BHI values (C). In order to calculate performance during an exemplary trial (Angle condition, depicted in A, left panel), the executed movement is decomposed into its horizontal and vertical components as a function of time (for both template and participant's trajectory, shown in A, right panel). Simple difference between performed and template trajectory is calculated for each time point and each movement component, resulting in 2 error time courses (green and red lines in B, left panel). Rate of error change (dE) is calculated as the root of squared differential error over time (B, right panel). Final trial performance is scored as the MI between those time courses (BHI). Illustrative examples of task performance error and their corresponding BHI values are shown in (C).

the errors over time from each hand are independent of one another. Thus, lower MI values are interpreted to reflect, at least partially, stronger uncoupling of each hand's movement (i.e., less interference between hands) and are consequently representative of better performance. Furthermore, trials where participants moved less than 33% of the total required trajectory length with either hand were excluded (1.3%, 1.1%, and 2.1% of trials were removed from the Line 1:1, Angle, and ZigZag conditions, respectively). This particular behavioral outcome was chosen as a potential indicator of inhibitory motor behavior, which has been shown to be impaired and associated with dedifferentiated networks in older age (Cassady et al. 2019).

Imaging Acquisition and Processing

All MRI scans were acquired using a Philips Achieva 3T scanner with a 32-channel head coil. Task fMRI scans were acquired with an ascending gradient echo-planar imaging pulse sequence for T2*-weighted images (repetition time [TR]=3000 ms; echo time [TE]=30 ms; flip angle=90°; 54 transverse slices; interslice gap=0.2 mm; voxel size=2.5 × 2.5 × 2.5 mm³; field of view=210 × 210 × 145.6 mm³; matrix=84 × 84; 120 dynamic scans plus 4 dummy scans discarded at the beginning of the sequence for each block). The high-resolution T1-weighted structural image was acquired using a magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence (TR=9.6 ms;

TE = 4.6 ms; flip angle = 8°; voxel size = 0.98 × 0.98 × 1.2 mm³; field of view = 250 × 250 × 192 mm³; matrix = 256 × 256; 160 coronal slices).

Each block of fMRI data was identically processed using a combination of Analysis of Functional Neuro Image (AFNI) software version 18.0.25 (Cox 1996), advanced normalization tools (ANTs; Avants et al. 2011, 2014), FSL 5.0.11 (Jenkinson et al. 2012), Python, and custom scripts. Firstly, differences in slice time acquisition were corrected by temporal resampling, filtering, and shifting using the *filtershift* method (Parker et al. 2017). Subsequently, images were realigned to the volume which minimized the average intensity difference to other volumes (*3dvolreg*). In order to normalize functional scans to the sample template in the Montreal Neurological Institute (MNI) space (created using DARTEL in SPM12), 3 steps were performed. An affine transform between functional scans and the high-resolution scan was calculated (*epi_reg*). Subsequently, a nonlinear warp, restricted to the anterior–posterior plane, was estimated to reduce magnetic field geometric distortions (*antsRegistration*, SyN transform). Finally, the high-resolution anatomical volume was registered to the group template (*antsRegistration*). The 4 transforms estimated in the previous steps were applied at a single step in order to convert all images to the MNI space (*antsApplyTransforms*). Finally, motion-related spikes were removed (*3dDespike*) and volumes were smoothed using a 6 mm full width at half-maximum Gaussian kernel (*3dmerge*).

Functional Networks Definition and Connectivity Analyses

Functional networks were defined using group-level compressed dictionary learning as implemented in the *Nilearn* library (Varoquaux et al. 2011; Abraham et al. 2014; Mensch et al. 2016). In this method, networks were obtained by optimizing component sparsity, that is, components with relatively few voxels and little spatial overlap (Daubechies et al. 2009). In order to estimate such components, firstly a reduced time representation of each data block was obtained as a means of lessening computational costs (Mensch et al. 2016). Reduced data blocks from all participants were then concatenated in time. Initialization of dictionary learning maps was performed using Canonical ICA with $k = 50$ components (Varoquaux et al. 2010). Finally, dictionary learning was used to optimize spatial sparsity, resulting in 50 distinct components corresponding to spatial representations of either functional networks or structured noise. Individual blood oxygen level-dependent (BOLD) signals were obtained by solving a least-square problem on the spatial decomposition results.

Prior to calculation of FC between component pairs, the average global, white matter, and cerebrospinal fluid signals, as well as motion estimates and their derivatives, were regressed from each component's signal. Importantly, we expected motion to coincide with the execution of the motor task (and, potentially, with changes of interest in BOLD signals), which can negatively impact estimation of brain activity, at least in generalized linear model (GLM) analyses (Johnstone et al. 2006). To avoid potentially removing both motion- and nonmotion-related variance coinciding with the task execution period, motion estimates were notched at 0.067 Hz (related to the trial length of 15 s, in order to include both motion related to task execution and potential postural readjustments during the preparation and intertrial periods). Global signal regression

has been shown to perform well in the removal of nuisance signals (Ciric et al. 2017) and to improve the association between connectivity (at rest) and behavior (Li et al. 2019). However, it has been previously shown that projecting out the variance explained by the global signal leads to a negative bias in functional correlation during resting state (Murphy et al. 2009). Furthermore, distortions in group comparisons (and within-group) might also be introduced (Saad et al. 2012). Despite those drawbacks, regression of the global signal remains a powerful and valid processing step in removing nuisance signals prior to connectivity analyses justifying its use in the present study (Power et al. 2014; Murphy and Fox 2017). After regressing out nuisance covariates, a high-pass filter (cutoff > 0.01 Hz) was applied. Finally, the number of time points where framewise displacement surpassed 1 mm was computed to be used as covariates in the statistical models (see Statistical Analyses). Those points were also removed from BOLD signals. Pearson's correlation coefficient between each pair of BOLD signals of each task condition was computed, resulting in 8 × 3 (task blocks × conditions) connectivity matrices for each of the 96 included subjects. In order to identify groups of closely connected components (i.e., networks), spectral clustering was calculated over the average connectivity matrix (Newman 2006). The identified groups of components were then manually classified into either functional or noise.

Crucially, global signal regression shifts the FC distribution for each subject toward a mean of approximately 0, with both positive and negative FC values in the distribution. As a result, this processing step potentially leads to the introduction of a negative correlation between nonconnected networks. Consequently, negative FC values might not reflect truly anticorrelated networks (for a more detailed discussion about the effects of global signal regression, see Murphy and Fox 2017). Thus, we avoid making a distinction between “less negative” and “more positive” connectivity (i.e., both are reported as increased connectivity). Similarly, we do not differentiate between “more negative” and “less positive” FC values, reporting both as reduced connectivity.

Statistical Analyses

Motor Behavior and Its FC Correlates

All statistical analyses were performed using the statistical toolbox in Matlab R2015b (The Mathworks). In this study, our main interest was the investigation of the effects of age and task complexity on motor behavior and FC. In order to assess those effects, we constructed a similar generalized linear mixed effect model of either the behavioral BHI or FC measure as a function of AGE GROUP (YA, MA1, MA2, OA) and TASK CONDITION (Line 1:1, Angle, and ZigZag). To account for repeated measures, subject intercepts were included as random factors. Furthermore, the number of rotations (averaged across both hands) performed in each trial were also included as random intercepts in order to account for variability related to following the target dot too slowly or too quickly (e.g., failing to track the dot after a wrong switch). Additionally, in the case of FC, we also included the number of spikes in the task block to account for variation in FC due to excessive motion. Task blocks that contained more than 24 motion spikes (corresponding to 20% of the block length) were not included in the statistical analyses (YA: 4.2%, MA1: 1.6%, MA2: 4.7%, OA: 17%). Importantly, even though motion was significantly different across age groups, it is unlikely that the results we report here are a consequence of differences in

