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Age-related differences in network flexibility and segregation at rest and during motor performance

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ABSTRACT

Brain networks undergo widespread changes in older age. A large body of knowledge gathered about those changes evidenced an increase of functional connectivity between brain networks. Previous work focused mainly on cortical networks during the resting state. Subcortical structures, however, are of critical importance during the performance of motor tasks. In this study, we investigated age-related changes in cortical, striatal and cerebellar functional connectivity at rest and its modulation by motor task execution. To that end, functional MRI from twenty-five young (mean age 21.5 years) and eighteen older adults (mean age 68.6 years) were analysed during rest and while performing a bimanual tracking task practiced over a two-week period. We found that inter-network connectivity among cortical structures was more positive in older adults both during rest and task performance. Functional connectivity within striatal structures decreased with age during rest and task execution. Network flexibility, the changes in network composition from rest to task, was also reduced in older adults, but only in networks with an age-related increase in connectivity. Finally, flexibility of areas in the prefrontal cortex were associated with lower error scores during task execution, especially in older adults. In conclusion, our findings indicate an age-related reduction in the ability to suppress irrelevant network communication, leading to less segregated and less flexible cortical networks. At the same time, striatal connectivity is impaired in older adults, while cerebellar connectivity shows heterogeneous age-related effects during rest and task execution. Future research is needed to clarify how cortical and subcortical connectivity changes relate to one another.

1. Introduction

Older age is associated with widespread changes in motor function and its neural correlates. Reduced accuracy and speed are the dominant signatures of aging in the context of motor behavior (Seidler et al., 2010; Serbruyns et al., 2015, 2013; Solesio-Jofre et al., 2014). At the neural level, older adults typically display increased functional magnetic resonance imaging (fMRI) responses during motor task execution in comparison with younger adults (Goble et al., 2010; Heuninckx et al., 2005; Ward and Frackowiak, 2003). Increased neural recruitment, particularly in areas involved in cognitive processing, is sometimes associated with better motor performance within the older population, suggesting a compensatory role for this phenomenon (Heuninckx et al., 2008; Monteiro et al., 2017).

Temporal features of fMRI responses characterize a network description of brain activity (Biswal et al., 1995; Sporns et al., 2004). Functional networks have been observed to be organized in a cost-effective topology called ‘small-world’ (Latora and Marchiori, 2001; van den Heuvel et al., 2008). Typically in this organization, nodes within the same network are tightly connected (*intra*-network connectivity, representative of functional specialization) whereas communication between networks is comparatively sparser (representative of *inter*-network connectivity/functional integration). Recent resting state fMRI studies have demonstrated a prominent increase in inter-network functional connectivity (FC) in older adults (Chan et al., 2014; King et al., 2017; Solesio-Jofre et al., 2018). Furthermore, older adults show reduced specificity in brain responses to various tasks, and this reduced functional specialization is generally associated with lower behavioural

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performance (Damoiseaux, 2017; Goh, 2011). It is worth noting that while the majority of studies explored connectivity changes in cortical networks, cortico-cerebellar networks have also been shown to be disrupted in older adults (Bernard et al., 2013).

In addition to the age-related changes highlighted above, network organization adaptively changes to meet upcoming task demands, a result that is referred to as flexibility (Gallen et al., 2016; Hearne et al., 2017; Wen et al., 2015; Yeo et al., 2015). Older adults retain the ability to reconfigure brain networks to execute attention and working-memory tasks, although with lessened differentiation relative to task complexity in comparison with younger adults (Geerligs et al., 2014). The ability to flexibly modulate brain network organization has been shown to positively correlate with better learning of a sequential motor task in young adults (Bassett et al., 2011), but such reorganization relative to motor tasks has not been studied in older adults so far.

Altogether, current evidence suggests that aging affects both network segregation and flexibility. It is not yet known whether dedicated motor task practice can reduce the effects of aging on network organization. Furthermore, connectivity changes in subcortical structures and the cerebellum, which play a key role in the execution of complex motor tasks, have been investigated during rest (Bernard et al., 2013), but not during performance of tasks. This is indeed difficult to justify, as the basal ganglia and cerebellum play a critical role in a variety of behaviors, including motor, cognitive and perceptual tasks (Brunamonti et al., 2014; Chalavi et al., 2018; Doyon and Ungerleider, 2002; Timmann et al., 2010).

In the present study, we investigate functional connectivity during rest and during the execution of a complex bimanual task. Furthermore, we investigate the effect of practice on connectivity and network flexibility. Three research questions regarding age-related changes in functional connectivity are addressed:

I. Is the altered connectivity pattern seen during rest in older adults affected by task execution?

Integration between neural systems is required to successfully perform complex motor tasks.

We expect, therefore, inter-network connectivity to increase during task execution in relation to rest. In older relative to younger adults, inter-network connectivity is typically higher. Consequently, there might be less room for task-related connectivity modulation in older adults, indicating a functional ceiling in network communication. For this reason, we hypothesize that younger adults will show stronger modulation of functional connectivity and age-related inter-network connectivity differences will be smaller during task execution in relation to rest. Furthermore, we include cortical, striatal and cerebellar structures in our analyses in order to investigate whether subcortical and cerebellar FC is similarly affected by age as cortical FC.

II. Is the increase in inter-network FC observed in older adults associated with reduced flexibility?

The ability to reduce (inhibit) and strengthen connections between networks is a requirement to flexibly respond to task demands. During rest, older adults show functionally irrelevant increased between-network connectivity (i.e. decreased network segregation). We hypothesize that the inability to properly modulate connectivity during rest is representative of a broader reduction in network modulatory capability. Consequently, we expect that FC patterns in highly interconnected networks are less likely to exhibit change as a function of task demands, and thus can be considered less flexible in older adults.

III. What are the relationships between network flexibility, motor performance and practice?

The ability to flexibly alter network configuration is considered beneficial for the quality of task (motor) performance. Consequently, we anticipate that the ability to flexibly reorganize and modulate connectivity will be associated with lower error scores in a visuomotor task. Furthermore, we hypothesize that practice will lead to reinforcement of task-relevant connection patterns and suppression of task-irrelevant ones. We expect thus an increase in network segregation and flexibility after practice, especially in older adults in view of their increased inter-network FC during rest.

2. Methods and materials

2.1. Participants & task

Twenty-six young (YA) and twenty-five older (OA) adults took part in a multi-session bimanual motor skill training paradigm. Participants and task features have been previously described in detail (Monteiro et al., 2017) and are only briefly described here.

All participants (N = 51) were naïve with respect to the paradigm, had normal or corrected-to-normal vision, and were right-handed according to the Edinburgh Handedness inventory (Oldfield, 1971). All participants completed the Dutch version of the Montreal Cognitive Assessment test using a cut-off score of 26 (Nasreddine et al., 2005). One OA scored 24 and was excluded from the analysis. Three OA were excluded due to brain lesions or substantial atrophy, as identified by a trained neuroradiologist, and were also excluded from the analysis. Finally, three OA were excluded due to failure to comply with task instructions (i.e. consistently moving during 'no-move' trials, resulting thus in similar 'move' and 'no-move' performance). One YA was excluded due to a technical problem in the scanner during the last session. Consequently, 25 YA (21.5 ± 2.3 years old; 14 female) and 18 OA (68.6 ± 6.0 years old; 11 female) were finally included in the study. Participants were financially compensated and gave their informed consent prior to participation. The protocol was in accordance with the 1964 Declaration of Helsinki (World Medical Association, 2008).

