Resting-state Functional Connectivity is an Age-dependent Predictor of Motor Learning Abilities

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Abstract

This magnetoencephalography study investigates how ageing modulates the relationship between pre-learning resting-state functional connectivity (rsFC) and subsequent learning. Neuromagnetic resting-state activity was recorded 5 min before motor sequence learning in 14 young (19–30 years) and 14 old (66–70 years) participants. We used a seed-based beta-band power envelope correlation approach to estimate rsFC maps, with the seed located in the right primary sensorimotor cortex. In each age group, the relation between individual rsFC and learning performance was investigated using Pearson’s correlation analyses. Our results show that rsFC is predictive of subsequent motor sequence learning but involves different cross-network interactions in the two age groups. In young adults, decreased coupling between the sensorimotor network and the cortico-striato-cerebellar network is associated with better motor learning, whereas a similar relation is found in old adults between the sensorimotor, the dorsal-attentional and the DMNs. Additionally, age-related correlational differences were found in the dorsolateral prefrontal cortex, known to subtend attentional and controlled processes. These findings suggest that motor skill learning depends—in an age-dependent manner—on subtle interactions between resting-state networks subtending motor activity on the one hand, and controlled and attentional processes on the other hand.

Key words: ageing, cross-network interaction, magnetoencephalography, motor sequence learning, resting-state functional connectivity

Introduction

Skills and habits are crucial components of everyday life activities. Preserving learning and motor skills is important for the sustained autonomy in senior persons (Seidler et al. 2010). However, age-related decline in cognitive processes such as decreased processing speed (Salthouse 1996) and working memory (Bo et al. 2009) may negatively impact motor abilities and skills in older adults. In young adults, brain connectivity patterns recorded during resting wakefulness before a learning episode predict, to some extent, acquisition performance (e.g., Wang et al. 2010b; Stillman et al. 2013; Hamann et al. 2014; Wu et al. 2014; Bonzano et al. 2015), suggesting that the organization of pre-existing large-scale functional brain networks may reflect a trait-like readiness to learn. Spontaneous brain activity at rest is organized in a set of large-scale spatiotemporal networks defined as resting-state networks (RSNs) (for a review,
To the best of our knowledge, no study has yet investigated the relationships between pre-learning resting-state functional connectivity (rsFC) and acquisition performance. Accordingly, rsFC between the hippocampus and posteromedial cortices was found to predict episodic memory in cognitively intact older individuals (Wang et al. 2010a), whereas it was linked to inter-hemispheric hippocampal rsFC in young adults (Wang et al. 2010b). To the best of our knowledge, no study has yet investigated the relations between rsFC and subsequent motor skill learning in the context of ageing.

In healthy young individuals, inter-individual rsFC differences in memory-related functional networks may predict subsequent motor learning abilities. For instance, functional magnetic resonance imaging (fMRI) studies showed that baseline rsFC in the fronto-striato-limbic network correlates with performance in a reward-based visuomotor learning task 4 weeks after training (Hamann et al. 2014), and that rsFC in striato-cortical and striato-hippocampal networks relates to performance levels in implicit motor sequence learning (Stillman et al. 2013). Using a seed-based connectivity approach with M1 cortex and SMA as seeds, Bonzano et al. (2015) evidenced that higher pre-training rsFC with the cerebellum and the thalamus is associated with better motor sequence learning. Finally, a high-density electroencephalography (hd-EEG) study disclosed correlations between performance improvement on a pursuit rotor task and the beta coherence between primary motor (M1), premotor and parietal cortices during the preceding resting state (Wu et al. 2014).