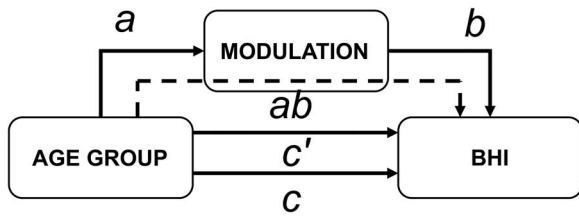


Figure 3. Mediator model used to probe the effect of FC on age-related changes in motor behavior. Mediation analysis is performed by solving a set of regression equations (MacKinnon et al. 2007). Regression coefficients from those equations are represented by the different depicted paths (a, b, c, c', and ab). The first requirement for mediation to be valid is the existence of a significant association between age group and BHI (path c). Furthermore, FC modulation must have a significant association with age group in order for the mediation to be justifiable (path a). Additionally, the direct effect of FC modulation on BHI must also be significant (path b). Finally, the association between age group and BHI after calculating the regression of age group and FC modulation on BHI is computed (direct effect, path c'). Mediation is measured by the indirect effect (path ab). If FC modulation exerts a mediation effect on the association between age group and BHI, c' must be significantly smaller than c. Statistical significance of the mediation coefficients was assessed through bootstrapping (10 000 samples).

motion, as relatively few FC pairs were significantly affected by motion and did not contradict the primary results reported in section Effects of Age and Task Complexity on FC (see Supplementary Fig. S1). Likewise, the higher number of excluded task blocks in the OA group did not greatly impact our primary FC results (see Supplementary Fig. S2). The false discovery rate (FDR) method (Benjamini and Hochberg 1995) was employed to correct type I errors due to multiple comparisons for FC ($q = 0.05$). Post hoc analyses were carried out using pairwise permutation testing ($N_{\text{PERMUTATIONS}} = 5000$).

Mediation Analysis

Associations between age-related changes in connectivity and BHI were established using mediation analyses (MacKinnon et al. 2007), which were performed with the M3 mediation toolbox using a single mediator model (Wager et al. 2008, 2009). Briefly, we were interested in the mediation effect of FC modulation on the relationship between age group and BHI changes between conditions (Fig. 3). To that end, we defined the average modulation as the mean FC change across network pairs between two task conditions. Only FC pairs where we observed an interaction between age group and task condition were included. Furthermore, we aimed to investigate how FC modulation is associated with performance changes from one condition to another. Therefore, we included performance in the simplest condition as a covariate of no interest in each mediation model. For similar reasons as stated in section Motor Behavior and Its FC Correlates, the number of rotations executed and the number of motion-related spikes were added to the mediation model as covariates of no interest. Modulation between all possible pairs of conditions was investigated: Line 1:1 to Angle, Line 1:1 to ZigZag, and Angle to ZigZag.

Results

Identified Functional Networks

The procedure described in section Functional Networks Definition and Connectivity Analyses resulted in 10 networks being identified as functionally relevant (composed of 33 components in total; Fig. 4 and Supplementary Table ST1) and 2 sets of

components identified as potentially artifactual (Supplementary Fig. S3). It is important to note that some networks may include functionally heterogeneous components. For example, the temporal network (TMP) includes both temporal and insular components. Nonetheless, those components were grouped due to their FC pattern at group (average) level and are accordingly treated here as a single network.

Effects of Age Group and Task Complexity on BHI

Task performance was assessed by the variable called BHI. It was computed based on the MI of the movement errors from the two hands whereby lower values are reflective of more independent errors and thus better bimanual performance. BHI was higher in older relative to younger age groups (main effect of AGE GROUP, Table 2, Fig. 5). Pairwise post hoc comparisons indicated significantly higher BHI scores in the older of each age group pair compared across all pairs (Supplementary Table ST2A). This suggests that decreases in bimanual performance start as early as middle age (MA1 group). Furthermore, BHI significantly increased as a function of task complexity (main effect of TASK CONDITION, Table 2, Fig. 5). Post hoc analyses indicate that BHI increased significantly between all pairs of task conditions (Line 1:1 < Angle, Line 1:1 < ZigZag, and Angle < ZigZag), even though this effect was less pronounced between Angle and ZigZag conditions (Supplementary Table ST2B). Finally, BHI increases with respect to task complexity were differentially affected by age (Table 2, Fig. 5). More specifically, relative to YA, BHI increased more from Line 1:1 to Angle or ZigZag conditions in the MA2 and OA groups (Supplementary Table ST2C). No interaction between age group and task complexity was observed between Angle and ZigZag conditions.

In summary, BHI increased in middle-aged and older adults, and such increase was more pronounced in complex relative to simpler task conditions. In late middle-aged and older adults, BHI increased more during the execution of both switching conditions relative to Line 1:1.

Effects of Age and Task Complexity on FC

Effects of Age Group

Increasing age was associated with significantly increased and decreased FC, both within and between networks (Fig. 6). In general, within-network FC was lower in older relative to younger age groups. Such age group-related decreases were observed in IVIS, CRB, TMP, cVIS, and DMN (Fig. 6, inside thick-lined squares). Age-related increases were observed within the STR/T, MOTOR, and CING networks.

With respect to between-network FC, connectivity between the DMN and remaining "cortical" (i.e., excluding CRB and STR/T) networks was generally higher in older relative to younger age groups. Age-related increased FC was also observed between cVIS and IVIS, STR/T, CRB, and CING networks. Further age-related increased between-network FC was observed between MOTOR and FPN. Finally, between the thalamus subcomponent of STR/T and other cortical networks, FC was generally higher in older relative to younger age groups (with the exception of the DMN and frontal opercular region of TMP). Conversely, FC between the DMN and the STR/T and CRB was lower in older relative to younger groups. Between the striatum (part of STR/T) and FPN, CING, and TMP networks, we observed an age-related decrease in FC. Finally, FC between TMP and MOTOR, IVIS, and