Imaging data were acquired in two scan sessions (pre- and post-training sessions). Each session started with 8 min of resting-state functional magnetic resonance imaging (fMRI) followed by 6 blocks of task-related fMRI. During task execution, participants were instructed to perform a bimanual tracking task (BTT). The goal of this task was to track a target cursor on the screen by simultaneously rotating two dials (5 cm diameter) with both hands. In order to do so, a custom-made non-ferromagnetic device was placed over the participants' laps. Clockwise and counter-clockwise rotation of the left-hand dial moved the cursor upward and downward (along the Y-axis), respectively. Analogously, clockwise and counter-clockwise rotation of the right-hand dial controlled the cursor left and right (along the X-axis), respectively (Fig. 1A). Angular displacements were recorded from each dial using a non-ferromagnetic high precision optical shaft encoder (HP, 2048 pulses per revolution, 100 samples per second).

A total of 144 BTT trials (6 blocks of 24) were performed at each scanning session. Trials were divided in active 'move' (N = 96) and control 'no-move' trials (N = 48). Half of the trials in each group were augmented with simultaneous visual feedback. Finally, trials were divided in 5 distinct relative frequency ratios: 1:1, 1:2, 1:3, 2:1, 3:1 (left:right hand rotational frequency) (Fig. 1B). Trials were randomly distributed such that 1/3 of trials required 1:1 ratio, 1/3 required 1:2 or 2:1 and 1/3 required 1:3 or 3:1. Each frequency ratio indicates the number of revolutions performed by each hand. For instance, in a 1:2 frequency ratio, for each revolution performed by the left hand, the right hand must perform 2 rotations. To promote motor learning, participants practiced the task during 5 training epochs of 1 h each (distributed across 2 weeks) which were completed between both scanning sessions. Trial error was computed as the average Euclidean distance between user and target positions at each sampling point. Performance in each scan session was calculated as the average error across all trials. *Absolute* behavioural outcome was assessed with a 2 × 2 (AGE x SESSION) repeated-measures

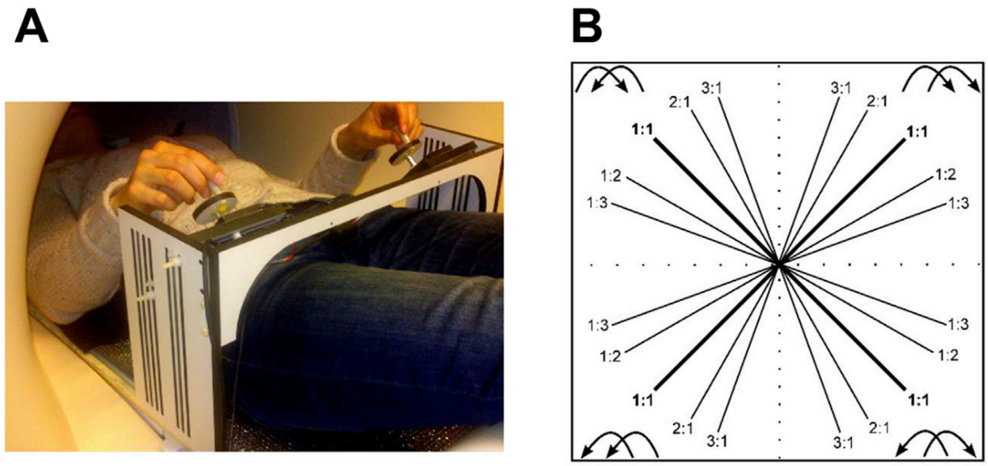

Fig. 1. Non-ferromagnetic apparatus used to record movements in the bimanual tracking task (A). Twenty possible coordination variations were used in the task (B). Importantly, multiple variants of the same frequency ratio are possible depending on rotation direction. Consequently, four target trajectories are possible for each frequency ratio: left-hand clockwise (CW) and right-hand counterclockwise (CCW), left-hand CW and right-hand CW, left-hand CCW and right-hand CW, and finally left-hand CCW and right-hand CCW. All trials were balanced across conditions (see main text).

ANOVA and *relative* improvement (defined as performance at post-training divided by performance at pre-training) was assessed with a one-way between-subject ANOVA. Only behavioural data from the pre- and post-training sessions were included in the analyses. The behavioural results regarding the 5 intermediate training sessions are described elsewhere (Chalavi et al., 2018; Monteiro et al., 2017).

2.2. Scan acquisition and data processing

Scans were acquired using a Siemens 3-T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with a 12-channel head coil. High-resolution 3-dimensional T1-weighted images were obtained for each participant (MPRAGE, repetition time [TR]/echo time [TE] = 2300/2.98 ms, $1 \times 1 \times 1.1$ mm voxels, field-of-view = 240×256, 160 sagittal slices). Afterwards, a field map was acquired to correct magnetic field distortions. Parameters for the T2-weighted 160 resting state blood-oxygen level dependent (BOLD)-fMRI scans and 6 blocks of 116 task-related BOLD-fMRI scans were identical. Descending gradient Echo-planar imaging (EPI) acquisition protocol was used (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^2, 80×80 matrix). The first 3 scans of each acquisition block (rest and task) were discarded to ensure steady-state magnetization.

Data were analysed using a combination of SPM12 (http://www.fil.ion.ucl.ac.uk/spm/), AFNI (Cox, 1996) and in-house developed scripts in Matlab R2015b (Mathworks, Natick, MI). Task-related blocks of fMRI scans were processed individually and then concatenated without inter-trial volumes. Processing procedure for resting-state and task-related scans was otherwise identical. Firstly, movement parameters were estimated, but not corrected. Data were then despiked using AFNI's *3dDespike* function and then realigned to the middle scan of each session using *3dvolreg*. Performing despike as a first step might improve realignment performance, though it might bias motion estimates (Power et al., 2017). Field inhomogeneity distortions were mitigated using SPM's Fieldmap functions and field map scans. Slice timing correction was performed according to the first slice (bottom) of each volume. EPI scans were then aligned to individual high resolution anatomical scans and normalised to the population specific template using DARTEL (2 mm^3 isovoxel, 5 mm FWHM Gaussian kernel smoothing). Cerebrospinal fluid (CSF) and white matter (WM) masks were extracted from the segmented T1-weighted scan and normalised to the population specific template. CSF and WM signals were extracted using principal component analysis on the corresponding masked functional data and selecting up to the first 5 components (2% explained variance cut-off). CSF and WM components, movement parameters (MP), squared MP, the first MP differential and their squared values, and linear trends were regressed from the functional data. BOLD time courses were filtered using a high pass 5th order Butterworth filter with 0.009 Hz cut-off. Finally, volumes where frame-wise displacement was greater than 0.5 mm or root mean squared intensity change was 50% above the median were excluded and linearly interpolated using surrounding volumes.