Despite the interest of electrophysiological measures to study the link between rsFC and behavior, fMRI has been so far the dominant imaging technique (Hall et al. 2014). However, a caveat of fMRI in the study of age-related changes in rsFC is that changes in the neurovascular coupling can affect the blood oxygenation level-dependent signal (for a review, see Liu 2013). Neurophysiological techniques such as magnetoencephalography (MEG) may circumvent this problem in measuring more directly the spontaneous neural activity. Multiple MEG studies used power envelope-based rsFC to derive RSNs spatially similar to those observed using fMRI (de Pasquale et al. 2010; Brokes et al. 2011b, 2012; Hipp et al. 2012; Hall et al. 2013; Wens et al. 2014a, 2014b), suggesting the reliability of this MEG rsFC approach. These studies highlighted the importance of the spectral and temporal dynamics of RSNs as well as their cross-network interactions (de Pasquale et al. 2012). However, the precise functional roles of both within-network and between-network envelope rsFC remains as yet unspecifiable. For instance in the Wens et al. (2014a) study, inter-subject fluctuations of MEG RSNs were considered without controlling possible cognitive influences. In the present study, we investigate how rsFC modulates subsequent learning performance in young and old adults.

More specifically, we considered the relationships between baseline (i.e., pre-learning) rsFC and subsequent motor sequence learning in young and old adults, in whom we previously reported an age-related reduction in experience-dependent plasticity (as indexed by post-movement mu rhythm enhancement) during simple movements after versus before learning a motor sequence (Mary et al. 2015). Starting from a primary sensorimotor (rSMI) seed involved in the motor task (Mary et al. 2015), baseline seed-based rsFC was estimated using a beta-band power envelope correlation approach (Brokes et al. 2012; Hipp et al. 2012; Wens et al. 2014a, 2014b). To identify possible interactions (both within the sensorimotor network and between the sensorimotor network and other RSNs) that modulate learning performance, correlation analyses between baseline rsFC and performance improvement during subsequent task practice were then performed in young and old adults. In young adults, we predicted associations between learning levels and seed-based rsFC in cortical regions known to be involved in motor sequence learning such as the supplementary motor area (SMA), the prefrontal, and premotor cortices and the cerebellum (e.g., Doyon et al. 2009; Penhune and Steele 2012). In ageing, the more consistent changes in RSNs have been identified in the attentional, executive, and DMNs (for a review, see Sala-Llonch et al. 2015), which may impact the coupling between these networks and the sensorimotor network. During the initial acquisition of a motor sequence, the frontal cortex plays an important role in mediating the interactions between the striatum and the medial temporal lobe (MTL) (Rieckmann et al. 2010; Albouy et al. 2012, 2013a). Although better sequence learning with time was associated with a progressive increase in striatal activity and decrease in MTL activity in young adults, increased activity was observed in both regions in old adults (Rieckmann et al. 2010). An age-dependent degradation of fronto-striatal circuits (Bennett et al. 2011) may explain the compensatory MTL recruitment in old adults (Rieckmann et al. 2010). Considering the known age-related dysfunctions in cortico-striatal networks involved in motor learning (for a review, see King et al. 2013), we hypothesized an age-dependent change in baseline rsFC patterns (Sala-Llonch et al. 2015) and in their association with motor learning levels.

Materials and Methods

Participants

Fourteen young (7 females; 24.2 ± 3.5 years (mean ± std); range 19–30 years) and 14 old (8 females; 69.1 ± 1.5 years; range 66–70 years) healthy adults without any reported history of neuropsychiatric, sleep, or movement disorders gave written informed consent to participate in this study approved by the ULB-Hospital Erasme Ethics Committee. They were right-handed (Edinburgh handedness questionnaire score young: 75.4 ± 19.9, old: 89.3 ± 13.1; Oldfield 1971), scored below the inclusion score (≤7) for depression at the Short version of the Beck Depression Inventory (Beck et al. 1974; French adaptation by Collet and Cottraux 1986) and below the inclusion score (≤45) for anxiety at the State-Trait Anxiety Inventory (STAI, French version: Bruchon-Schweitzer and Paulhan 1990). Old and young participants had a similar level of education (t(26) = −0.27, P = 0.79). Sleep habits for the preceding month were assessed using the Pittsburgh Sleep Quality Index (PSQI global score young 4.2 ± 3.1 vs. old 3.4 ± 2.2, t(26) = 0.84; P = 0.41; Buysse et al. 1989). Old adults exhibited a intermediate morning-type at the Morningness–Eveningness Questionnaire (MEQ score 60.8 ± 7.3, range: 51–76; Horne and Ostberg 1976) whereas young adults exhibited neutral type (MEQ score 49.8 ± 7.9, range: 35–61; t(26) = −3.8; P < 0.001). Additionally, old participants scored within the normal range for the risk of dementia (score 141.5 ± 1.9, inclusion score > 123; Mattis Dementia Rating Scale; Mattis 1976). The night before the MEG acquisition, sleep duration was similar in young (7.6 ± 1.3 h) and old (7.2 ± 1.2 h) adults (t(25) = 0.79; P = 0.44).

