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Age differences in predicting working memory performance from network-based functional connectivity

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Abstract

Deterioration in working memory capacity (WMC) has been associated with normal aging, but it remains unknown how age affects the relationship between WMC and connectivity within functional brain networks. We therefore examined the predictability of WMC from fMRI-based resting-state functional connectivity (RSFC) within eight meta-analytically defined functional brain networks and the connectome in young and old adults using relevance vector machine in a robust cross-validation scheme. Particular brain networks have been associated with mental functions linked to WMC to a varying degree and are associated with age-related differences in performance. Comparing prediction performance between the young and old sample revealed age-specific effects: In young adults, we found a general unpredictability of WMC from RSFC in networks subserving WM, cognitive action control, vigilant attention, theory-of-mind cognition, and semantic memory, whereas in older adults each network significantly predicted WMC.

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Moreover, both WM-related and WM-unrelated networks were differently predictive in older adults with low versus high WMC. These results indicate that the within-network functional coupling during task-free states is specifically related to individual task performance in advanced age, suggesting neural-level reorganization. In particular, our findings support the notion of a decreased segregation of functional brain networks, deterioration of network integrity within different networks and/or compensation by reorganization as factors driving associations between individual WMC and within-network RSFC in older adults. Thus, using multivariate pattern regression provided novel insights into age-related brain reorganization by linking cognitive capacity to brain network integrity.

Keywords

Working memory; Brain networks; Aging; Resting-state fMRI; Machine learning; Relevance vector machine; Performance prediction

1. Introduction

Decline in various cognitive and executive functions has been recognized as a part of normal aging (Glisky, 2007; Salthouse et al., 2003). In particular, age-related deterioration in working memory (WM) functionality, that is, the capability to temporarily maintain, update and manipulate information, has received increased attention (Braver & West, 2008). WM decline has been addressed in a majority of cognitive aging theories (Park & Festini, 2017) and is considered a source of age-related deficits in a wide range of cognitive tasks (Gazzaley et al., 2005; Park et al., 1996; Salthouse, 1991) and social-affective behaviors (Moran, 2013; Opitz et al., 2012).

While the neural underpinnings of age-related deficits in cognitive functions were found to be associated with activation differences in task-related brain networks (Cabeza et al., 2016a; Hedden, 2007; Nielson et al., 2006), several findings have demonstrated that age-related WM decline may in part be accounted for by changes in resting-state functional connectivity (RSFC) architecture of the brain (Charroud et al., 2016; Jockwitz et al., 2017; Sala-Llonch et al., 2012). It remains unclear, however, to which extent neurobehavioral features of aging manifest in individual differences in WM capacity (WMC) associated with variations in interregional coupling at rest across different cognitive networks. To investigate how WM performance relates to other cognitive systems in an aging population prone to WM decline is particularly interesting as it has been shown that WMC is strongly associated with variations among other executive functions (Courtney, 2004; Miyake et al., 2000) as well as constitutes an underlying executive function in a broad range of higher-order cognitions including language comprehension and reasoning (Kane et al., 2007). Hence, shared neurobehavioral variance can be expected among executive and higher-order cognitive functions that are regulated by the degree these functions depend on WMC. This interplay may potentially be affected by variation in WMC in older adults that associate with neural-level reorganization as previously reported for age-related brain-behavior relationships (Grady, 2012; Sala-Llonch et al., 2015). It is, however, still unclear which role RSFC within brain networks related to different cognitive functions may play as a marker of

individual WMC, raising the question whether RSFC within these networks can be considered (equally) informative about individual WMC and how this relationship may change with age.

Here we addressed this question by taking a novel approach leveraging the power of coordinate-based meta-analyses (Eickhoff et al., 2016; Müller et al., 2018) to robustly define regions of the brain that are consistently recruited across dozens to hundreds of neuroimaging studies examining a particular mental function. In turn, in the commonly used data-driven approach to define networks from whole-brain RSFC data by means of independent component analysis (ICA), the mental functions associated with these networks are usually derived via reverse inference, as there is no a priori knowledge about the mental functions these networks subserves (Poldrack, 2011). Although the ICA-based approach has yielded stable and reproducible resting-state networks, the networks are usually defined from the same data set as used for the subsequent analysis (Cole et al., 2010). In contrast, our meta-analytically derived network model approach offers an a priori, unbiased definition of nodes forming a functional network, among which RSFC may then be computed for individual participants (cf. Pläschke et al., 2017; Schilbach et al., 2014; Varikuti et al., 2016). That is, meta-analyses provide robust information on the most likely location of the brain network subserving a task by integrating over task-activation findings based on hundreds of participants. Such a network can then be used to study individual RSFC connectivity profiles, which in turn can be linked to specific cognitive processes. Given that mental functions should best relate to interactions between multiple regions (Genon et al., 2018), we assume that the pattern of within-network connectivity may capture a substantial degree of inter-individual differences in cognitive performance. Using machine learning (ML)-based regression methods, previous studies have successfully predicted cognitive performance from RSFC distributed across the brain (Rosenberg et al., 2016) and revealed age effects in the prediction of executive functions from connectivity profiles between specific resting-state networks (La Corte et al., 2016). In the current work we employed the relevance vector machine (RVM; Tipping, 2001) in order to identify the relationship between input features (here: RSFC within a predefined functional network) and a continuous target variable (here: WMC score). The capability of such an approach to predict individual WMC in previously unseen subjects was evaluated using a repeated cross-validation scheme, yielding a scalar measure of average prediction performance for each network. To investigate the relationship between functional network integrity and WM performance and resolve the above-mentioned question about network specificity (see also Pläschke et al., 2017), we here examined five different meta-analytically defined networks. To examine how these relationships were affected by age, we compared prediction performance in young and old samples. The five networks comprised: WM (Rottschy et al., 2012), cognitive action control (CogAC; Cieslik et al., 2015), vigilant attention (VigAtt; Langner & Eickhoff, 2013), theory-of-mind cognition (ToM; Bzdok et al., 2012), and semantic memory (SM; Binder et al., 2009). Importantly, the WM network reflects consistent neural recruitment during WM tasks that primarily demand recognition-related processes, such as the n-back paradigm, rather than tapping free retrieval-under-interference processes as examined via complex WM span tasks (Kane et al., 2007).