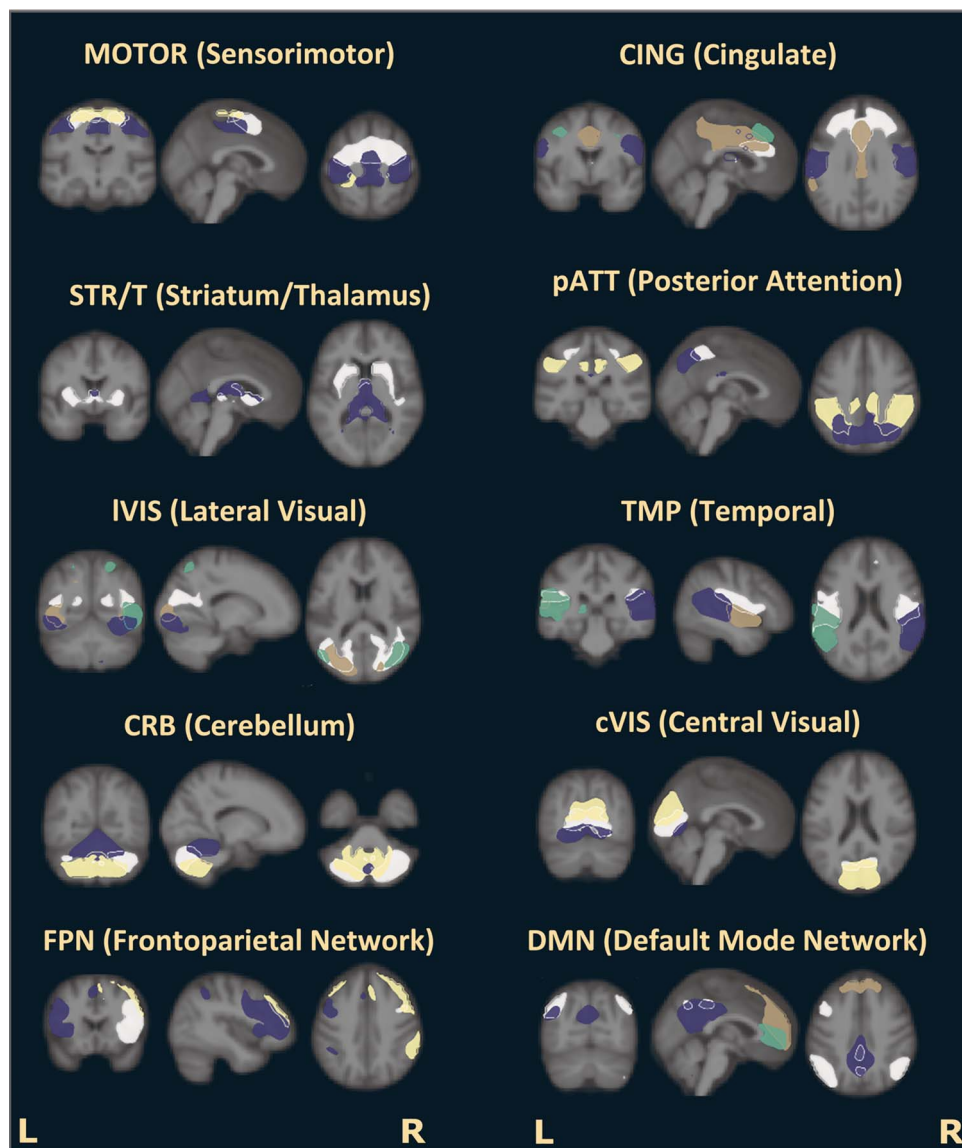


Figure 4. Identified functional networks overlaid on the sample-specific MNI template. Each network is identified by a representative name (in parenthesis) and abbreviation. Components within the same network are represented by a single filled contour color. Components are thresholded at the 99% percentile level for visualization purposes. More detailed information about components and networks is reported in [Supplementary Table ST1](#).

CRB networks was overall lower in older relative to younger age groups.

Notably, age-related differences in between-network connectivity were not consistent across all network pairs. More specifically, between specific pairs of networks, we observed both age-related increased and decreased FC (depending on network subcomponents). Such heterogeneous age-related differences in FC were observed among MOTOR, CING, and pATT networks. Similarly, age-related increased and decreased FC was observed between TMP network and CING, STR/T, and cVIS networks. Finally, FC between DMN, CING, and pATT networks showed heterogeneous age-related differences.

Altogether, our results indicate widespread and heterogeneous changes in task-related FC across age groups. In older relative to younger age groups, the emerging general picture is that within-network FC decreased, whereas between-network

FC increased (total within- and between-network FC are shown in [Supplementary Fig. S4](#)). For the purpose of completeness, pairwise age-group comparisons are depicted in [Supplementary Figure S5](#). In general, those analyses indicate that connectivity changed more sharply starting at early to late middle age and remained relatively stable afterward.

Effects of Task Complexity and Its Interaction with Age Group

Increasing task complexity was associated with widespread changes in connectivity across all networks ([Fig. 7A](#)). Complex relative to simpler task conditions were generally associated with higher FC within and between MOTOR, STR/T, and IVIS networks. Additionally, FC between those networks and CRB also increased as a function of task complexity, suggesting stronger communication among (visuomotor) task-relevant networks. Connectivity similarly increased between DMN, cVIS, and TMP,

Table 2 Effects of age groups and task complexity on BHI scores

Model						
BHI ~ age group × condition + (1 participant) + (1 rotation)						
F[3284] = 351.04 (P < 0.00001)						
Fixed effects (DF = 284)						
Name	Estimate	SE	Lower	Upper	t-Stat	P (corr)
Intercept	0.9907	0.1564	0.81	1.17	10.79	2.20e-22
Age group	0.1509	0.0258	0.10	0.20	5.86	1.28e-08
Condition	0.2256	0.0318	0.16	0.29	7.09	3.24e-11
Age group × condition	0.0815	0.0119	0.06	0.11	6.88	7.74e-11
Random effects						
Name	Estimate	Levels				
Participant	0.2215	96				
Rotation	0.2353	24				

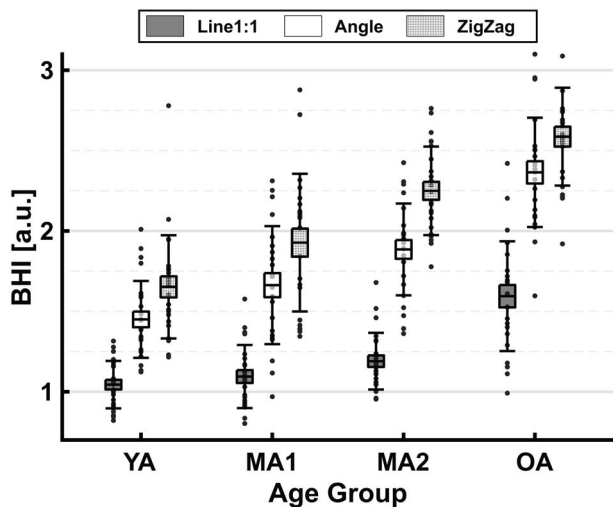


Figure 5. Between-hand mutual error for each age group and different task complexity levels. Horizontal black lines within boxes indicate average BHI, size of the vertically oriented colored rectangles depict the standard error from the mean, vertical black bars represent the standard deviation, and circles indicate individual BHI averages across trials.

as well as within DMN. Furthermore, FC between MOTOR, STR/T, CRB, and IVIS and remaining networks generally decreased as a function of increasing task complexity. Interestingly, FC between the precuneus component of the pATT and IVIS and MOTOR networks increased in higher relative to lower task complexity. Analogously, the fusiform gyrus area of the IVIS network became more connected to cVIS and DMN and less connected to MOTOR and remaining IVIS components.

The observed task complexity-related FC modulations were less prominent in older relative to younger age groups (Fig. 7B). It is important to emphasize that the interaction effects reported in this paragraph reflect stronger FC modulations in younger, but not older age groups. In the latter, FC remained relatively stable across task conditions pointing to reduced modulation. Nearly all FC pairs where a negative age × condition interaction effect (blue FC pairs in Fig. 7B) was observed (98.5% of

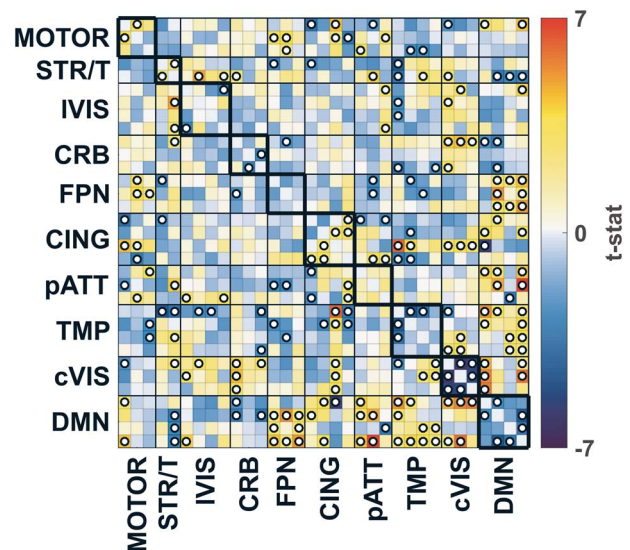


Figure 6. Effect of age group on FC. Within-network FC is represented in the thick-lined squares along the diagonal, the remaining pairs representing between-network FC. Blue colors indicate reduced connectivity in older relative to younger groups. Yellow-red colors represent increased connectivity in older relative to younger age groups. Pairs where we observed a significant effect of age group are marked with a white circle ($P_{FDR} < 0.05$).