Experimental Design

The experimental design has been reported elsewhere (Mary et al. 2015). Only essential information is reported here.
Resting-state data were first acquired during 5 min before the motor learning session. Participants were instructed to remain still and awake, and to keep their eyes open while looking at a fixation cross projected on a screen.

Following the 5-min resting session, participants were instructed to execute a Simple Movement Task (SMT) and then to learn a novel motor sequence in a Finger-Tapping Task (FTT). In the SMT, participants used all four left fingers simultaneously (index to little finger) to perform 100 auditory-cued key presses (interstimulus interval: 5 s). Analysis of the suppression/enhancement of the mu rhythm power during the SMT has been previously reported (Mary et al. 2015) and was used to determine, for each individual, the seed location within the right primary sensorimotor (rSM1) cortex (see MEG Source Reconstruction). During the FTT learning session (adapted from Karni et al. 1995), participants had to reproduce, as fast and accurately as possible, a 5-element motor sequence with the fingers of the left non-dominant hand, by pressing the corresponding keys on a MEG-compatible button box (FOP; Current Designs Inc.). The sequence (4-1-3-2-4) numbered from index (1) to little finger (4) was executed twice for each trial (70 trials). Each trial can be decomposed in 8 successive, overlapping three-element chunks (i.e. [413], [132], [324], [244], [441], [413], [132], [324]). Speed performance was computed for each individual based on the assumption that performance evolves according to a power law (Newell and Rosenbloom 1981). The learning evolution of mean chunk execution time to correctly reproduce the 8 successive three-element chunks (Hotermans et al. 2006, 2008). Accuracy was computed as the percentage of correctly executed chunks per trial. The two first trials of the session were excluded from statistical analyses. MEG data were not analyzed during the FTT session.

To assess the evolution of learning, a motor learning index was calculated for each interval based on the assumption that performance evolves according to a power law (Newell and Rosenbloom 1981). The learning evolution of mean chunk execution times $ET_i$ at chunk number $i$ was individually fitted to a model $ET_i = C_i$ using a logarithmic linear regression. The motor learning index was then estimated as the exponent $C_i$, since higher values of $C_i$ indicate faster decreases in sequence execution time.

MEG Data Acquisition and Preprocessing

Neuromagnetic signals were recorded with a whole-scalp 306-channel MEG system installed in a light-weight magnetically shielded room (Vectorview & Maxshield; Elekta Oy, Helsinki, Finland). The MEG device has 102 sensor chips, each comprising one magnetometer and two orthogonal planar gradiometers. Head position inside the MEG helmet was continuously monitored using four head position indicator coils. The locations of the coils and at least 300 head-surface points with respect to the subjects’ anatomical fiducials (nasion and tragus) were digitized prior to MEG acquisition using an electromagnetic tracker (Fastrak, Polhemus, Colchester, VT, USA). Eye movements and blinks were recorded using electrooculogram (EOG). Bipolar EOG electrodes were located below the left outer canthus and above the right outer canthus. Electrocardiogram (ECG) was recorded with bipolar electrodes placed below the right collarbone and on the left last rib. Movements of the left hand were monitored using surface electromyogram (EMG) based on bipolar electrodes placed on the left extensor carpi ulnaris muscle. EOG, ECG, and EMG signals were recorded simultaneously to MEG signals; all signals were sampled at 1 kHz and bandpass filtered at 0.1–330 Hz.