The choice of these networks was based on our intent to cover a range of functional systems that are functionally (and neurally) either closely or only distantly related to WM (Chun, 2011; Diamond, 2013; Mutter et al., 2006; Nyberg et al., 2003; Unsworth et al., 2014). WM, CogAC, and VigAtt networks are representatives of executive function networks closely related to WM, whereas ToM and SM networks are linked to higher-order cognitive processes involving reasoning and language comprehension (i.e., more distantly associated with WM). Thereby, the ToM network is linked to social reasoning, and the SM network is linked to semantic memory/processing and associated with language comprehension (Martin & Chao, 2001; Van Overwalle, 2009). Given that several lower-level sub-processes contribute to higher-level executive functioning (Miyake et al., 2000; Müller et al., 2015), it may be argued that networks associated with the former may predict WMC better than do higher-order networks.

In addition, three WM-unrelated (“control”) meta-analytic networks were included to assess whether WMC predictability is specifically associated with the above-mentioned cognitive networks closely or distantly related to WM. These control networks were linked to task-negative, social-affective and introspective processes, as well as motor and sensory processes. In particular, the three networks comprised (i) the extended social-affective default network (eSAD; Amft et al., 2015), (ii) a combined motor network associated with finger tapping and prosaccade eye movements (Motor + PS; Cieslik et al., 2016; Witt et al., 2008), and (iii) a combined motor-sensory network linked to finger tapping and hand stimulation/somatosensory processing (Motor + SS; Lamp et al., 2019; Witt et al., 2008). These motor-sensory systems are strongly interconnected compared to large-scale cognitive networks with transitions between network boundaries, and converge less with fronto-parietal cognitive areas (Cieslik et al., 2016; Fox & Raichle, 2007; Yeo et al., 2011). While the coupling between the default-mode and WM networks has been associated with WM performance (Keller et al., 2015; Piccoli et al., 2015), the eSAD network is strongly involved in social-affective and introspective processes (Amft et al., 2015). Hence, it may be positioned between (broadly) WM-linked networks and WM-unrelated control networks. For all three “control” networks, age-related functional connectivity changes have been reported (Chan et al., 2017, 2014; Roski et al., 2013; Wang et al., 2010). Furthermore, we combined all individually investigated networks (related to cognitive action control, vigilant attention, theory-of-mind cognition, and semantic memory as well as eSAD) with the WM network to assess the predictability of intra- and inter-network connectivity. To further expand on this, we also examined predictability based on a connectome-wide network of 264 functional areas (Power et al., 2011), in order to compare the performance of the whole-brain connectome with that of our “sparse” functional networks and network combinations.

Previous findings and theories strongly suggest a general factor involved in age-related cognitive decline across several domains (Gazzaley et al., 2005; Mather, 2016; Moran, 2013; Park et al., 1996; Salthouse, 1991), which can partly be attributed to a general slowing in information processing (Salthouse, 1994, 1996). This, in turn, may possibly be related to a dedifferentiation/decreased segregation of functional networks (Chan et al., 2017, 2014; Goh, 2011; Roski et al., 2013; Sala-Llonch et al., 2015). Alternatively, performance decline with age might reflect a global age-related deterioration in network integrity, observable across various functional networks throughout the brain (Varangis et al., 2019; Zonneveld et

al., 2019). Either or both of these network-related changes should result in less specific associations between performance and RSFC within any given network in advanced age. We therefore hypothesized similar predictive power across different networks with advanced age, as compared to greater network specificity in young adults, for whom we expected to find better prediction performance in networks more closely related to WM processing. Such an age-related “broadening” (i.e., network non-specificity) of WMC predictability should not only apply to distinct though related brain systems but might as well extend to WM-unrelated networks.