FC pairs showing significant age group × condition interaction) corresponded to pairs where we detected increased FC in more complex task variants. Likewise, all positive (red FC pairs in Fig. 7B) interaction effects corresponded to pairs where we observed a negative main effect of task complexity. In conjunction, this indicates overall reduced modulation in older relative to younger age groups (see also Supplementary Figs S6 and S7). In more detail, among visuomotor-related networks (MOTOR, IVIS, CRB, STR/T), task complexity-related FC increases were less pronounced in older relative to younger age groups. A similar age-related effect was observed between cVIS and the DMN. Task complexity-related decreases in FC between the set of visuomotor networks (MOTOR, IVIS, and STR/T) and nonvisuomotor networks (cVIS/DMN) were generally lower in older relative to younger age groups. Age-related reduced FC

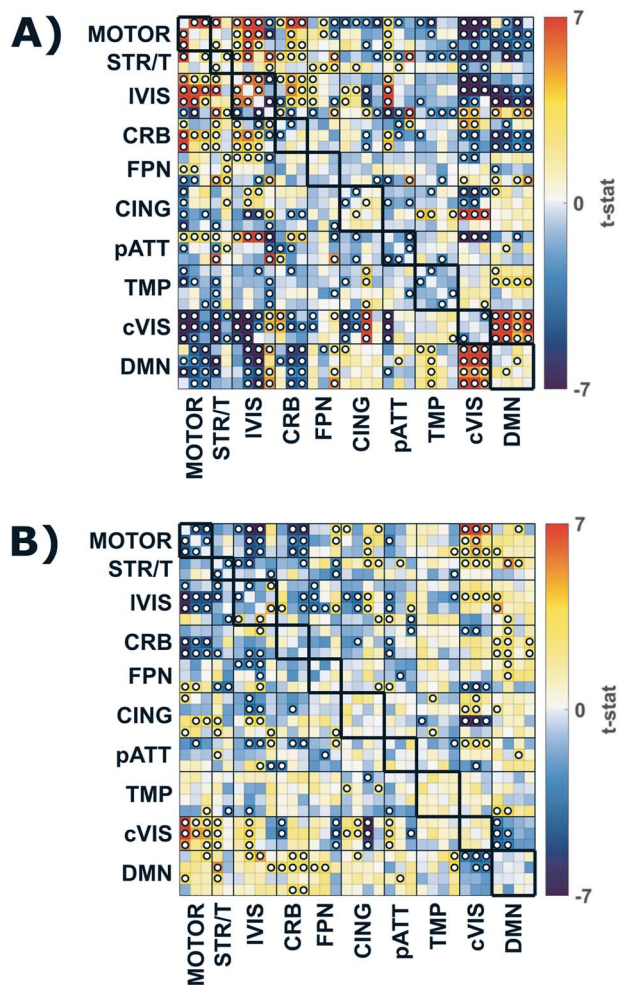


Figure 7. Connectivity changes relative to (A) task complexity conditions and (B) the interaction between task condition and age group. (A) Red colors indicate task complexity-related increased connectivity. In (B), blue colors indicate less task complexity-related increased FC in older relative to younger age groups. In both panels, pairs where we observed a significant effect are marked with a white circle ($P_{FDR} < 0.05$).

modulation (positive and negative) was also observed between visuomotor-related networks and FPN, CING, and pATT.

Altogether, our results indicate complexity-related increased connectivity among networks typically involved in visuomotor tasks. The set of visuomotor-related networks became less connected to (i.e., more segregated from) other networks during the execution of more complex task variants. Such FC modulation (both positive and negative) was less pronounced in older relative to younger age groups.

FC Modulation and Its Association with Bimanual Task Performance

Here, we were interested in studying how FC modulation mediated age-related changes in the ability to cope with increasing motor task demands. As we observed both increased and decreased FC associated with task complexity (see results reported in Effects of Age and Task Complexity on FC), we performed the mediation analysis outlined in section Mediation Analysis separately for positive and negative age-group \times

task condition interaction effects on FC. More specifically, we divided FC modulation into positive (FC pairs where complexity-related increase in magnitude was positive) and negative (FC pairs where complexity-related increase in magnitude was negative). In both positive and negative FC groups, we selected those where we observed significant age \times task complexity interaction effects. By selecting those FC pairs, we aimed to investigate whether the observed age-related differences in FC modulation were linked with motor performance.

In the case of age-task-positive modulation, we observed a significant association (after controlling for age group, number of rotations, and motion spikes) between FC modulation and lower relative BHI increase between Line 1:1 and Angle conditions ($r = -0.27$, $P = 0.0049$) (Fig. 8). More specifically, greater complexity-related increase in FC was associated with lower increase in BHI from Line 1:1 to Angle condition. A similar effect was observed between Line 1:1 and ZigZag condition ($r = -0.37$, $P = 0.0003$) but not between Angle and ZigZag conditions ($r = -0.10$, $P = 0.1375$). Analogously, larger complexity-related decrease in FC was associated with reduced error increase from Line 1:1 to ZigZag ($r = 0.32$, $P = 0.0001$) but not from Line 1:1 to Angle ($r = 0.17$, $P = 0.0616$) nor from Angle to ZigZag ($r = 0.19$, $P = 0.2177$) (Fig. 9).

Altogether, stronger FC modulation (positive or negative)—which is negatively affected by older age—was associated with better ability to cope with increasing task difficulty.

Discussion

We have provided evidence that older age is associated with increased FC dedifferentiation during the execution of a bimanual coordination task of varying degrees of complexity. Performing rotational switches was associated with widespread changes in FC relative to continuous movement. As age increased, network modulatory capacity decreased. Lower ability to modulate connectivity was linked to greater changes in BHI values (worse performance) associated with performing more complex bimanual coordination movements. In conjunction, our results indicate an age-related reduction in the ability to optimally modulate connectivity in response to task demands.

Reduced Ability to Cope with Bimanual Task Complexity as Age Increases

In the bimanual coordination task that we employed here, target rotational frequency was kept constant across all task variants for both limbs. Therefore, successful execution of the continuously moving hand depended, to a degree, on the ability to prevent interference from the contralateral hand, which performed a movement of similar or higher complexity (0, 1, or 4 rotational reversals). Our findings indicate that the amount of interference depended on the complexity of the bimanual movement pattern, that is, higher complexity led to a stronger association between errors from each hand. Our findings are in line with previous work showing decreased motor performance, indicative of reduced uncoupling of hands, as coordination complexity increased (Sisti et al. 2011).

Typically, as age increases, bimanual coordination quality decreases (see Maes et al. 2017 for a review). In agreement with current evidence, we observed a strong decrease in movement quality as age increased. Moreover, task complexity-related