Continuous MEG data during the rest and the SMT sessions were pre-processed offline using the signal space separation (SSS) method to remove external interferences and correct for head movements (Taulu et al. 2005) and bandpass filtered in the 0.5–45 Hz frequency range. MEG data were subsequently visually inspected and further de-noised using an independent component analysis (Vigário et al. 2000). Independent components (IC) corresponding to cardiac and ocular artifacts were first identified using correlations between the time course of the IC and of the signals from the ECG and EOG and then removed from the MEG signals (average IC removed across subjects: $2.81 \pm 0.78$).

MEG Source Reconstruction

Individual MRIs were acquired using a 1.5 T MRI scanner (Intera, Philips, The Netherlands) and segmented using the Freesurfer software (Martinos Center for Biomedical Imaging, Massachusetts, USA). Co-registration between MEG and MRI coordinate systems was realized using the three anatomical landmarks for initial estimation and the head-surface points for precise manual adjustment. The Boundary Element Method implemented in the MNE software suite (Martinos Center for Biomedical Imaging, Massachusetts, USA) was used to compute individual MEG forward models. To facilitate group averaging and inter-group comparisons, a regular 5-mm grid source space covering the whole Montreal Neurological Institute (MNI) brain volume was transformed onto each subject’s MRI using the non-linear spatial-normalization algorithm implemented in Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Inverse modeling was performed using a band-specific Minimum Norm Estimation (MNE) (Dale and Sereno 1993; Wens et al. 2015) and restricted to the planar gradiometers to avoid possible issues associated with SSS (Lucchino et al. 2012). An artifact-free empty room (5 min) recording was filtered in the beta band and used to estimate the sensor-space noise covariance matrix. The MNE regularization parameter was set as in Hämäläinen et al. (2010). The MEG cleansed signal during resting-state was filtered in the beta band (12–30 Hz), given evidence that MEG slow envelope correlation is frequency-specific (Brookes et al. 2011b; Hipp et al. 2012). Indeed, the best spatial agreement between fMRI and MEG for the sensorimotor network was evidenced when MEG data are filtered into the beta band (Brookes et al. 2011a), and the strongest correlation between homologous sensory regions are known to occur in the alpha to beta frequency ranges (Hipp et al. 2012).

Seed-based Resting-state Functional Connectivity

The seed-based rsFC analysis used in this work was adapted from seminal works of MEG rsFC (Brookes et al. 2012; Hipp et al. 2012) and detailed elsewhere (Wens et al. 2014a, 2014b, 2015). First, the linear effect of the seed on sources’ analytic signals was corrected using the instantaneous orthogonalization (Hipp et al. 2012) in order to limit spurious correlations due to the spatial leakage effects in MNE (Wens 2015; Wens et al. 2015). Slow envelope fluctuations (~1 Hz) were then extracted by averaging the Hilbert envelope of the seed and the leakage-corrected sources over sliding windows (size: 1 s, step: 0.5 s), as previously described (Wens et al. 2014a, 2014b, 2015). Pearson’s correlation coefficients between the seed and the orthogonalized sources were finally computed to derive individual SM1 maps for the pre-training resting state.