2. Materials and methods

2.1. Sample

In the following we report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Resting-state functional magnetic resonance imaging (fMRI) data of 50 young (age range: 20–34 years) and 45 old (age range: 51–71 years) participants were acquired at the Research Centre Jülich, Germany. For this explorative study, we did not estimate predictability effect sizes a priori for determining sample size. Participants did not report any present or past psychiatric or neurological disorders (including dementia), as assessed in a structured interview. Older adults’ cognitive performance was age-adequate as evaluated by the Mild Cognitive Impairment and Early Dementia Detection assessment (DemTect; Kalbe et al., 2004; scores 13–18: age-adequate cognitive performance). None of the participants showed clinically relevant symptoms of depression as evaluated via the Beck Depression Inventory-II (all BDI-II scores < 13; Beck et al., 1996). For further sample characteristics, please see Table 1. Written informed consent was obtained from all participants before entering the study, which was approved by the ethics committee of the RWTH Aachen University Hospital, Aachen, Germany.

2.2. Performance measures

2.2.1. Working memory span tasks: Corsi block-tapping—Visuo-spatial WMC was assessed by the computerized version of the Corsi block-tapping task (forward and backward versions) from the Schuhfried Test System (<https://www.schuhfried.com/test/CORSI>; test forms S1 and S5). Here, participants were presented with a spatial array of nine irregularly arranged cubes on the monitor and observed a cursor that tapped a sequence of cubes. After an acoustic signal, participants were asked to re-tap the sequence either in the same (forward) or reverse (backward) order. Starting with three block taps, sequence length increased after three runs of a given length up to a maximum of 9 taps. The visuo-spatial WM span scores (forward and backward) correspond to the longest sequence correctly reproduced twice in a row.

2.2.2. Complex working memory span tasks: operation and reading span—Complex verbal WMC was assessed by a shortened version of the “operation and reading span tasks” (Oswald et al., 2015). For each trial in the operation span task, participants were first presented with an arithmetic equation, then had to decide whether a presented answer is

true or false. After each trial, a letter was presented to remember for later recall. After 3 to 7 trials, a 4×3 letter matrix was presented, and participants were asked to recall the letter sequence by clicking on the letters in the correct order. The reading span task was similarly structured except for the distractor task presented between letters, which consisted of sentences (approximately 10–15 words) for which participants had to decide whether or not they made sense. In total, each of the five sequence lengths (3–7 trials) was presented once in a pseudorandomized order per subtests. The verbal WM complex span was then calculated by the average number of letters recalled in the correct order across all trials of each subtest.

2.2.3. Composite working memory capacity score—As we aimed to assess global WMC, we aggregated all three test scores (Corsi forward and backward scores, complex span score) into a composite WMC score per subject by expressing individual performance per test as a fraction of the theoretically maximal score for this test and summing these values. The intercorrelations and age-controlled partial correlation between the single WMC subscores were calculated. Differences in WMC scores between young and old adults were assessed by independent-sample *t*-tests, the relationship between WMC and age by a Pearson correlation analysis.

2.3. fMRI data acquisition and processing

Whole-brain fMRI data were collected using a 3-T MR scanner (Tim-TRIO, Siemens Medical Systems) with a T2*-weighted echo-planar imaging (EPI) sequence (200 volumes; TR: 2200 msec; TE: 30 msec; flip angle: 80°; voxel size: $3.1 \times 3.1 \times 3.1$ mm³; 36 axial slices; inter-slice gap: .47 mm). During fMRI data acquisition, participants were instructed to lie still, close their eyes, let their mind wander and not fall asleep (confirmed at debriefing). After discarding initial four EPI volumes to allow for field saturation, images were processed using SPM12 (www.fil.ion.ucl.ac.uk/spm) involving EPI unwarping (using additionally acquired field maps), two-pass affine realignment for motion correction, spatial normalization to the MNI-152 template brain provided by SPM12 using the “unified segmentation” approach (Ashburner & Friston, 2005), as well as spatial smoothing with a 5-mm FWHM Gaussian kernel.

The above-mentioned five cognitive brain networks examined here comprised, to varying degrees, common and distinct brain regions. For instance, the WM, CogAC, VigAtt, and SM networks included peak coordinates in the inferior frontal gyrus, parietal regions, and midline structures. All but the SM and ToM networks included the anterior insula, while the SM and ToM networks were the only ones to include temporal regions and the mid-orbital gyrus. Moreover, only the SM network exhibited a strong left lateralization, presumably due to its involvement in language. In contrast, the ToM network uniquely included the right posterior temporo-parietal junction. Subcortical structures were only part of the WM, CogAC, and VigAtt networks (see Fig. 1, Table SI for an overview and Table SII for detailed network coordinates and corresponding brain regions).