2.3. Network construction

Brain network nodes were defined using a previously calculated functional connectivity-based brain parcellation (Schaefer et al., 2018; Thomas Yeo et al., 2011). This scheme identifies 17 cortical functional networks in 7 coarse functional domains: visual, somatomotor, dorsal attention, ventral attention, limbic, executive, default-mode and temporo-parietal. This 17 network parcellation was further divided into 200 local parcels (Schaefer et al., 2018).[1] Importantly, to allow intra-network calculation, the two limbic networks were considered as a single network, resulting in 16 cortical networks. The striatum and cerebellum were also functionally divided according to their correspondence to the 17 functional cortical networks originally described by Yeo and colleagues (Buckner et al., 2011; Choi et al., 2012). Subcortical networks were not further subdivided into individual parcels within each network. Two subcortical nodes (Limbic B and DMN B) were excluded due to lack of coverage in the EPI scans, resulting in a total 15 striatal nodes. In total, the 200 cortical, 15 striatal and 17 cerebellar nodes amounted to 232 nodes representing typically observed resting-state. In order to validate the presence of the networks in the present data, we firstly computed Pearson's correlation coefficients among individual cortical parcels within each network (visual, somatomotor, dorsal attention, salience/ventral attention, limbic, executive, default-mode, and temporoparietal) and other parcels during resting state and task execution. The average network correlation coefficient was calculated and transformed to a z-score. As this procedure allows for overlapping networks, whenever an overlap occurs, the network was assigned to the spatial map with the highest z-value among all components.

In order to calculate connectivity between nodes, the first eigenvector based on the BOLD time course for each of the nodes were extracted. Connectivity strength between each pair of nodes was computed using Pearson's correlation, converted to z-scores using Fisher's r-to-z transform, resulting in a 232×232 weighted symmetric matrix (parcel level). One such matrix was computed for resting-state and task-related scans at pre- and post-training sessions, amounting to four connectivity matrices per participant.

We further grouped the 200 cortical nodes into their corresponding

[1] Obtained from https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal.

functional networks, resulting in a 48 × 48 weighted connectivity matrix (network level: 16 cortical, 15 striatal and 17 cerebellar nodes, as visualized in Fig. 2). The main diagonal at this level represents connectivity within networks (*intra*-network) and off-diagonal values depict between-network connectivity (*inter*-network). *Intra*-network connectivity was calculated only for cortical networks, as only those are sufficiently divided for such calculation.

Throughout this text, we use the term parcel to refer to each individual node within the 232 × 232 matrices and networks to refer to the nodes in the 48 × 48 matrices. Unless explicitly noted, the analyses presented were performed on network matrices.

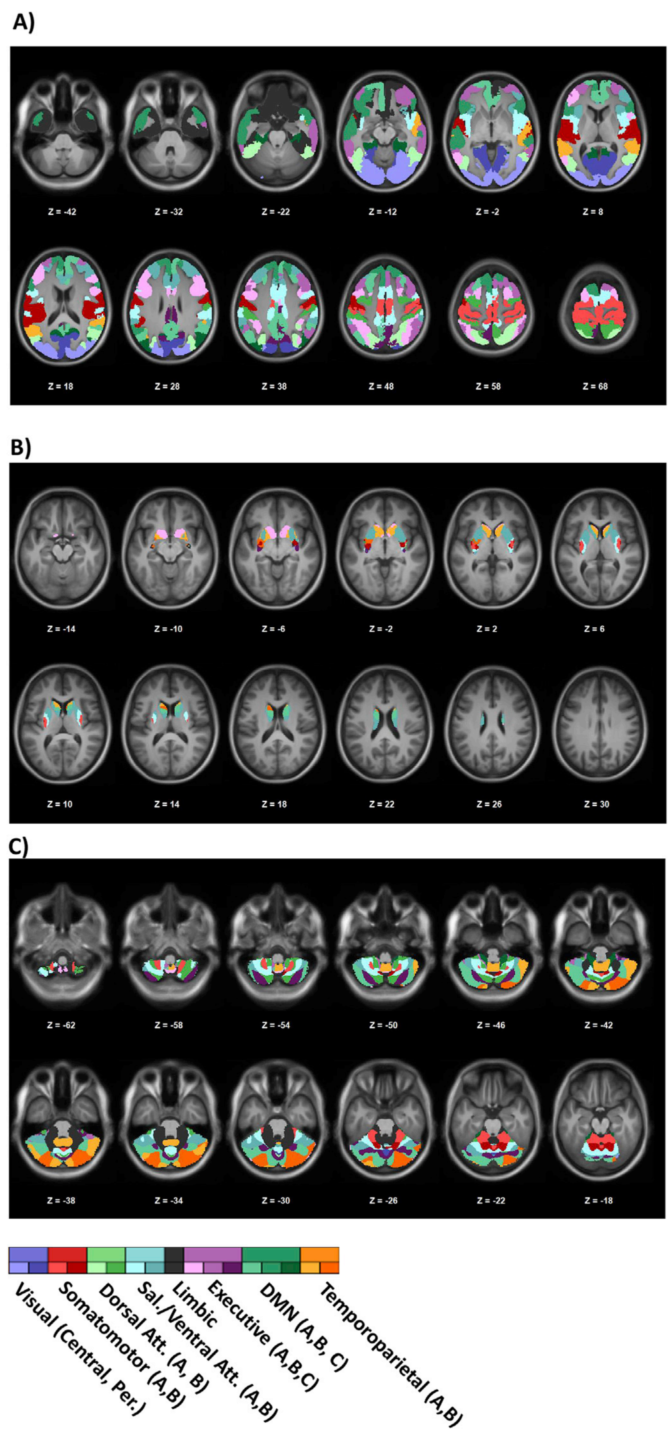

Fig. 2. Network parcellation of cortical (A), striatal (B), and cerebellar (C) regions at the network level.

2.4. Network analyses

Effects of age and task on functional connectivity were estimated on the network level using GraphVar v1.03 (Kruschwitz et al., 2015). Age and practice effects on connectivity were evaluated with an AGE [old, young] x SESSION [pre-training, post-training] model separately for rest and task-related-fMRI matrices at the network level (48 × 48 matrices). Statistical significance was calculated against a null distribution obtained using a permutation approach (10,000 group reassignments/iterations). False discovery rate (FDR) correction was applied to account for the multiple comparisons. It is important to emphasize that the comparisons performed in this manner distinguish arithmetic differences in connectivity, but not connection strength (e.g. a connection value of −0.1 might be significantly smaller than +0.1, although their absolute weight is the same).

Association between motor performance (average task error pre- and post-training) and connectivity was done within each age group at edge level (i.e. correlation between connectivity strength at each pair and task error) and at overall connectivity level (i.e. sum of connections per network correlated with task error). In both cases, we tested connectivity at rest, during task performance and the change in connectivity from rest to task.

Network flexibility analyses were performed using a combination of in-house scripts and the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). We defined flexibility as the change in network membership from individual parcels to meet task demands (node-network membership). To assess such change, we calculated the mutual information between network partitions at the parcel level (232 nodes) at rest and during task execution. Networks were defined using the Newmann's spectral community detection (Newman, 2006) separately for rest and task execution. In order to mitigate spurious connections, values below a specific cut-off threshold were discarded (Rubinov and Sporns, 2010). Cut-off thresholds ranged between 5% and 30% of the total number of edges in increments of 5%.