The topography and the connectivity level of individual RSNs (i.e., sensorimotor, auditory, and visual networks) in MEG show high variability when using template seeds common to
all subjects, whereas the use of an individual seed decreases this variability (Wens et al. 2014b). Therefore, the rSM1 seed was individually chosen using a functional localizer (as in Brookes et al. 2012) based on the mu rhythm enhancement or resynchronization during SMT (see Mary et al. 2015). First, event-related time–frequency power analysis using a 7-cycle Morlet wavelet transformation (Tailon-Baudry et al. 1996) was performed over a pre-selection of 9 pairs of gradiometers underlying the rSM1 cortex (Kim and Chung 2003) during SMT. These pairs of gradiometers were selected based on evidence from a previous study showing that the most prominent oscillatory activities during the SMT are observed in these 9 pairs of gradiometers, with the source of the mu-alpha localized in the post-central gyrus and the source of the mu-beta in the precentral gyrus (Mary et al. 2015). Second, post-movement time (young 2653.3 ± 672.9 ms; old 2279.3 ± 707.6 ms) and frequency (young 21.1 ± 2.5 Hz; old 19.1 ± 4.1 Hz) of maximum power were selected. Third, the wavelet coefficients at selected time and frequency were projected on source space using MNE and the depth bias was corrected using the sLORETA noise normalization (Pascual-Marqui 2002). Fourth, the seed location was selected as the local maximum peak in the rSM1 cortex contralateral to hand movement for each subject.

Relations Between rsFC and Behavioral Performance
The relation between the motor learning index (see Experimental Design) and baseline rsFC was investigated using inter-subject Pearson’s correlations at each source. Correlational analyses were first performed separately for the young and the old groups. A positive (respectively, negative) correlation in a given brain area indicates that higher (respectively, lower) pre-learning rsFC between the rSM1 seed and that region is predictive of the subsequent ability to learn a new motor sequence. We also investigated the differences in the correlation maps (between motor learning index and pre-training rsFC) obtained in the young and the old groups. To that aim, we built a map of t-scores of group differences (two-tailed, unpaired t(25)-tests) in the Fisher-transformed correlation values and assessed statistical significance for each source location.

Reported results are significant at $P_{corr} < 0.05$ after correction for the multiple comparisons involved in testing source-level statistical maps. The family-wise error was controlled for the number of spatial degrees of freedom involved in MNE reconstructions using a Bonferroni correction (Wens et al. 2015). This technique is somewhat analogous to the random field theory approach considered in SPM (Kilner et al. 2005; Litvak et al. 2011), wherein the number of independent voxels is estimated from the smoothness of the images, and to adaptations in MEG (Barnes et al. 2011). In the context of MNE, the smoothness of source activity is completely controlled by the forward model (Wens 2015) and the number of spatial degrees of freedom can be estimated as the rank of the lead field matrix (Wens et al. 2015). The correction corresponded effectively to the significance level $P < 0.0009$.

Results
Finger Tapping Task
The motor learning index did not significantly differ between young and old participants ($t(26) = 0.4; P = 0.7$), as both groups displayed similar learning curves (Fig. 1).

In addition, we tested the accuracy and execution times by comparing the average of the first 20 trials (3–23) and last 20 trials (51–70) of the session. A repeated measures ANOVA on the percentage of correctly executed chunks with the trial type during learning (20 first vs. 20 last trials) as within-subject factor and group (young vs. older) as between-subject factor yielded a main effect of group ($F(1,26) = 4.38; P < 0.05$). Although accuracy was high in both groups, old adults ($95.7 ± 5.8$) were globally less accurate than young adults ($98.2 ± 2.2$). A repeated measures ANOVA on mean execution times revealed a main effect of trial type ($F(1,26) = 45.99; P < 0.001$), indicating that both young and old adults improved significantly their speed performance during learning.

Correlations Between Pre-learning rsFC and Subsequent Motor Learning Index
Sensorimotor rsFC maps for the young and old groups are illustrated in Figure 2.

Before to compute correlational analyses, we checked for difference between groups in the sensorimotor network and evidenced that old adults exhibit higher pre-learning rsFC between rSM1 and the right insula (36 9 5 mm; young: $r = 0.03$, old: $r = 0.11$) and the left cerebellum (VIIB (-19 -66 -46 mm; young: $r = 0.02$, old: $r = 0.06$) as compared with young adults ($t(25) = -4.2; P_{corr} < 0.05$). However, correlations between pre-learning rsFC and motor learning performance were not identified in these regions.