RSFC within each of the meta-analytically defined networks was computed by first extracting the BOLD-signal time course of each node as the first eigenvariate of all voxels

located within a 6-mm sphere around the meta-analytic peak voxel and conforming to the CanLab gray-matter mask (<https://canlabweb.colorado.edu>). In order to reduce spurious correlations, variance explained by (i) the six movement parameters obtained during preprocessing, (ii) their derivatives (each modeled as first- and second-order effects), as well as (iii) the mean white-matter and cerebrospinal-fluid signal time courses were statistically removed from each node's time series (Ciric et al., 2017; Satterthwaite et al., 2013), which has been shown to yield reliable estimates of within- and between-network connectivity (Varikuti et al., 2016). Moreover, this approach ensures that less gray-matter-specific, motion-unrelated variance of BOLD-signal fluctuations of neural origin will be removed from the data (Chen et al., 2012), as compared to global signal regression. Subsequently, time series were high-pass filtered retaining frequencies above .01 Hz.

Although we regressed out motion-related variance such that afterwards the correlation between RSFC and motion was near zero, we conducted further analyses to follow up on this important issue, given that motion-related artifacts in resting-state fMRI data can lead to spurious functional connectivity. In particular, two additional RSFC denoising procedures were separately applied: First, global signal regression was performed (Ciric et al., 2017; Power et al., 2018; Satterthwaite et al., 2013). Second, data censoring was applied to remove data points in each time series that were contaminated by motion (using the method proposed by Afyouni & Nichols, 2018) and to account for spuriously inflated RSFC of short-distance connections and spuriously decreased RSFC of long-distance ones (Ciric et al., 2018).

Pair-wise functional connectivity was computed as Fisher's Z-transformed Pearson correlation between the first eigenvariate of the time series of each network's nodes. Connectivity values were then adjusted (via linear regression) for effects of age, gender and movement based on the derivative of root mean squared variance over voxels (DVARs) within each age group to avoid predictions based on spurious between-subject differences (Duncan & Northoff, 2013; Power et al., 2012; Satterthwaite et al., 2013). Analogously, WMC scores were adjusted for effects of age and gender within each age group.

2.4. RVM features and prediction

RSFC values for all connections within a given network and subject represent individual features from which the individual WMC score were predicted using RVM (Tipping, 2001; Tipping & Faul, 2003) as implemented in the SparseBayes package (version 2.0 Matlab R2017b; <http://www.relevancevector.com>). To estimate the generalizability of the RVM models, a 10-fold cross-validation scheme was employed (see Fig. 2 for a schematic analysis workflow). The available data (subjects) were randomly split into 10 equally sized subgroups. In each cross-validation fold, a RVM was trained on 9 of these and then used to predict the WMC score of the left-out split (i.e., the subjects not used during training). Input features (= all RSFC values of a given network) and target variables were scaled to zero mean and unit SD based only on the training sample as to avoid any leakage. Deconfounding of input features and targets (as described above) was done once outside the cross-validation as recently proposed as the optimal strategy for prediction studies on individual phenotypes from RSFC (Pervaiz et al., 2020). To ensure the robustness of performance evaluation

against the initial folds, the cross-validation procedure was repeated 250 times using independent splitting. These analyses were performed for each network separately in young ($n = 50$) and old ($n = 45$) adults to investigate age-related differences in predictive performance. To examine whether residual movement-related effects may be a relevant contributor to WMC predictability, additional analyses were conducted with including DVARS as a predictor in the models (see supplementary method section for details).

Prediction accuracy (i.e., the ability of a given network's RSFC pattern to predict individual WMC scores) was indicated by the mean Pearson's correlation (\bar{r}) and mean absolute error (\overline{MAE}) between the real and predicted WMC scores computed first within each of the 10-folds and subsequently across all 250 cross-validation replications. To test whether performance was significantly different from zero, one-sample t -tests were performed on the 250 correlation coefficients, correcting for multiple comparisons over the assessed networks using Bonferroni's method. In addition, we only considered those predictions relevant that were at least of a medium effect size (i.e., $\bar{r} \geq .24$, corresponding to Cohen's $d = .5$). When WMC predictability was significant in either the young or old group, group differences were calculated using independent-sample t -tests (Bonferroni-corrected for the number of networks). To evaluate effect sizes of group differences, Fisher's Z -transformed mean correlation coefficients of the young and old groups were subtracted from each other. Subsequently, Cohen's q served for effect size interpretation (Cohen, 1988).

Moreover, to statistically examine differences in prediction performance between significantly predictive networks within each group, paired-sample t -tests were performed on prediction accuracies obtained from the 250 cross-validation replications of the RVMs (significance threshold: $p < .05$, Bonferroni-corrected for the number of comparisons). For a given network to be considered notably different, its prediction accuracy needed to differ to an at least small degree (Cohen's q) from most of the other networks (i.e., from at least 6 out of 8 networks).

To examine a potential performance dependence of WMC predictability from network-based RSFC in advanced age, the older sample was median-split into high- and low-WMC subgroups (post-hoc to the prediction analyses). The prediction accuracies (\bar{r}) were calculated within each subgroup, and significance tests were conducted as described above.

Given the inherent sparsity of RVM prediction models, induced by forcing feature weights to be zero to indicate irrelevant network connections, the remaining non-zero (i.e., contributing) connections in each RVM model were inspected to determine which connections of a given network were predictive of individual WMC scores. Connections used in at least 90% of the total 2500 predictive models per network are reported as the most frequently used and, therefore, most consistently predictive connections and are visualized with the BrainNet Viewer (Xia et al., 2013).