3. Results

3.1. Behavioural findings

Average tracking error was markedly higher among older adults [Main effect of AGE, $F(1,41) = 39.63$, $p < 0.00001$]. Error was reduced across both age groups following practice [$F(1,41) = 94.99$, $p < 0.00001$] and training-induced *absolute* performance improvements were even stronger in older adults [AGE × SESSION interaction, $F(1,41) = 16.75$, $p < 0.001$]. *Relative* improvement, however, was not different between age groups [$F(1,41) = 0.02$, $p = 0.88$]. This suggests a larger room for absolute error reduction in older adults, but a similar improvement rate relative to initial performance across age groups. Those results are in line with analyses performed on data drawn from the same group of participants (Chalavi et al., 2018; Monteiro et al., 2017).

3.2. Observed functional networks

We first sought to verify that the presence of the networks in the present dataset were comparable to those from the template used, and between age groups (Fig. 3). Critically, the networks obtained in the current study are comparable to those identified in previous literature (see Supplementary Material S1 for a more detailed report). It is important to point out that, when considered in isolation (i.e. one network at a time), visual and frontoparietal networks included additional regions that were not present in the template. Nonetheless, the observed network division provides a qualitative validation that functional networks, as defined in the template, are also present in the reported dataset.

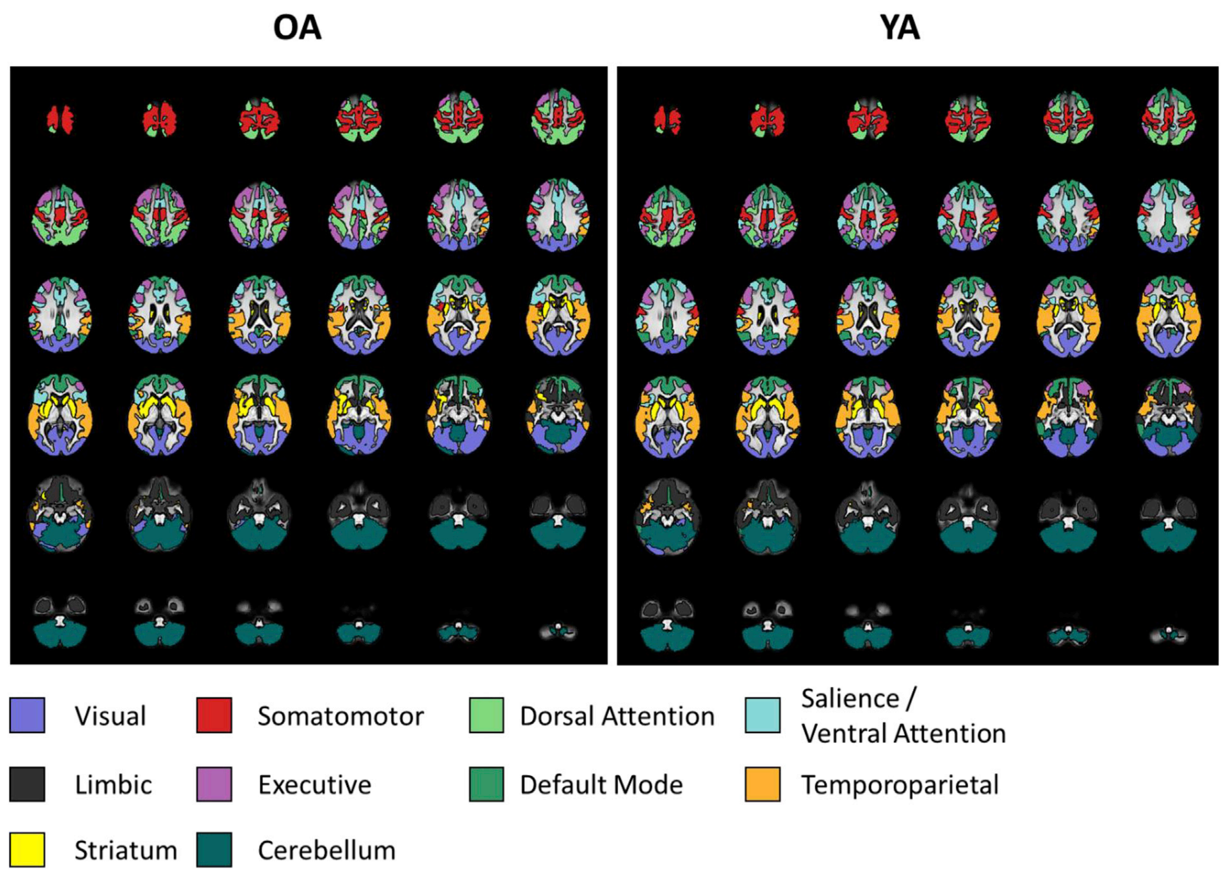

Fig. 3. Functional networks identified in each age group. Each colour represents a functional network as identified in the present dataset based on the 232 × 232 connectivity matrices.

3.3. No effects of practice on functional connectivity

We expected to see an overall reduction in task-irrelevant inter-network connectivity following the training intervention (i.e. 5 training days between pre- and post-scanning sessions) (see intro, hypothesis 3). We found, however, no significant session effect on resting state nor task-related functional connectivity. There was a general pattern of reduced cortical FC and increased subcortical/cerebellar task-related FC, but none of these results reached significance and therefore no further considerations were made. AGE × SESSION interactions were similarly not significant. Those results suggest that 5 training sessions of the bimanual tracking task were apparently not sufficient to detect age-related differences in inter-network connectivity. As we found no effects of practice, we collapsed the remaining analyses across pre- and post-training sessions.

3.4. Age-related increased within-cortical FC, but decreased within-striatal FC during rest

We observed widespread increased *inter-network* connectivity in older adults within cortical networks (Fig. 4A, top left square). Although connection pairs can be detected for each cortical network, connection pairs exhibiting significant age effect were more numerous among visual, attention, executive, and default mode networks. *Intra-network* FC decreased in older age within visual, somatomotor B, ventral attention A, and DMN B cortical networks (Fig. 4A, main diagonal of top left square).

Within striatal networks, ageing was associated with a marked decrease in connectivity at rest. Such age effect was observed across most network pairs, with the exception of those including executive A and DMN A striatal networks. Striatal-cerebellar connectivity also decreased in older age, prominently for striatal visual networks and cerebellar ventral attention networks. Both age-related increased and decreased FC was observed in cortico-striatal connectivity. Age-related reduction in cortico-striatal connectivity was present in somatomotor B, ventral attention B, and temporoparietal cortical networks. Older adults displayed increased cortico-cerebellar connectivity in cortical executive network C and cerebellar nodes of central visual network. Finally, within cerebellar nodes, FC mostly increased with age, notably among DMN and temporoparietal network nodes, but also between central visual and somatomotor cerebellar network nodes.

Altogether, our results indicate opposite ageing effects on intra-cortical and intra-striatal connectivity. More specifically, between-network connectivity within the striatum was reduced in older relative to younger adults during rest. To a lesser degree, ageing was associated with reduction in striatal-cerebellar connectivity, but increase in cortico-cerebellar connectivity.

3.5. Ageing is associated with decrease in striatal and cerebellar FC during task execution

During task execution, inter-network FC within cortical networks showed a similar age-related increase as observed during rest (Fig. 4B). Intra-network cortical connectivity was higher in older adults in central visual, somatomotor A, dorsal attention B, and executive A and C networks. Age-related intra-network decrease in FC was observed within somatomotor B, limbic, DMN C, and temporoparietal networks.