![Figure 1. Mean execution times (ms) in the FTT for the 70 trials during learning, averaged for young (dark gray) and old (light gray) participants. The error bars represent the standard deviations. Red lines indicate the power law fitting model.](image1)

![Figure 2. Sensorimotor rsFC maps in young and old participants, superimposed on the MNI brain template. The lower and upper thresholds of the color bar are, respectively, fixed at the minimum and maximum of connectivity. The white dot represents the mean localization of the rSM1 seed in young [30–17 47 mm] and old [30–21 45 mm] subjects.](image2)
stationary approach. Here the cross-network couplings functionally affecting the subsequent learning process were identified thanks to their inter-individual variability rather than their temporal dynamics, using an inter-subjects correlation approach. One caveat of this approach is the low number of subjects included in this study. Indeed, correlation estimates with a low number of samples exhibit large random fluctuations, making their statistical testing conservative, which explains the limited extent of significant correlations reported in Figures 3 and 4. It is therefore likely that our analyses missed other cross-network interactions predicting learning performance.

An alternative and sensible method to analyze functional connectivity is phase synchronization (Garcés et al. 2016; Stam et al. 2007; Hillebrand et al. 2012), which might also have evidenced other networks not disclosed using our seed-based connectivity approach. Furthermore, investigations of the test–retest reliability of source-space MEG rsFC have shown that RSN reliability actually depends on the choice both of the FC metric and the frequency band (Garcés et al. 2016). Results indicate that although phase synchrony exhibits a greater reliability in connectivity for theta and gamma frequency bands, the envelope correlation approach is more reliable for connectivity in the beta frequency band. Thus, envelope correlation seems to be the most appropriate method to investigate sensorimotor networks using the beta frequency band in the present study.

Finally, it might be argued that our learning index does not only represent motor learning, but also general cognitive abilities. However, the learning index is calculated based on a power law that does not represent an overall measure of response speed, but rather reflects the evolution of speed performance through practice trials. Therefore, we argue that this learning index does not merely reflect general cognitive abilities such as motor execution or sustained attention, but first of all represents an estimation of motor sequence learning. In agreement with this proposal, correlations with the learning index in young adults were disclosed in a learning-dependent network involving sensorimotor, cerebellar, and striatal regions. Accordingly, previous studies evidenced dynamic changes within the cortico-striatal (Ma et al. 2010; Debas et al. 2014; Albouy et al. 2015) and cortico-cerebellar (Tamás Kincses et al. 2008; Ma et al. 2010) networks in the course of motor learning. Additionally, similar results were obtained using two other measures of learning performance which are (1) the motor learning index calculated on the basis of an exponential law (instead of a power law); and (2) the percentage changes between the 20 first and 20 last trials of learning.

Cross-network Interactions Predicting Learning Performance

In young adults, we found that lower connectivity between rSM1 cortex and the putamen and the cerebellum is strongly correlated with higher improvement during learning. These results are in line with a fMRI study that evidenced lower rsFC between the caudate nucleus and frontal motor regions (including precentral and postcentral gyri) correlated with better implicit motor sequence learning (Stillman et al. 2013). At variance, Bonzano et al. (2015) reported that stronger baseline rsFC between M1 cortex and cerebellum is predictive of faster sequence execution. M1 cortex, striatum, and cerebellum are crucial players in motor sequence learning (e.g., Doyon et al. 2009). Active in the early learning phase, the associative dorsal putamen areas disengage with practice whereas ventral
Figure 3. Pre-learning rsFC with seed rSM1 in relation to the motor learning index in young (A) (top panels) and old (B) (lower panels) participants. Statistical maps ($P_{	ext{cor}} < 0.05$) show negative correlations between rsFC and the learning index. The right panels show the linear trend between individual rsFC values and the associated learning index in regions reaching significance (see Table 1 for MNI coordinates). The $r$ value represents the Pearson’s correlation coefficient. The lower and upper thresholds of the color bar are, respectively, fixed at the minimum and maximum of correlation for each region. rSM1, right sensorimotor cortex; R, right. In young participants, the putamen location corresponds to the correlation peak in this structure (see Supplementary Figure S1 for all observed correlations in old participants).
sensorimotor regions are more and more involved (Lehéricy et al. 2005). Likewise, cerebellum activity is required at an early learning stage for error detection and correction, sensorimotor integration and movement timing (Penhune and Steele 2012), and then becomes less necessary with the automatization of the motor sequence. Negative relation between rSM1–cerebellum rsFC and performance in young adults might be linked to a reduced need to perform error detection and correction. Our results also differ from another neurophysiological study using hd-EEG (Wu et al. 2014) that found a positive association between higher baseline beta coherence between M1 and parietal cortices and motor improvement during learning, and a negative association with higher M1-premotor beta coherence. However, source reconstruction was not performed in this latter study, preventing a precise localization of the neural basis of coherence effects. Furthermore, motor skill acquisition was measured using a pursuit rotor task, which relies on distinct cortico-subcortical networks than motor sequence learning (Doyon et al. 2009). Finally, coherence and envelope correlation measure different aspects of neural couplings. Coherence estimates the phase consistency and envelope correlation estimates the amplitude correlation between different signals (for a review, see Siegel et al. 2012). These three points may explain discrepancies with our results.