3. Results

3.1. Working memory capacity

WMC was significantly lower in the older sample compared to the young sample ($t = 6.07$, $p < .001$) and the variance did not differ ($F = .69$, $p = .21$; see Table 1 and Fig. 3). This is corroborated by a significant negative correlation between WMC and age in the entire sample ($r = -.48$; $p < .001$). The correlations between all three WMC subscores were significant in the entire sample with and without removing the effects of age. This suggests that age had very little influence on the relationship between single subscores (Table SIII).

3.2. Working memory capacity predictability from network RSFC

3.2.1. Young and old sample—All cognitive networks significantly predicted WMC in the older group: WM: $\bar{r}_{old} = .35$; $\overline{MAE} = .30$; cognitive action control (CogAC): $\bar{r}_{old} = .37$; $\overline{MAE} = .28$; vigilant attention (VigAtt): $\bar{r}_{old} = .33$; $\overline{MAE} = .33$; theory-of-mind cognition (ToM): $\bar{r}_{old} = .52$; $\overline{MAE} = .24$; and semantic memory (SM): $\bar{r}_{old} = .43$; $\overline{MAE} = .27$. All four control networks significantly predicted WMC in the older group: extended social-affective demand (eSAD): $\bar{r}_{old} = .45$; $\overline{MAE} = .27$; finger tapping and prosaccade eye movements (Motor + PS): $\bar{r}_{old} = .24$; $\overline{MAE} = .34$; finger tapping and somatosensory processing (Motor + SS): $\bar{r}_{old} = .52$; $\overline{MAE} = .24$; connectome-wide network (Connectome): $\bar{r}_{old} = .42$; $\overline{MAE} = .27$. The Fig. 4 and Table 2 provide an overview of the averaged prediction accuracies of the RVM results. The Fig. 5 summarizes the scatter plots of real and predicted WMC scores based on each network. Furthermore, Table SIV provides the detailed statistics on the WMC predictability from each network's RSFC. When compared to all other eight predictive networks in the older group, the ToM network showed significantly better predictability (between-network comparison of prediction performance r at $p < .001$: WM: $t = 21.39$; CogAC: $t = 19.53$; VigAtt: $t = 24.81$; SM: $t = 13.04$; Motor + PS: $t = 34.79$; Connectome: $t = 12.86$). In contrast, only the predictability of the Motor + PS network combination was significantly lower (WM: $t = -13.68$; CogAC: $t = -15.72$; VigAtt: $t = -10.69$; ToM: $t = 34.79$; SM: $t = -22.68$; eSAD: $t = -24.03$; Motor + SS: $t = 32.67$; Connectome: $t = -22.06$), whereas the Motor + SS combination exhibited significantly better predictability (WM: $t + 21.41$; CogAC: $t = 18.79$; VigAtt: $t = 22.59$; SM: $t = 11.52$; Motor + PS: $t = 32.67$; Connectome: $t = 12.76$ [see Table SV]).

In contrast, in the young group none of the networks was significantly predictive of WMC, only slight trends were observed for the WM: $\bar{r}_{young} = .17$ and $\bar{r}_{young} = .16$ for the SM, Motor + PS and Connectome networks. Using global signal regression (compared to white-matter and cerebrospinal-fluid signal removal) resulted in an increase in the specificity of predictability across networks mainly linked to a decrease in prediction accuracy (see Table 3). Although global signal regression has a particular impact on WMC predictability in the old group, for which potential motion-unrelated sources are discussed later, additional analyses controlling for movement-related artifacts in RSFC data did not corroborate that residual motion effects unduly influenced WMC predictability in the old group (see Table SVI for RVM results based on data for which preprocessing included censoring as well as Table SVII for results of analyses that included DVARS as a predictor). Moreover, neither

the predictiveness from intra- and inter-network connections nor from the entire connectome demonstrated substantial improvements over that of individual functional networks (see Table SVIII and Table 2).

We observed significant age-related differences in WMC predictability for all networks with effect sizes ranging from small to large: Cohen's q : WM = .19; CogAC = .38; VigAtt = .40; ToM = .55; SM = .30; eSAD = .54; Motor + SS = .46 and Connectome = .29 ($p < .001$; see Table 2 and Table SIX).

Moreover, the analyses of high- versus low-WMC participants of the older subsample revealed that overall predictability in the elderly might have been mainly driven by low-WMC older adults for the majority of networks: WM: $\bar{r}_{\text{old low}} = .37$, $\bar{r}_{\text{old high}} = .22$; CogAC: $\bar{r}_{\text{old low}} = .41$, $\bar{r}_{\text{old high}} = .19$; VigAtt: $\bar{r}_{\text{old low}} = .40$, $\bar{r}_{\text{old high}} = .18$; ToM: $\bar{r}_{\text{old low}} = .33$, $\bar{r}_{\text{old high}} = .30$; SM: $\bar{r}_{\text{old low}} = .49$, $\bar{r}_{\text{old high}} = .29$; Motor + PS: $\bar{r}_{\text{old low}} = .28$, $\bar{r}_{\text{old high}} = .02$; Motor + SS: $\bar{r}_{\text{old low}} = .40$, $\bar{r}_{\text{old high}} = .24$ (see Table 4, Table SX for additional predictions based on intra- and inter-network connectivity, Tables SXI and SXII for statistics).