Older age was associated with widespread reduction in cortico-striatal, cortico-cerebellar, striatal-cerebellar, and striatal functional connectivity (Fig. 4B). Connectivity among cerebellar nodes showed a mixed pattern of age-related increases and decreases. Age-related decreases in FC were mostly observed among visual, somatomotor and attention networks, whereas increases in FC were not prominent in any

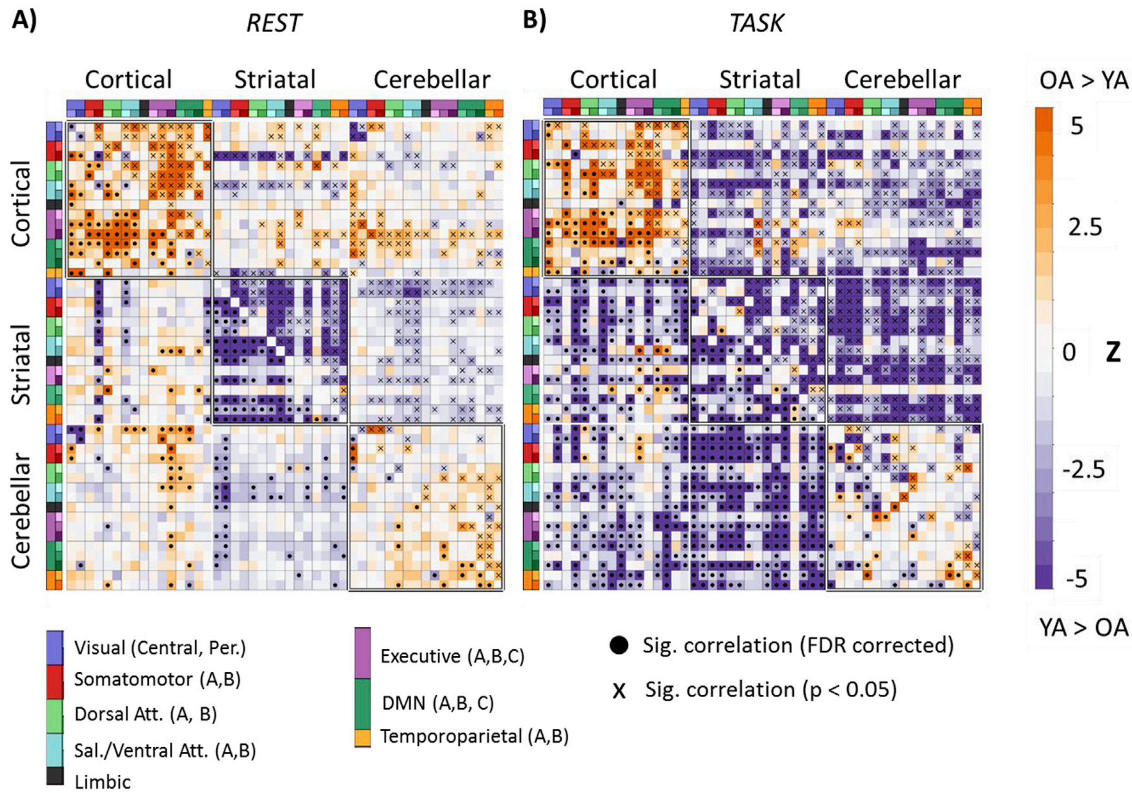

Fig. 4. Modulation of FC by Age during rest (A) and task execution (B). Significant connections are marked in the upper (uncorrected) and lower (after FDR correction) triangles of the matrix. Orange colors indicate positive association with age and purple colors indicate negative association with age.

single network.

Contrary to our first hypothesis (see Introduction), our findings suggest that increased *inter*-network cortical connectivity observed in older adults was also present during task performance. Age-related *intra*-network cortical connectivity patterns, however, were less consistent between resting state and task performance. Communication between cortical and striatal/cerebellar nodes was markedly reduced during task execution in older age.

3.6. Cortical connectivity modulation from rest to task associated with task performance in older adults

We investigated whether tracking error was associated with connectivity between pairs of networks during rest, task execution, and connectivity change from rest to task. Although trends were observed in both age groups, especially during task execution and from rest to task, no association remained significant after FDR correction (Fig. 5).

In addition to studying age-related effects at single connection pair level, we investigated the association between error scores and connectivity at the network level within each age group. In light of the heterogeneous age-related connectivity patterns observed (see sections 3.4 and 3.5), we performed this analysis for three coarsely defined set connections: (1) whole-brain, (2) within cortical networks only, and (3) among striatal and cerebellar networks only. Additionally, given the marked differences observed between rest and task performance, we probed connectivity strength changes from rest to task in addition to overall connectivity (across rest and task). False discovery rate correction was calculated to account for the multiple networks compared within each correlation model. Thus, we investigated overall connectivity and its modulation at different levels (cortical, striatal and cerebellar) in association with task performance.

Increase in inter-network connectivity strength from rest to task within cortical networks was associated with higher error scores in older adults for the majority of networks (Fig. 6). No other association was found between overall connectivity and error scores during task performance.

Altogether, we found no association between edge-level connectivity patterns at rest and during task execution and bimanual tracking task error (Fig. 5). However, task related increase in inter-network connectivity among cortical networks was found to be associated with higher error among older adults; and, this relationship was statistically different from that in young adults in most networks.

3.7. Reduced flexibility in networks with higher FC in older adults

We evaluated node-network membership changes from rest to task execution as a measure of network flexibility. We limited our analyses to cortical networks which showed significant age-related effects in FC strength across conditions (central visual, somatomotor A, dorsal attention A and B, executive A and C, and DMN A, see Supplementary Material S2), as we expected that increased inter-network FC would be associated with lower network flexibility.

As predicted, there was a significant decrease in network flexibility among those cortical networks which showed higher connectivity in OA (Fig. 7). Those differences are unlikely to originate from possible outlier data points (Supplementary Material S3). For completeness, we also ran the analyses across the entire brain and among cortical networks with more positive FC in young relative to older adults, but no statistically significant differences between groups were observed.

3.8. No association between error scores and network flexibility

We evaluated whether network flexibility was associated with error scores during task execution for each group separately. To that end, we correlated average tracking error (across pre- and post-training) with average mutual information between node-network membership