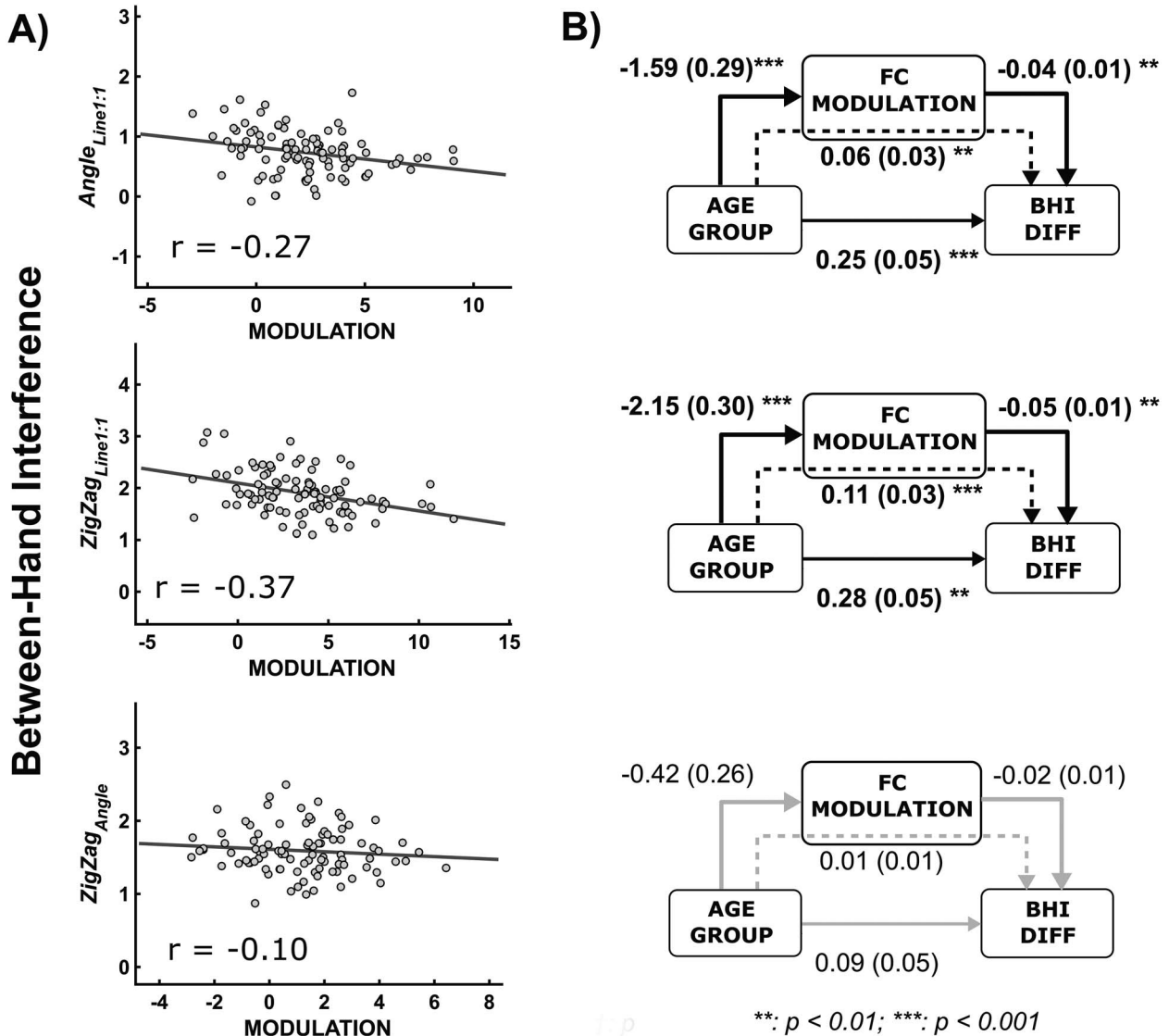


Figure 8. Mediation effect of positive FC modulation on age-related changes in BHI. (A) The scatter plots show the correlation between FC modulation and BHI after accounting for variance explained by age group, baseline condition (in subscript), number of rotations, and number of motion spikes. (B) Mediation path coefficients (a, b, c, and ab; see Figure 3) for each analyzed condition pair. The mediation effect of interest is depicted as a dashed line. Paths that did not reach statistical significance are shown in gray.

increase in BHI became more pronounced in older age groups, supporting the notion that older adults are less able to flexibly adapt to varying task demands (Swinnen et al. 1998; Ketcham et al. 2002; Goble et al. 2010). Altogether, older age was associated with less accurate motor behavior and reduced ability to adapt to increased coordination complexity. Particularly, middle-aged and older adults were less able to decouple hand movements in order to prevent switch-related disruptions of the contralateral continuous movement pattern, resulting in larger declines in motor performance.

Less-Differentiated Network Connectivity in Older Age

We were interested in investigating task complexity-related FC modulation and how it is affected by increasing age. Brain communication in older age typically undergoes a process termed

dedifferentiation, defined as a reduction in the specificity of brain activity representations (Park et al. 2001; Goh 2011; Ferreira et al. 2016). Within the framework of functional networks, an unspecific increase in between-network FC (e.g., unrelated to the successful execution of a task) is a prominent characteristic of dedifferentiation. Such altered FC pattern has been observed both at rest and during task execution (Damoiseaux et al. 2008; Dennis and Cabeza 2011; Bernard and Seidler 2014; Geerligs et al. 2014a; Damoiseaux 2017; King et al. 2018; Monteiro et al. 2019). In agreement with current literature, our findings indicate that older age was associated with less segregated networks, suggesting a less efficient network organization during the execution of bimanual motor tasks. Similar to our behavioral findings, significant effects of age on FC were observed already in the early middle-aged group. Initially gradual, those age-related differences in FC were accentuated in the oldest group.

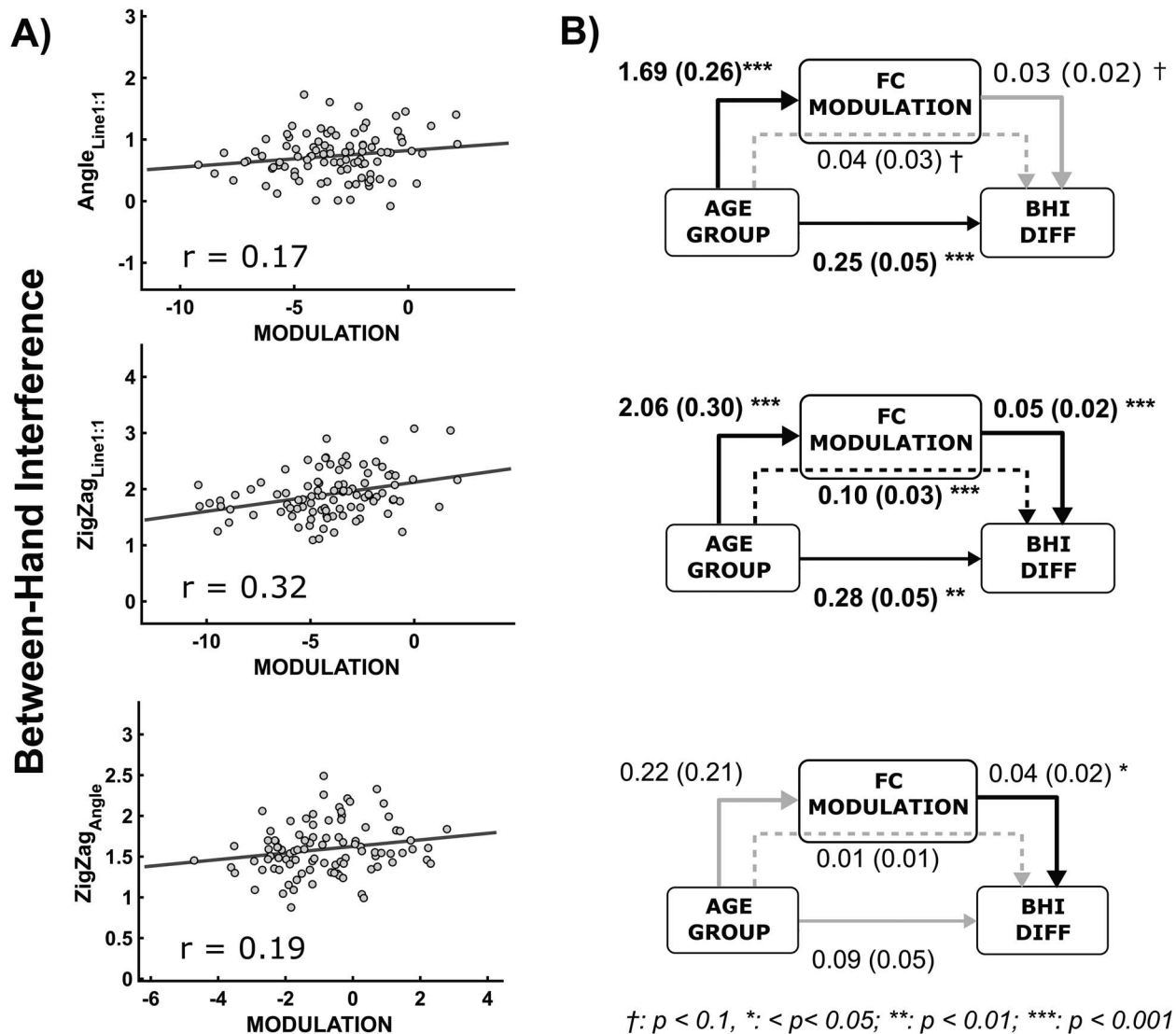


Figure 9. Mediation effect of negative FC modulation on age-related changes in BHI. (A) The scatter plots show the correlation between FC modulation and BHI after accounting for variance explained by age group, baseline condition (in subscript), number of rotations, and number of motion spikes. (B) Mediation path coefficients (a, b, c, and ab; see Figure 3) for each analyzed condition pair. The mediation effect of interest is depicted as a dashed line. Paths that did not reach statistical significance are shown in gray.