In old adults, we found that better motor learning is associated with lower rsFC between the rSM1 seed and right DLPFC, right ACC, right angular gyrus, right V2, left cerebellum, and bilateral precuneus. To the best of our knowledge, no other studies investigated baseline rsFC and its relation with motor learning in old adults, preventing direct comparisons. The precuneus, the ACC and the angular gyri are part of the DMN (for reviews, see Buckner et al. 2008; Raichle 2015) whereas the dorsal frontal and parietal cortices are associated with the dorsal-attentional network (DAN; Fox et al. 2006). The DMN is thought to relate on self-related and internal processes (Raichle 2015) whereas the DAN would be associated with voluntary or goal-directed orientation of attention (Fox et al. 2006). Our result suggests that lower cross-network connectivity between rSM1 cortex and parts of the DMN and the DAN facilitate subsequent learning in old adults. Age-related decreases in rsFC within the DMN and the DAN have been consistently reported in the literature (for a review, see Salionch et al. 2015). Using MEG, these changes were characterized by increased information flow into the medial temporal regions and decreased inflow into the posterior regions (precuneus/posterior cingulate), associated with reduced cognitive performance (Schlee et al. 2012). Additionally, the motor network and the DMN can be interconnected. Indeed, DMN deactivation found during a simple manual motor task correlates with putamen activity (Marchand et al. 2007) and deep brain stimulation of the external globus pallidus (GPe) in Huntington disease reduces resting-state connectivity between GPe and posterior regions of the DMN (Ligot et al. 2011). In line with our results, Baidassarre et al. (2012) found that young adults with stronger negative correlation between the visual cortex and DMN regions (i.e., angular gyrus, medial prefrontal and middle temporal cortices) exhibited better performance in a perceptual learning task. Likewise, motor imagery training induces rsFC changes between DMN regions (Ge et al. 2014; Zhang et al. 2014). Increased rsFC in the lateral parietal cortex after motor imagery training negatively correlated with the improvement in actual motor sequence execution after imagery training (Ge et al. 2014). Altogether, these findings further support the proposal that the DMN is highly interconnected with other networks, and acts as a functional core integration network (de Pasquale et al. 2012, 2013). Accordingly, we suggest that old adults who learn faster the sequence might feature a greater ability to integrate information (e.g., visual, spatial, and sensorimotor) from multiple