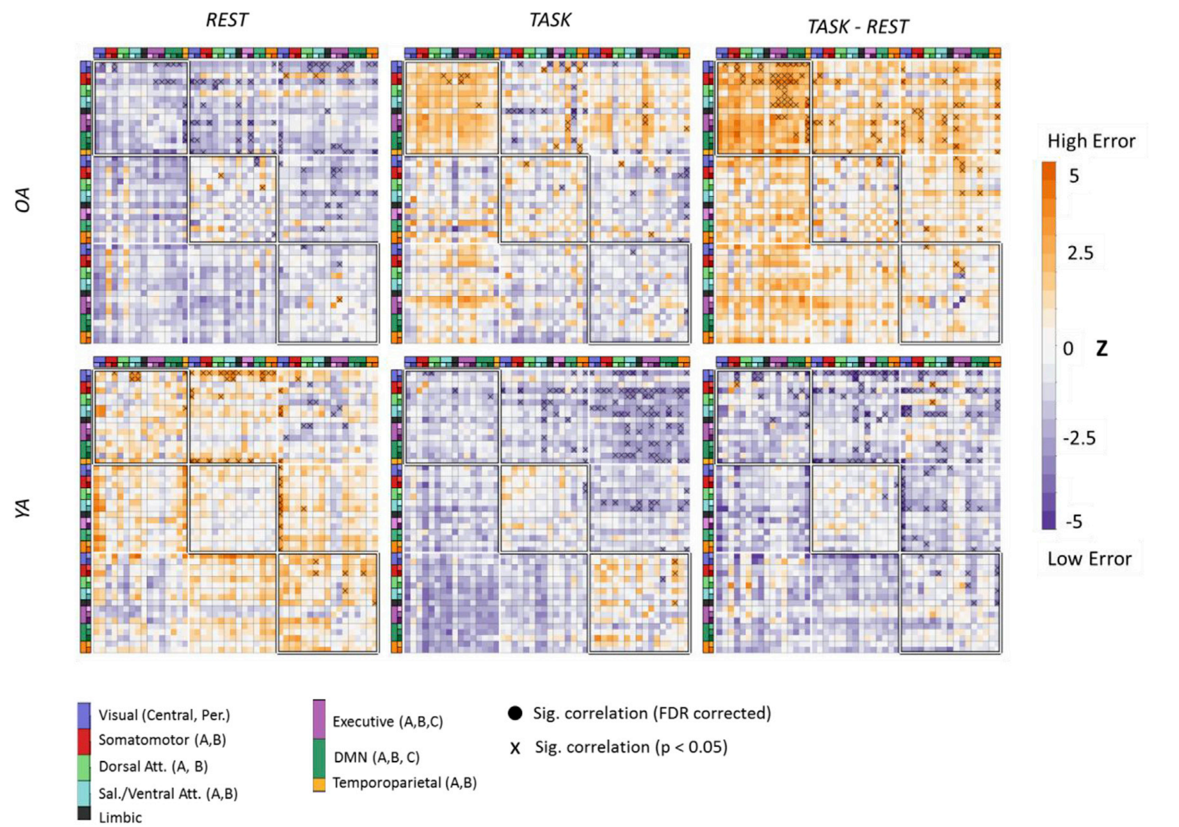

Fig. 5. Association between task error and connectivity at rest (leftmost column), during task execution (middle column), and change from rest to task (rightmost column) for older (top row) and young adults (bottom row). In older adults, connectivity changes from rest to task, mainly within cortical networks, were generally detrimental to performance. Cortico-cerebellar connectivity during task execution was generally associated with better performance in young adults. None of the associations at edge level survived FDR correction.

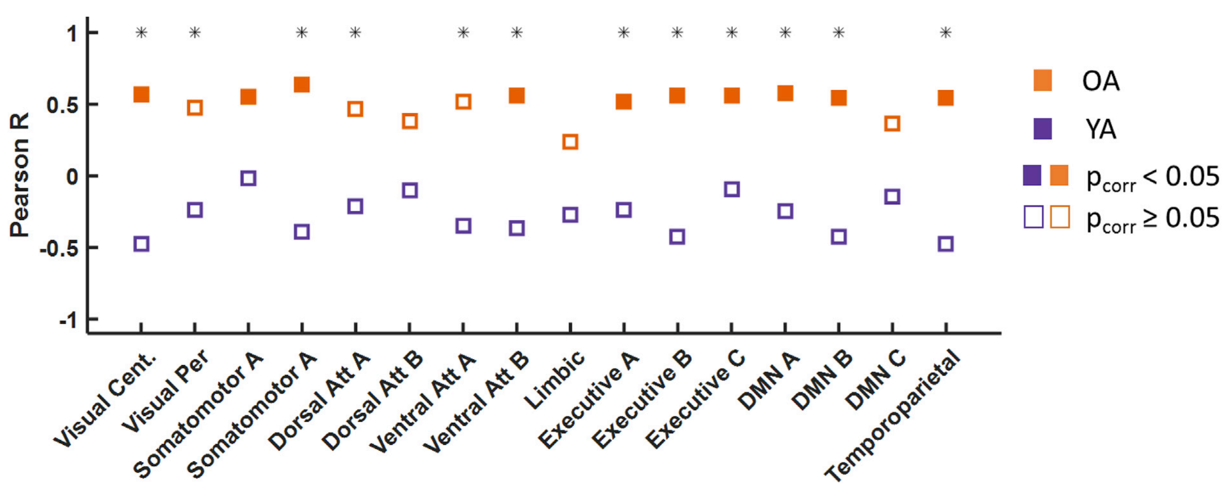

Fig. 6. Association between overall connection strength from rest to task exclusively among cortical networks and error during task performance. Correlation coefficients statistical difference was computed for each network and is marked with an '*' when significantly different between groups. Our results evidence a general association between increases in inter-network connectivity among cortical networks from rest to task and higher tracking error among older, but not young adults. Correlation coefficients have been FDR corrected.

partitions from rest to task execution for the same networks tested in section 3.7. We observed no significant association between task performance and network flexibility for all tested density levels in neither age group (all p values > 0.11).

3.9. Connectivity in the prefrontal cortex associated with lower error

We have previously analysed the task-related fMRI data of the sample presented in this study and observed evidence of a positive association between left prefrontal BOLD activity and more accurate task performance in older adults (Monteiro et al., 2017). In the network parcellation used in the network analyses presented here, regions identified in our previous work were part of distinct functional networks (left salience/ventral attention B, left executive A and B, left DMN A, and right executive B). We investigated whether flexibility and FC measures restricted to parcels roughly corresponding to regions where we had

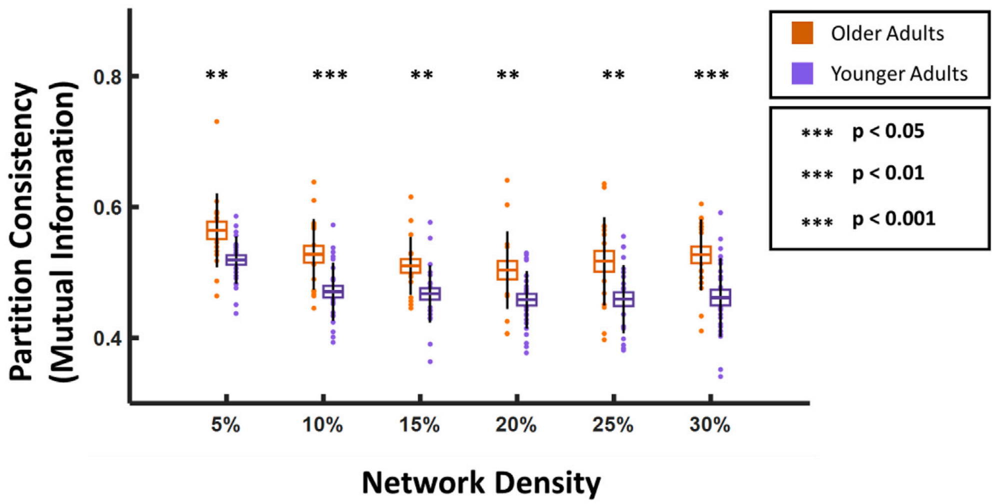

Fig. 7. Age-related difference in network flexibility. Mutual information between networks partition from rest to task execution was higher in older adults for cortical networks with age-related increased degree. All p-values are corrected using the Bonferroni-Holm procedure. The central horizontal lines represent each group's average mutual information. Individual dots represent single subjects, vertical black bars the standard deviation and box indicates the standard error of the mean. The higher consistency between partitions suggests reduced flexibility in reorganizing highly connected networks in the older adults group.

previously identified association between BOLD activity and performance would show a similar association to behavioural outcome. To that end, we used two robust linear models to assess whether average tracking error (continuous, across pre- and post-training) was associated with FC (continuous) or flexibility (continuous), and age group (young, old). We included in the analysis FC and flexibility across 7 nodes, all in the prefrontal cortex.