Aging Associated with Reduced Task Complexity-Related FC Modulation

We expected that relatively more complex task variants would require stronger communication among task-related networks. Indeed, we observed strong complexity-related FC modulation. More specifically, FC increased among the motor, lateral visual, frontoparietal, and subcortical networks. Brain areas encompassed by these networks have previously been shown to be active during complex bimanual behavior (Coxon et al. 2010; Ronsse et al. 2011; Beets et al. 2015; Chalavi et al. 2018). At the same time, connectivity between this set of networks and default mode and central visual networks decreased during the execution of relatively more complex task variants. Albeit to a lesser extent, a similar reduction in inter-network FC was observed in temporal and (frontal) parts of the cingulate network. Typically, these networks are not associated with functions required for the performance of a visually guided bimanual

movement. In conjunction, our findings indicate that higher motor complexity requirements were associated with stronger task-related visuomotor network communication, as well as higher segregation from remaining networks.

Importantly, the observed changes in network configuration during the execution of relatively more complex coordination tasks (i.e., task-related FC modulation) were impaired with aging, starting already at early middle age. Previously, reduced modulatory capacity in older age had been observed among networks involved in multiple cognitive tasks (Geerligts et al. 2014b). Our findings expand the current understanding of how task-related modulation takes place across the whole brain during the performance of bimanual tasks with varying complexity requirements. Furthermore, the general reduction in network segregation at the task-related network group level is in line with previous work demonstrating that older age is typically associated with reduced segregation between distinct brain

functional systems during resting state (Chan et al. 2014; Soleis-Jofre et al. 2014; La et al. 2015; Ferreira et al. 2016; King et al. 2018). These age-related differences in connectivity patterns may be reflective of, and consistent with, the dedifferentiation hypothesis of aging (Cabeza et al. 2018). At the neurochemical level, age-related dedifferentiation of network connectivity has been linked to reduced inhibitory capacity in older adults (Cassady et al. 2019). More specifically, lower levels of γ -aminobutyric acid (GABA; inhibitory neurotransmitter) have been linked to higher connectivity between default mode and control (prefrontal) networks (Chen et al. 2019). Besides reduced GABA levels, older age has been associated with lower glutamate (excitatory neurotransmitter) levels (Suri et al. 2017). Altered glutamate and GABA levels have been associated with reduced connectivity within the default mode network (Kapogiannis et al. 2013) and reduced DMN deactivation during a working memory task (Hu et al. 2013). Our findings showing altered FC patterns in older adults, especially in the DMN, are consistent with those studies showing an association between age-related changes in neurochemical levels and FC. Consequently, the differences in FC related to aging and task complexity observed here might reflect imbalances in the inhibitory and excitatory mechanisms taking place with increasing age. Importantly, additional exploratory analyses controlling for gender suggested that this process is largely similar between men and women.

Altogether, our findings provide further evidence that increasing age is associated with less-differentiated functional networks and reduced capacity to reorganize those networks flexibly in response to increasing task demands.

Less Optimal FC Features Linked to Higher BHI

We expected that connectivity modulation would be indicative of flexible network engagement in response to task demands and, consequently, be beneficial for the successful execution of the required bimanual task. As such, we hypothesized that age-related impairments in FC modulatory capability would be associated with higher increases in BHI when performing complex relative to simpler task conditions. In line with our hypothesis, we observed that weaker positive and negative FC modulation mediated higher increases in relative BHI between Line 1:1 and the more complex conditions. Those results underline the behavioral relevance of FC modulation, especially in highly demanding motor tasks. However, it is noteworthy that the mediation model employed here is unable to compare mediators (see Methodological Considerations). Thus, we avoid differentiating Angle and ZigZag conditions, as well as upmodulation and downmodulation of connectivity.

Altogether, reduced ability to modulate FC and higher BHI scores provides further evidence for the view that the age-related reduction in task specificity of neural communication is generally associated with poorer task performance. More specifically, we have shown that the less differentiated the connectivity patterns between conditions are, the stronger the task complexity-related increase in error (BHI) is. Successful performance of the more complex task variants in this study is contingent on inhibiting/suppressing interference from the switching hand onto the continuously moving hand. As such, it is likely that the mediation effect of FC on BHI, as observed here, is linked to imbalances in inhibitory/excitatory systems in the brain, leading to reduced capacity to both modulate network connections and inhibit interhand interference in older adults,

although further studies are required to specifically investigate this link.

Methodological Considerations

Mediation analysis is a powerful statistical tool to analyze the relationship among multiple variables, though it is important to be mindful of its limitations. There is enough empirical evidence to believe that FC strength is indeed one of many mediators of age-related changes in motor behavior. Nonetheless, the mediation analysis toolset provides information, in the simplest case, about the 3-way relationship among variables but does not provide any method to test whether FC modulation is truly a mediator (Fiedler et al. 2011). It also provides no test to identify whether one particular mediator is better suited than other potential candidates. Widespread functional and structural changes take place in older age. There is a strong interplay among those changes and between them and motor behavior changes in aging. Consequently, our results must be interpreted conservatively in terms of how much they explain the relationship between age, brain function, and performance. In spite of those limitations, mediation analysis can provide valuable information about changes in functional network characteristics and their impact on bimanual motor performance.

Age-related differences in bimanual coordination are likely a consequence of multiple interacting factors. In the present task, bimanual movements were performed while visually tracking a moving dot on a screen. Previous research has indicated that increasing age is associated with higher deviations from target during visual tracking (Maruta et al. 2017). Furthermore, during saccadic eye movements, older relative to younger and middle-aged adults showed reduced posterior–anterior functional activity differentiation (Raemaekers et al. 2006). It is worth explicitly stating that eye movement information was not collected in the current study, and thus, additional research is necessary to disambiguate visual from motor effects in the age-related differences in bimanual visuomotor task performance.

Conclusion

Here, we have shown that age-related reduction in connectivity modulation mediates lower motor performance (i.e., higher BHI during the execution of complex bimanual coordination tasks). This effect is presumably related to reduced recruitment of inhibitory control mechanisms in older adults. Importantly, starting already at early middle age, we observe increased functional dedifferentiation between networks and across task complexity levels. Further investigation is warranted, however, to elucidate the various underlying mechanisms of those age-related changes in network modulation during the performance of complex motor tasks.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Conflict of Interest

The authors declare no competing interests.