3.2.2. Relevance of single connections—As RVMs generate sparse solutions, we could identify specific connections within each of the cognitive networks that were frequently used by the prediction models (i.e., in at least 90% of the 2500 [10 foldings \times 250 repeats] models per network), hence representing consistent and potentially relevant contributions to predicting WMC. In the older group, these frequently used connections were as follows (see Figure SI): for the WM network, the connection between left inferior frontal gyrus and left thalamus, and for the ToM network, the connection between right superior medial gyrus/frontal pole and left angular gyrus/temporo-parietal junction. For the CogAC, VigAtt and SM networks, none of the connections met our criteria. For all the networks the percentages of connection usage across models are displayed in Fig. 6.

4. Discussion

We examined whether and to what degree individual RSFC patterns in any of eight meta-analytically defined functional brain networks and a connectome-wide network predicted WMC in previously unseen young and old participants using ML-based regression analysis with the aim to investigate age-related differences (young vs old adults). Our results demonstrate that individual WMC could be predicted from all five cognitive WM-related networks ($\bar{r} \geq .33$) with the highest accuracy of $\bar{r} = .52$ (ToM network), whereas predictability from WM-unrelated networks varied with differential degree, with the Motor + PS network showing the lowest significant predictability ($\bar{r} = .24$) in the older group. In the young group, none of the networks was predictive. WMC predictability across networks in the old group was primarily linked to lower WMC.

4.1. Age differences in WMC predictability

In the old sample, individual WMC could be similarly well predicted from the RSFC patterns of the WM network and networks both closely related to WM (i.e., CogAC and VigAtt) and distantly related to WM (i.e., ToM and SM). This demonstrates that the

interregional coupling in a task-unconstrained state within robustly defined brain networks recruited for executive functions and higher-order cognitive tasks contains information about individual WM performance. Moreover, WM-unrelated networks associated with task-negative, social-affective and introspective processes (eSAD), finger tapping and prosaccade eye movements (Motor + PS), or finger tapping and somatosensory processing (Motor + SS) also predicted WMC in advanced age. Thus, the strength of functional coupling (at rest) between these regions (defined by consistent activation during tasks) is associated with WM abilities tested outside the MRI scanner. The similarity to which WMC is predicted across different networks, related or unrelated to WM, is potentially linked to a decreased segregation of functional brain networks in advanced age (Chan et al., 2014, 2017), which in turn may be related to the often proposed neural-level dedifferentiation with aging (i.e., a declining specificity of neuro-functional systems; Goh, 2011; Grady, 2012; Sala-Llonch et al., 2015). The fact that networks become less segregated with age may lead to a situation where predictive information on individual WMC can be extracted from a broad range of networks. Alternatively, this “broadened” predictability of WMC may reflect widespread age-related changes that lead to similarly reduced network integrity within different networks (Varangis et al., 2019; Zonneveld et al., 2019), through which all the networks sampled here come to contain reasonably predictive information on performance.

While all of the cognitive networks may be expected to relate to some degree to WM, given some shared neural and behavioral variance between WM and other executive and cognitive processes, it should be noted that the predictive capacity of the CogAC and VigAtt networks was not primarily driven by their partial spatial overlap with regions of the WM network (Camilleri et al., 2017; Müller et al., 2015). That is, spatial similarity does not automatically lead to a similar pattern of RSFC–performance associations (see Fig. 6). The significant predictability of WMC in the old sample from the RSFC patterns of multiple networks (WM, CogAC, VigAtt, ToM, SM, eSAD, Motor + PS and Motor + SS) extends previous aging research that revealed age differences in univariate associations between WM performance and RSNs (Charroud et al., 2016; Jockwitz et al., 2017; Sala-Llonch et al., 2012).

In addition, not finding any substantial improvement in predictiveness from intra- and inter-network connectivity over individual networks suggests, first, that it is not the sheer (higher) number of features that determines prediction performance here, and second, that it is not the connectivity between the different networks that provides higher information content with respect to WMC. In line with this, even the connectome-based prediction, which rests on an even higher number of connections, was not superior, suggesting that no additionally predictive information can be distilled from a functionally agnostic, though spatially comprehensive, brain-wide representation of RSFC, as compared to sparse but functionally meaningful brain networks. Alternatively, finding no substantial improvement in predictiveness for the whole-brain connectome might partly also be due to a less favorable feature-to-sample ratio.