Across all density levels, we observed a strong main effect of network flexibility (Table 1A), indicating that higher flexibility in those prefrontal regions is associated with lower error scores. In half of the tested density levels, we also observed a trend towards AGE × FLEXIBILITY interaction (Table 1A), suggesting that prefrontal flexibility is more strongly associated with better performance in older in comparison with younger adults. For the majority of tested density levels, we observed no main effect of connectivity strength nor FC × AGE interaction (Table 1B).

3.10. Training did not alter age-related differences in flexibility

In order to assess the effect of practice on network flexibility, we evaluated the change in mutual information between rest and task execution from pre-to post-training. We observed neither a main effect of AGE, nor an AGE × SESSION interaction for all tested density levels, suggesting that task-related changes in node membership were not modulated by training.

4. Discussion

In the present study, we carried out a comprehensive investigation of age-related changes in whole-brain functional connectivity and network flexibility during rest and execution of a complex bimanual task set practiced over the course of two weeks.

In line with current evidence, we found consistently higher cortical between-network connectivity in older adults during rest. This altered connectivity pattern was also present during task execution. Striatal, but not cerebellar connectivity, however, was reduced in older participants. Connectivity strength was more positive during task in relation to rest, although it did not differ between age groups. Network reorganization from rest to task was diminished in the older population, but only in networks with age-related increase in FC. Increase in cortical between-network connectivity correlated with higher error in older, but not young adults. Finally, flexibility in nodes located in the prefrontal cortex was found to be associated with lower error scores across both age groups, although we observed a trend towards an interaction between age and flexibility, suggesting a stronger association in older adults.

4.1. Consistent age-related cortical inter-network, but not intra-network age-related effects during rest and task execution

Consistent with previous work, we observed increased between-network functional connectivity among cortical networks in older as compared to younger adults during rest (Archer et al., 2015; Betzel et al., 2014; Damoiseaux, 2017; Ferreira et al., 2016; Geerligs et al., 2015; King et al., 2017). Contrary to our hypothesis, this age-related altered pattern was present both during resting state and task performance, despite the overall increase in FC associated with task execution. We observed similar effects in an additional analysis where information about connection weight was discarded (see Supplementary Material S4). In conjunction, those results indicate both changes in connection strength (weight) and network configuration (connection distribution) in older as compared to younger adults. Furthermore, increased between-network connectivity from rest to task performance in older adults was associated with higher error during the bimanual tracking task. Taken together, our results suggest the presence of a detrimental modulation of cortical inter-network connectivity in older adults, and those participants who better inhibit such modulation commit less errors in the bimanual tracking task. This is consistent with the notion that increased inter-network FC does not appear to be functionally meaningful in older adults (King et al., 2017).

The observed age-related reduction in intra-network connectivity in visual, somatomotor, salience/ventral attention and default-mode networks during rest is in line with previous studies (Damoiseaux, 2017; Huang et al., 2015). During task execution, however, we observed both increased and decreased intra-network connectivity in older adults. Specifically, cortical intra-network FC was more positive in older adults during task performance within central visual, somatomotor A, dorsal attention B, and executive A and C networks, suggesting that those networks remain more prominently connected during the performance of the bimanual motor task in older adults.

Altogether, our results provide evidence that the typically observed increase in between-network connectivity among older adults during rest is also present during motor task execution. Intra-network connectivity was lower during rest, but heterogeneously affected by age during task execution.

4.2. Weaker FC in OA during task execution in striatal and cerebellar networks

Increased age is associated with decreased subcortical function (Maes et al., 2017; Monteiro et al., 2017) and reduced structural integrity in the

Table 1
Association between tracking error and prefrontal (6 left PFC nodes and 1 right PFC node) flexibility (A) and connectivity strength (B). Entries in bold are significant at Bonferroni adjusted α level of $p < 0.0083$ (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

A)		
EFFECT	F	p
5% Density		
AGE	**56,249**	**< 0,0001*****
FLEXIBILITY	**12,657**	**0,001****
AGE x FLEXIBILITY	4702	0,036*
10% Density		
AGE	**48,85**	**< 0,0001*****
FLEXIBILITY	**8002**	**0,007****
AGE x FLEXIBILITY	0,304	0584
15% Density		
AGE	**65,765**	**< 0,0001*****
FLEXIBILITY	**8632**	**0,006****
AGE x FLEXIBILITY	4261	0,046*
20% Density		
AGE	**57,199**	**< 0,0001*****
FLEXIBILITY	**9068**	**0,005****
AGE x FLEXIBILITY	3578	0,066
25% Density		
AGE	**40,286**	**< 0,0001*****
FLEXIBILITY	6192	0,017*
AGE x FLEXIBILITY	4394	0,043*
30% Density		
AGE	**44,799**	**< 0,000*****
FLEXIBILITY	2979	0,092
AGE x FLEXIBILITY	1778	0,19

B)		
EFFECT	F	p
5% Density		
AGE	**50,058**	**< 0,0001*****
FC	**8163**	**0,007****
AGE x FLEXIBILITY	3276	0,078*
10% Density		
AGE	**47,168**	**< 0,0001*****
FC	5928	0,02**
AGE x FLEXIBILITY	2331	0,135
15% Density		
AGE	**43,798**	**< 0,0001*****
FC	3879	0,056**
AGE x FLEXIBILITY	1446	0,236*
20% Density		
AGE	**41,647**	**< 0,0001*****
FC	2,53	0,12**
AGE x FLEXIBILITY	0,964	0332
25% Density		
AGE	**40,895**	**< 0,0001*****
FC	1786	0,189*
AGE x FLEXIBILITY	0,65	0,425*
30% Density		
AGE	**40,318**	**< 0,0001*****
FC	1178	0,284
AGE x FLEXIBILITY	0,391	0536

striatum (Raz et al., 2003; Chalavi et al., 2018). It is not surprising, thus, that we observed consistently reduced connectivity within striatal networks in older adults, both during rest and task execution.

Activity in both striatal and cerebellar regions have been associated with the execution/learning of bimanual motor tasks (Debaere et al., 2003, 2004a; 2004b; Puttemans et al., 2005). Our results indicate that cortico-striatal and cortico-cerebellar functional connection strength are decline in old age during task execution. During rest, age effects on cortico-striatal and cortical-cerebellar connectivity are less prominent and more heterogeneous. Interestingly, we observed an age-related increase in connectivity between cortical executive networks and the cerebellum during rest. Those findings seem to contradict previously reported disrupted cortico-cerebellar connectivity in older adults at rest (Bernard et al., 2013). Differences in network definition and analyses must be noted, however. Furthermore, despite being largely reduced in older age, Bernard et al. also identified age-related increases in cortico-cerebellar connectivity.