References

- Abraham A, Pedregosa F, Eickenberg M, Gervais P, Muller A, Kossaifi J, Gramfort A, Thirion B, Varoquaux G. 2014. *Machine Learning for Neuroimaging with Scikit-Learn*. *Front Neuroinform.* 8:14.
- Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage.* 54:2033–2044.
- Avants BB, Tustison NJ, Stauffer M, Song G, Wu B, Gee JC. 2014. The insight Toolkit image registration framework. *Front Neuroinform.* 8:44.
- Baldassarre A, Corbetta M. 2015. Resting state network changes in aging and cognitive decline. *Hear Balance Commun.* 13:58–64.
- Bangert AS, Reuter-Lorenz PA, Walsh CM, Schachter AB, Seidler RD. 2010. Bimanual coordination and aging: neurobehavioral implications. *Neuropsychologia.* 48:1165–1170.
- Beets IAM, Gooijers J, Boisgontier MP, Pauwels L, Coxon JP, Wittenberg G, Swinnen SP. 2015. Reduced neural differentiation between feedback conditions after bimanual coordination training with and without augmented visual feedback. *Cereb Cortex.* 1991. 25:1958–1969.
- Benjamini Y, Hochberg Y. 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol.* 57:289–300.
- Bernard JA, Peltier SJ, Wiggins JL, Jaeggi SM, Buschkuhl M, Fling BW, Kwak Y, Jonides J, Monk CS, Seidler RD. 2013. Disrupted cortico-cerebellar connectivity in older adults. *Neuroimage.* 83:103–119.
- Bernard JA, Seidler RD. 2014. Moving forward: age effects on the cerebellum underlie cognitive and motor declines. *Neurosci Biobehav Rev.* 42:193–207.
- Braun U, Schäfer A, Walter H, Erk S, Romanczuk-Seiferth N, Haddad L, Schweiger JI, Grimm O, Heinz A, Tost H et al. 2015. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. *Proc Natl Acad Sci U. S. A.* 112:11678–11683.
- Cabeza R, Albert M, Belleville S, Craik FIM, Duarte A, Grady CL, Lindenberger U, Nyberg L, Park DC, Reuter-Lorenz PA et al. 2018. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat Rev Neurosci.* 19:701–710.
- Cassady K, Gagnon H, Lalwani P, Simmonite M, Foerster B, Park D, Peltier SJ, Petrou M, Taylor SF, Weissman DH et al. 2019. Sensorimotor network segregation declines with age and is linked to GABA and to sensorimotor performance. *Neuroimage.* 186:234–244.
- Chalavi S, Adab HZ, Pauwels L, Beets IAM, van Ruitenbeek P, Boisgontier MP, Monteiro TS, Maes C, Sunaert S, Swinnen SP. 2018. Anatomy of subcortical structures predicts age-related differences in skill acquisition. *Cereb Cortex.* 28:459–473.
- Chan MY, Park DC, Savalia NK, Petersen SE, Wig GS. 2014. Decreased segregation of brain systems across the healthy adult lifespan. *Proc Natl Acad Sci.* 111:E4997–E5006.
- Chen X, Fan X, Hu Y, Zuo C, Whitfield-Gabrieli S, Holt D, Gong Q, Yang Y, Pizzagalli DA, Du F et al. 2019, 1991. Regional GABA concentrations modulate inter-network resting-state functional connectivity. *Cereb Cortex.* 29:1607–1618.
- Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, Shinohara RT, Elliott MA, Eickhoff SB, Davatzikos C et al. 2017. Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *NeuroImage, Cleaning up the fMRI time series: Mitigating noise with advanced acquisition and correction strategies.* 154:174–187.
- Cox RW. 1996. AFNI: software for analysis and visualization of functional magnetic resonance Neuroimages. *Comput Biomed Res.* 29:162–173.
- Coxon JP, Goble DJ, Van Impe A, De Vos J, Wenderoth N, Swinnen SP. 2010. Reduced basal ganglia function when elderly switch between coordinated movement patterns. *Cereb Cortex.* 1991. 20:2368–2379.
- Damoiseaux JS. 2017. Effects of aging on functional and structural brain connectivity. *NeuroImage, Functional Architecture of the Brain.* 160:32–40.
- Damoiseaux JS, Beckmann CF, Arigita EJS, Barkhof F, Scheltens P, Stam CJ, Smith SM, RB RS A. 2008. Reduced resting-state brain activity in the “default network” in normal aging. *Cereb Cortex.* 18:1856–1864.
- Daubechies I, Roussos E, Takerkart S, Benharrosh M, Golden C, D’Ardenne K, Richter W, Cohen JD, Haxby J. 2009. Independent component analysis for brain fMRI does not select for independence. *Proc Natl Acad Sci U. S. A.* 106:10415–10422.
- Dennis NA, Cabeza R. 2011. Age-related dedifferentiation of learning systems: an fMRI study of implicit and explicit learning. *Neurobiol Aging.* 32:2318.e17–2318.e30.
- Ferreira LK, Busatto GF. 2013. Resting-state functional connectivity in normal brain aging. *Neurosci Biobehav Rev.* 37:384–400.
- Ferreira LK, Regina ACB, Kovacevic N, Martin M da GM, Santos PP, Carneiro C de G, Kerr DS, Amaro E, McIntosh AR, Busatto GF. 2016. Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. *Cereb Cortex.* 26:3851–3865.
- Fiedler K, Schott M, Meiser T. 2011. What mediation analysis can (not) do. *J Exp Soc Psychol.* 47:1231–1236.
- Geerligs L, Maurits NM, Renken RJ, Lorist MM. 2014a. Reduced specificity of functional connectivity in the aging brain during task performance. *Hum Brain Mapp.* 35:319–330.
- Geerligs L, Saliassi E, Renken RJ, Maurits NM, Lorist MM. 2014b. Flexible connectivity in the aging brain revealed by task modulations. *Hum Brain Mapp.* 35:3788–3804.
- Goble DJ, Coxon JP, Van Impe A, De Vos J, Wenderoth N, Swinnen SP. 2010. The neural control of bimanual movements in the elderly: brain regions exhibiting age-related increases in activity, frequency-induced neural modulation, and task-specific compensatory recruitment. *Hum Brain Mapp.* 31:1281–1295.
- Goh JOS. 2011. Functional dedifferentiation and altered connectivity in older adults: neural accounts of cognitive aging. *Aging Dis.* 2:30–48.
- Gooijers J, Caeyenberghs K, Sisti HM, Geurts M, Heitger MH, Leemans A, Swinnen SP. 2013. Diffusion tensor imaging metrics of the corpus callosum in relation to bimanual coordination: effect of task complexity and sensory feedback. *Hum Brain Mapp.* 34:241–252.
- Heitger MH, Goble DJ, Dhollander T, Dupont P, Caeyenberghs K, Leemans A, Sunaert S, Swinnen SP. 2013. Bimanual motor coordination in older adults is associated with increased functional brain connectivity – a graph-theoretical analysis. *PLoS One.* 8:e62133.