The generally low predictability of WMC in young adults based on the networks investigated here (chosen according to theoretical considerations as detailed in the introduction) indicates that RSFC patterns within these networks do not hold information on

individual WM performance in younger age. While this remains somewhat surprising, particularly for the WM network, it may be attributable to the differences in task demands between WM paradigms used in the scanner (and hence defining the meta-analytic network) and the WMC score employed here (Kane et al., 2007). This assumption would reinforce the notion of a higher specificity in brain-behaviour relations in young adults, as compared to a less segregated and/or altered integrity situation among the elderly, leading to a more global predictability of cognitive capacities from a broad range of brain networks (cf. Ward et al., 2015). Alternatively, this observation could also simply mean that young adults reconfigure their networks in task states more extensively to meet task-specific demands and, therefore, RSFC patterns at rest are less predictive, whereas task and rest configurations are more similar to, or predictive of, each other in advanced age. Ultimately, the overall low predictability, with only slight predictive trends for some networks, indicates a lack of shared variance between RSFC and WMC. Accordingly, young adults appear to not exhibit typical network-based RSFC patterns that correspond to certain WMC levels, at least in the functional networks investigated in relation to the composite WMC score used here.

The better overall prediction in the older group might be related to factors of age-related neural decline that include brain atrophy and white-matter degeneration (Allen et al., 2005; Cabeza et al., 2016b; Cox et al., 2016), which may be related to altered network integrity and, hence, altered within-network processing efficiency. Together these may lead to brain organizational changes that strengthen the association between WMC and the integrity of brain networks as assessed by RSFC. This suggests that the composite WMC score contains information related to advanced age. Hence, the high predictability across networks in older adults may, in part, result from age-related neural reorganization that is associated with performance and includes RSFC changes across different networks (Sala-Llonch et al., 2015). These age-related changes in older adults were then picked up by the prediction models, leading to better prediction performance. Importantly, predictability across networks differed between low- and high-WMC older adults. Differential age-related neural plasticity may be related to low versus high WM abilities represented by reorganization mechanisms linked to a decreased segregation of functional brain networks. This seems to be associated with reduced functional specificity across networks and/or reduced network integrity within different networks as well as, possibly, compensation through reorganization. Each reorganizational process may manifest itself in altered patterns of within-network RSFC, which may drive associations between networks' RSFC patterns and WMC. The higher predictability across cognitive networks (closely or distantly linked to WM) as well as task-negative and motor-sensory networks (WM-unrelated) in older adults with lower WMC may be related to a stronger association such as a blurring of functionally distinct network systems almost exclusively linked to declined performance. This might represent reorganization mechanisms related to a decreased segregation of functional brain networks (e.g., a tighter link between cognitive, task-negative and motor-sensory systems) manifested in altered patterns of within-network RSFC, and may drive associations with lower WMC scores.

Alternatively, the high predictability across networks might be linked to widespread age-related changes leading to a weakening of within-network connectivity associated with an increase in networks' susceptibility to interference and, hence, performance deterioration

(Stevens et al., 2008; Varangis et al., 2019; Zonneveld et al., 2019). These alterations may lead to a similarly reduced network integrity in distinct networks, which are linked to low WMC. Either way or in combination, this suggests that especially very low performance levels in the old subsample are predictable from RSFC across networks possibly because the network changes are so pronounced that they cannot be compensated during WM-related task-demands. As a consequence, reduced WM functioning may result from this decreased network segregation and/or reduced network integrity due to a loss of effective neural communication. Such a decrease in functional specificity of multiple brain systems has previously been shown to have a negative impact on WM functioning (Chan et al., 2017, 2014; Goh, 2011). These assumptions are based on graph-theoretical analyses of major RSNs demonstrating that aging is concomitant with a loss in distinctiveness of functionally specific networks (Geerligs et al., 2015) and decline in episodic memory performance (Chan et al., 2014). In response to detrimental neuro-functional changes with age such as less segregated networks, older adults may also show compensatory neural reorganization to maintain cognitive functioning, including altered RSFC patterns associated with increased neural efficiency in particular systems (Cabeza et al., 2018). Concretely, we found RSFC patterns associated with high WMC for the ToM network, rather distantly related to WM but linked to higher-order social cognition, and for a control network involved in motor and somatosensory processing (Motor + SS). The association between higher WMC and significantly better predictiveness of the higher-order social-cognition network (compared to other cognitive networks) but significantly lower predictability from motor-sensory systems (Motor + PS: $\bar{r}_{\text{old high}} = .02$, Motor \bar{p} SS: $\bar{r}_{\text{old high}} = .31$; compared to the higher predictability of motor-sensory networks in lower performers Motor + PS: $\bar{r}_{\text{old low}} = .28$, Motor \bar{p} PS: $\bar{r}_{\text{old low}} = .45$) may be related to network configurations more responsive to neuroplastic adaptation to improve cognitive functions (Gallen et al., 2016; Jordan et al., 2018). Hence, network configurations in older adults with higher WMC may constitute a marker for compensatory reconfiguration that may be relevant for (and thus predictive of) task performance, counteracting the neuro-functional deterioration of cognitive systems in advanced age. Alternatively, this pattern of results may indicate the beginning of neural-level dedifferentiation with aging, at an as-yet less pronounced stage of decline than exhibited in old adults with low WMC. In turn, RSFC patterns associated with declined WMC may indicate a marker for less efficient network configurations during WM task performance (and possibly other cognitive functions that depend on WMC) potentially due to less segregated network systems (Chan et al., 2014; Grady, 2012) and/or altered network integrity (Varangis et al., 2019; Zonneveld et al., 2019).