In summary, our results indicate an age-related reduction in cortico-striatal and cortico-cerebellar connectivity modulation during task execution. Striatal connectivity is strongly reduced in older adults, both during rest and performance of motor tasks. Cerebellar and cortico-cerebellar connectivity, however, seem to undergo complex changes in connectivity pattern. In view of the critical importance of the basal ganglia and cerebellum in motor performance and learning, further investigation of these network connectivity properties and their age-related alterations is highly desirable.

4.3. Reduced network flexibility in older adults

Dynamic changes in network composition from resting-state to task execution were not globally different between young and older adults. Flexibility decreased, however, in cortical networks which showed higher age-related increases in functional connectivity. Those results are in line with previous work demonstrating reduced network reorganization in response to performance on various tasks in older adults (Geerligs et al., 2014). Furthermore, subcortical and cerebellar network organizations were relatively more stable across both age groups in comparison to cortical nodes.

We found no association between the ability to flexibly rearrange cortical networks and task performance in either age group. Our findings deviate from a previously reported association between flexibility and task performance in young adults (Bassett et al., 2011). Basset et al. examined flexibility in a shorter scale than the one presented here, i.e. within the task execution period. Here, on the other hand, we present changes in connectivity pattern from a task-free to a task-execution condition. Age effects on network flexibility during task execution and whether it affects behavioural performance are interesting research avenues that require further investigation.

4.4. Left prefrontal cortex flexibility is associated with better bimanual coordination performance

Multiple sources of evidence suggest that the altered connectivity patterns seen in older adults are not functional, but rather detrimental to performance (Bernard et al., 2013; King et al., 2017; Solesio-Jofre et al., 2018, 2014). In this study, we found no significant associations between either functional connectivity or network flexibility and bimanual coordination error scores. We observed, however, a significant association between flexibility in the prefrontal cortex and lower error scores, with a trend toward being more strongly associated with performance in older in relation to young adults. There was a trend towards an association between connectivity strength in prefrontal cortex nodes and lower error scores, though most of the association is explained by the age factor. Those results are in line with previous work demonstrating an increasing relevance of prefrontal connectivity and flexibility in the older population (Gallen et al., 2016; Michely et al., 2018).

Taken together, our findings underline the importance of dynamic reorganization of cortical networks in response to task performance demands. At the inter-network level, increased connectivity correlated with poorer task performance. Higher flexibility in the prefrontal cortex, however, was associated with better performance. This suggest that the connectivity changes seen in older age might be heterogeneous, rather than purely detrimental. The findings also underscore the increasing involvement of prefrontal brain areas in supporting motor performance in older adults (Heuninckx et al., 2005, 2008). Further investigation is required to differentiate compensatory from detrimental changes in connectivity and network flexibility, as well as the interplay between them.

4.5. Training modulated neither FC nor network flexibility

There is evidence for short term changes in motor network functional connectivity at rest immediately following practice of a motor task (Solesio-Jofre et al., 2018) and after 4 weeks of motor practice (Ma et al., 2011). In the present study, however, we found no longer-term resting-state or task-related connectivity changes between pre- and post-training sessions. We did find a non-significant practice-related reduction in connectivity among highly connected cortical networks in older adults. This suggests that perhaps a longer training program might help to further clarify whether training indeed alleviates the reduced network segregation in older adults. In a recent study where only a subset of three bimanual tasks was practiced, older adults, subjected to a more challenging practice context, were able to significantly reduce activity in areas that are part of the default mode network (task-negative) as a result of training and this reduction was associated with better motor performance (Pauwels et al., 2018).

We hypothesized that practice would lead to increased network flexibility, especially in older adults. Our results, however, did not find evidence of any training related change in flexibility. In conjunction with the lack of significant training-related changes in connectivity strength, this suggests that such a complex bimanual task set requires more extensive practice to show more prominent effects. Alternatively, the practice effects may also become more prominent when fewer subtasks are practiced and higher levels of automaticity are reached. More generally, it is possible that flexibility at the network level is a relatively stable characteristic of the brain that is not easily modified by training interventions that are limited in duration. More research is required to clarify the nature of training-induced effects on brain networks across the lifespan.

4.6. Methodological considerations and limitations

A vast amount of processing strategies have been proposed to process data prior to functional connectivity analyses (Ciric et al., 2017; Pruim et al., 2015; Shirer et al., 2015). One particular prevalent issue in this type of analysis is the effect of motion on detected correlations (Power et al., 2012). Average motion increases during execution of the motor task (see Supplementary Material S5). In a motion estimate-matched analysis, age-related changes in cortico-noncortical connectivity during task execution were less prominent (Supplementary material S5). Furthermore, we observed age-related increase in within-network cortical connectivity. Finally, we observed fewer significant connections displaying more positive connectivity in younger relative to older adults. Such difference might arise from the small subsample used in the analysis, or might eventually be due to in-scanner motion. We have included various steps in our data processing to mitigate the effect of motion on the data while still preserving non-spurious BOLD signals. To the best of our knowledge, no method currently is able to perfectly achieve such motion artefact correction. Consequently, the data analysed in this article represents a trade-off between noise and true effect removal. Thus, care is warranted in the interpretation of the presented results.

Importantly, negative weights (anti-correlations) might be detected or introduced depending on the particular processing steps used (Chai et al., 2012; Weissenbacher et al., 2009). Furthermore, it has been observed that anti-correlation is reduced in older age, with implications for working memory performance (Keller et al., 2015). In the present article, we observed no significant presence of anti-correlations in either age group (see Supplementary Material S6 for age group average connectivity). Moreover, removal of negative correlations did not substantially alter the primary results presented here, though we did observe a higher presence of negative weights in OA during task execution (see Supplementary Material S7). Consequently, although negative weights were included in the analysis, we refrained from making any interpretation about their physiological significance. Finally, the reported age-related differences in connectivity reported here cannot distinguish between arithmetic and connectivity strength differences, and the reported results must be interpreted accordingly.

5. Conclusion

Altogether, our findings show large scale age-related changes in brain network connectivity characteristics. At the cortical level, our results corroborate the hypothesis that older age is associated with increased connectivity (reduced segregation) among various specialized brain networks during task and rest conditions, consistent with the notion of age-related brain dedifferentiation. In contrast to cortical connectivity, striatal and cortico-striatal connectivity was reduced as a function of age, especially during task performance. Interestingly, cerebellar and cortico-cerebellar connectivity underwent more complex changes during rest and task conditions. In addition to the widespread connectivity changes, older adults were less able to modulate and reorganize cortical networks which showed increased between-network connectivity, indicative of decreased flexibility in network reorganization in order to cope with task demands. Nevertheless, at the individual level, higher prefrontal cortex flexibility was associated with better performance, particularly among older adults. Further research is warranted on the relationship between age-related changes in connectivity and flexibility, as well as their supporting and detrimental effects during motor task performance.

Conflicts of interest

The authors declare no competing interests.

Author contributions

Conceived the study: SPS. Analysed the Data: TSM, DM. Wrote the paper: TSM, BRK, HZA, DM, SPS.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.03.015.

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