- Hu Y, Chen X, Gu H, Yang Y. 2013. Resting-state glutamate and GABA concentrations predict task-induced deactivation in the default mode network. *J Neurosci Off J Soc Neurosci*. 33:18566–18573.
- Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. 2012. FSL. *Neuroimage*, 20 YEARS OF fMRI. 62:782–790.
- Johnstone T, Walsh KSO, Greischar LL, Alexander AL, Fox AS, Davidson RJ, Oakes TR. 2006. Motion correction and the use of motion covariates in multiple-subject fMRI analysis. *Hum Brain Mapp*. 27:779–788.
- Kapogiannis D, Reiter DA, Willette AA, Mattson MP. 2013. Posteromedial cortex glutamate and GABA predict intrinsic functional connectivity of the default mode network. *Neuroimage*. 64:112–119.
- Ketcham CJ, Seidler RD, Van Gemmert AWA, Stelmach GE. 2002. Age-related kinematic differences as influenced by task difficulty, target size, and movement amplitude. *J Gerontol B Psychol Sci Soc Sci*. 57:P54–P64.
- King BR, van Ruitenbeek P, Leunissen I, Cuypers K, Heise K-F, Santos Monteiro T, Hermans L, Levin O, Albouy G, Mantini D et al. 2018, 1991. Age-related declines in motor performance are associated with decreased segregation of large-scale resting state brain networks. *Cereb Cortex*. 28:4390–4402.
- Koen JD, Rugg MD. 2019. Neural dedifferentiation in the aging brain. *Trends Cogn Sci*. 23:547–559.
- Krehbiel LM, Kang N, Cauraugh JH. 2017. Age-related differences in bimanual movements: a systematic review and meta-analysis. *Exp Gerontol*. 98:199–206.
- La C, Mossahebi P, Nair VA, Bendlin BB, Birn R, Meyerand ME, Prabhakaran V. 2015. Age-related changes in inter-network connectivity by component analysis. *Front Aging Neurosci*. 7:237.
- Levin O, Weerasekera A, King BR, Heise KF, Sima DM, Chalavi S, Maes C, Peeters R, Sunaert S, Cuypers K et al. 2019. Sensorimotor cortex neurometabolite levels as correlate of motor performance in normal aging: evidence from a 1H-MRS study. *Neuroimage*. 202:116050.
- Li J, Kong R, Liégeois R, Orban C, Tan Y, Sun N, Holmes AJ, Sabuncu MR, Ge T, Yeo BTT. 2019. Global signal regression strengthens association between resting-state functional connectivity and behavior. *Neuroimage*. 196:126–141.
- MacKinnon DP, Fairchild AJ, Fritz MS. 2007. Mediation analysis. *Annu Rev Psychol*. 58:593.
- Madden DJ, Costello MC, Dennis NA, Davis SW, Shepler AM, Spaniol J, Bucur B, Cabeza R. 2010. Adult age differences in functional connectivity during executive control. *Neuroimage*. 52:643–657.
- Maes C, Gooijers J, Orban de Xivry J-J, Swinnen SP, Boisgontier MP. 2017. Two hands, one brain, and aging. *Neurosci Biobehav Rev*. 75:234–256.
- Maruta J, Spielman LA, Rajashekar U, Ghajar J. 2017. Visual tracking in development and aging. *Front Neurol*. 8:640.
- Mensch A, Varoquaux G, Thirion B. 2016. Compressed online dictionary learning for fast resting-state fMRI decomposition. In: 2016 IEEE 13th International Symposium on Biomedical Imaging (ISBI). Presented at the 2016 IEEE 13th International Symposium on Biomedical Imaging (ISBI). p. 1282–1285.
- Monteiro TS, Beets IAM, Boisgontier MP, Gooijers J, Pauwels L, Chalavi S, King B, Albouy G, Swinnen SP. 2017. Relative cortico-subcortical shift in brain activity but preserved training-induced neural modulation in older adults during bimanual motor learning. *Neurobiol Aging*. 58:54–67.
- Monteiro TS, King BR, Zivari Adab H, Mantini D, Swinnen SP. 2019. Age-related differences in network flexibility and segregation at rest and during motor performance. *Neuroimage*. 194:93–104.
- Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage*. 44:893–905.
- Murphy K, Fox MD. 2017. Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *Neuroimage*. 154:169–173.
- Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. 2005. The Montreal cognitive assessment, Moca: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 53:695–699.
- Newman MEJ. 2006. Finding community structure in networks using the eigenvectors of matrices. *Phys Rev E*. 74:036104.
- Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 9:97–113.
- Park DC, Polk TA, Mikels JA, Taylor SF, Marshuetz C. 2001. Cerebral aging: integration of brain and behavioral models of cognitive function. *Dialogues Clin Neurosci*. 3:151–165.
- Parker D, Liu X, Razlighi QR. 2017. Optimal slice timing correction and its interaction with fMRI parameters and artifacts. *Med Image Anal*. 35:434–445.
- Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage*. 84:320–341.
- Raemaekers M, Vink M, van den Heuvel MP, Kahn RS, Ramsey NF. 2006. Effects of aging on BOLD fMRI during Prosaccades and Antisaccades. *J Cogn Neurosci*. 18:594–603.
- Ronsse R, Puttemans V, Coxon JP, Goble DJ, Wagemans J, Wenderoth N, Swinnen SP. 2011. Motor learning with augmented feedback: modality-dependent behavioral and neural consequences. *Cereb Cortex*. 21:1283–1294.
- Saad ZS, Gotts SJ, Murphy K, Chen G, Jo HJ, Martin A, Cox RW. 2012. Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. *Brain Connect*. 2:25–32.
- Sambataro F, Murty VP, Callicott JH, Tan H-Y, Das S, Weinberger DR, Mattay VS. 2010. Age-related alterations in default mode network: impact on working memory performance. *Neurobiol Aging*. 31:839–852.
- Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, Kwak Y, Lipps DB. 2010. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev*. 34:721–733.
- Serbruyns L, Gooijers J, Caeyenberghs K, Meesen RL, Cuypers K, Sisti HM, Leemans A, Swinnen SP. 2013. Bimanual motor deficits in older adults predicted by diffusion tensor imaging metrics of corpus callosum subregions. *Brain Struct Funct*. 220:273–290.
- Serrien DJ, Swinnen SP, Stelmach GE. 2000. Age-related deterioration of coordinated interlimb behavior. *J Gerontol Ser B*. 55:P295–P303.
- Sisti HM, Geurts M, Clerckx R, Gooijers J, Coxon JP, Heitger MH, Caeyenberghs K, Beets IAM, Serbruyns L, Swinnen SP. 2011. Testing multiple coordination constraints with a novel bimanual visuomotor task. *PLoS One*. 6:e23619.
- Solesio-Jofre E, Beets IAM, Woolley DG, Pauwels L, Chalavi S, Mantini D, Swinnen SP. 2018. Age-dependent modulations

- of resting state connectivity following motor practice. *Front Aging Neurosci.* 10.
- Solesio-Jofre E, Serbruyns L, Woolley DG, Mantini D, Beets IAM, Swinnen SP. 2014. Aging effects on the resting state motor network and interlimb coordination. *Hum Brain Mapp.* 35:3945–3961.
- Spreng RN, Stevens WD, Viviano JD, Schacter DL. 2016. Attenuated anticorrelation between the default and dorsal attention networks with aging: evidence from task and rest. *Neurobiol Aging.* 45:149–160.
- Suri S, Emir U, Stagg CJ, Near J, Mекle R, Schubert F, Zsoldos E, Mahmood A, Singh-Manoux A, Kivimäki M et al. 2017. Effect of age and the APOE gene on metabolite concentrations in the posterior cingulate cortex. *Neuroimage.* 152:509–516.
- Swinnen SP, Verschueren SM, Bogaerts H, Dounskaia N, Lee T, Stelmach GE, Serrien DJ. 1998. Age-related deficits in motor learning and differences in feedback processing during the production of a bimanual coordination pattern. *Cogn Neuropsychol.* 15:439–466.
- Varoquaux G, Gramfort A, Pedregosa F, Michel V, Thirion B. 2011. Multi-subject dictionary learning to segment an atlas of brain spontaneous activity. In: Székely G, Hahn HK, editors. *Information processing in medical imaging. Lecture notes in computer science.* Berlin Heidelberg: Springer, pp. 562–573.
- Varoquaux G, Sadaghiani S, Pinel P, Kleinschmidt A, Poline JB, Thirion B. 2010. A group model for stable multi-subject ICA on fMRI datasets. *Neuroimage.* 51:288–299.
- Vatansever D, Menon DK, Manktelow AE, Sahakian BJ, Stamatakis EA. 2015. Default mode network connectivity during task execution. *Neuroimage.* 122:96–104.
- Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. 2008. Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron.* 59:1037–1050.
- Wager TD, Waugh CE, Lindquist M, Noll DC, Fredrickson BL, Taylor SF. 2009. Brain mediators of cardiovascular responses to social threat: part I: reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage.* 47:821–835.
- Wishart LR, Lee TD, Murdoch JE, Hodges NJ. 2000. Effects of aging on automatic and effortful processes in bimanual coordination. *J Gerontol - Ser B Psychol Sci Soc Sci.* 55: P85–P94.
- Yan JH. 2000. Effects of aging on linear and curvilinear aiming arm movements. *Exp Aging Res.* 26:393–407.