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<tr>
<th>Location of maxima</th>
<th>MNI coordinates (mm)</th>
<th>Peak r-scores</th>
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<tr>
<td>A. Young participants</td>
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<tr>
<td>L putamen</td>
<td>−31 −11 0</td>
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<tr>
<td>L cerebellum (crus I)</td>
<td>−14 −90 −30</td>
<td>−0.79</td>
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<tr>
<td>B. Old participants</td>
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<td>R angular gyrus</td>
<td>51 −56 30</td>
<td>−0.79</td>
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<td>R middle frontal gyrus (DLPFC)</td>
<td>45 34 28</td>
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<td>R precuneus</td>
<td>31 −82 25</td>
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<td>R cuneus (V2)</td>
<td>27 −61 16</td>
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<td>R ACC</td>
<td>3 35 10</td>
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<td>L precuneus</td>
<td>−4 −61 38</td>
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<td>L cerebellum (crus I)</td>
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Brain regions in which pre-learning rsFC with the seed (rSM1) significantly correlates with the motor learning index in young (A) and old (B) participants. MNI coordinates indicate the location of the correlation peak in each region of significance. Peak r-scores show the correlation coefficients in the group for which a significant correlation has been identified (young or old). R, Right; L, Left.
networks, which would be associated with a lower rsFC with the DMN.

We noticed that during motor practice in the FTT, several old participants experienced difficulties to execute the sequence without resorting to the visual cues, i.e., without watching their hand while practicing, which was not the case in young participants who integrated and automatized more easily the motor sequence. Given that the medial superior temporal region and the temporoparietal junction are involved in visual motion processing (Bosco et al. 2008), it is possible that stronger connections between rSM1 cortex, V2 and visual motion processing areas are needed by these old adults to learn the motor sequence. Finally, activations in ACC, DLPFC, posterior parietal regions, M1 cortex, and cerebellum decrease during the course of a first learning practice (Floyer-Lea and Matthews 2005), suggesting a progressive disengagement of this network throughout the practice session. In this framework, lower baseline rsFC between rSM1 cortex and these areas may facilitate disengagement and explain the correlation with better learning performance.

Finally, correlational differences between young and old adults were identified in the right dorsolateral prefrontal cortex (DLPFC). In young adults, baseline rsFC between rSM1 and DLPFC was positively related to motor performance whereas in old adults this association was negative. The DLPFC is known to be involved in cognitive control processes such as attentional selection, necessary for goal-directed behaviors (Abe and Hanakawa 2009), and preparation of sequential actions based on information stored in working memory (Pochon et al. 2001). Accordingly, rsFC between rSM1 and DLPFC might relate to controlled processes through goal selection and sequence monitoring, which are required in the early stage of skill acquisition. In addition, it has been suggested that prefrontal areas, possibly the DLPFC (Stillman et al. 2013), mediate the recruitment of the striatum and the MTL in the initial steps of motor sequence learning (Albouy et al. 2012, 2013a). Explicit sequence learning was shown to involve the MTL, the prefrontal cortex and the striatum in young adults (Schendan et al. 2003; Albouy et al. 2012, 2013b, 2015). However, age-dependent alteration of the caudate-DLPFC circuitry was associated with the age-related decline in sequence learning (Bennett et al. 2011). Altogether, these findings suggest that age-related changes in the frontostriatal network may indirectly impact rsFC between rSM1 and DLPFC in old adults.

Conclusions

To sum up, we have found that baseline cross-network rsFC predicts individual learning levels in a new memory task, in agreement with prior studies conducted in young adults (Baldassarre et al. 2012; Stillman et al. 2013; Hamann et al. 2014; Wu et al. 2014; Bonzano et al. 2015). In addition, our results evidence age-related changes in the neural networks predicting motor sequence learning abilities. In young adults, better motor learning is associated with lower baseline corticostriato-cerebellar rsFC, i.e., a network known to subend motor sequence learning and the automatization of motor skills. In old adults, better performance is associated with lower baseline rsFC between rSM1 cortex and regions involved in visual motion processing, DAN, and DMN, i.e., networks related to visuomotor, attentional, and integrative processes. Finally, we found age-related correlational differences in the DLPFC subsuming attentional and controlled processes. Hence, our findings suggest that with age, motor skill learning abilities become more dependent upon the organization of pre-existing neural networks subsuming controlled and attentional processes, which are likely to increase pressure on the availability of cognitive resources.

Supplementary Material

Supplementary Material can be found at http://www.cercor.oxfordjournals.org.

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Notes

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References