Eventually, the pattern of our results suggests that normal aging is accompanied by some rather global brain reorganization, broadly affecting brain systems linked to various functions including WMC (Pläschke et al., 2017). Accordingly, brain systems involved in executive functions and other higher-order cognitive functions, as well as perceptuo-motor systems would be affected by this age-related reorganization, which seems to share some variance with normal age-related WMC decline.

4.2. Contribution of network connections to WMC predictability in advanced age

In the older group, the most consistently informative connections (i.e., used > 90% throughout all prediction models) of the WM and ToM networks may, at least in part, account for inter-individual differences in WMC. In particular, the connection between the left inferior frontal gyrus (*p. opercularis*) and the left thalamus of the WM network may play a potential role in gating access to WM within the basal ganglia-thalamo-cortical loops (Bäckman et al., 2006; Nyberg & Eriksson, 2016; Schroll et al., 2012). Within the ToM network the most prominent connection is located between the right superior medial gyrus/ frontal pole (FP) and the left angular gyrus/temporo-parietal junction (AG/TPJ). The AG/TPJ has been associated with the retrieval of verbal material implicated in verbal WM, whereas the FP has been associated with the planning and organization of future actions. Both regions may hence subservise cognitive processes that overlap between ToM and WM. Therefore, this connection's strength may reflect a substrate of the crucial interplay between retrieval of verbal information and the planning of task execution associated with WM tasks.

The observed key connections seem to play a relevant role in the corresponding network at rest, suggesting that older adults with low WMC (potentially related to less segregated systems/deteriorated network integrity) might recruit these networks differently in demanding task settings than do older adults with larger WMC (possibly linked to compensatory reorganizational adaptations; see Fig. 3, Table 4 and Figure SI).

4.3. Conceptual considerations and outlook

Using ML in an out-of-sample prediction framework, we investigated the association between WMC and the multivariate intrinsic coupling pattern within functional brain networks and its modulation by age, which extends results of previous univariate approaches examining the relationship between cognitive decline and RSFC in advanced age (Andrews-Hanna et al., 2007; Sala-Llonch et al., 2012). We would like to highlight that our predictions are based on RSFC in meta-analytically defined functional networks, which offers the key advantage of being able to relate WMC to particular well-circumscribed functional systems, allowing for a specific interpretation of functionally distinct brain network–WMC associations revealed by ML-based predictions.

Remarkably, our prediction performance of about $r = .40$ in the older group based on sparse single functional networks, as opposed to whole-connectome approaches, can compete with WM performance predictions from combined measures of structural and functional imaging (alpha span and digit backwards: $r = .35$) in a sample of 132 older adults (Y. Wang et al., 2013). Furthermore, our observed prediction performance is quite noteworthy given the relatively small sample size in the groups and the application of a robust and rather conservative approach to testing model generalizability (viz., 250 repetitions of a 10-fold cross-validation scheme), than using the optimistic leave-one-out approach known to be prone to overfitting (Varoquaux et al., 2016). However, for the young sample we cannot exclude that the absent to low predictability might also be related to the moderate sample size. Besides, it needs to be acknowledged that the meta-analytical networks were derived from imaging studies primarily done in young and middle-aged adult samples. Therefore, it is likely that networks defined from studies in older samples would reveal age-specific

differences in network topology. For instance, additional regions might turn out to be implicated in altered network configurations linked to reorganizational processes in advanced age and, hence, may result in differences in brain–behavior associations between young and older adults (Burianová et al., 2013). As such, the observed age-related prediction differences may also reflect topological differences in network architecture between age groups. Nevertheless, because the meta-analyses defining the networks comprised samples with varying mean age and age range, we would argue that they reflect the normative definition of the spatial network layout, even if this means a certain bias against the average network layout that may develop in advanced age.

Despite proper state-of-the-art removal of variance related to potential confounds (Ciric et al., 2017; Pervaiz et al., 2020; Power et al., 2012; Satterthwaite et al., 2013) as well as motion-related control analyses, we cannot entirely exclude that the alteration in WMC predictability when applying GSR may in part be related to residual motion-related effects. However, the global signal may contain neural signal of interest that is unduly removed, which in turn may have contributed to reduced predictability. In line with this, recent evidence points to the need to be especially cautious with applying GSR when comparing groups with different noise characteristics, as in young versus older adults, or with varying neural network structures (Murphy & Fox, 2017).

Given that multiple functional networks were predictive of WMC and the connectome-wide network showed similar predictability, we cannot rule out that RSFC between regions distributed across the entire brain (i.e., outside our predefined networks) is a marker for WMC in advanced age. Support for this notion stems from data-driven whole-brain approaches, demonstrating that RSFC between regions outside the well-known attention-related network can be crucial to predict sustained-attention performance (Rosenberg et al., 2016). This may similarly apply to WMC, particularly in younger adults. Moreover, we cannot exclude that factors of non-neural origin such as physiological changes linked to aging and their impact on the hemodynamic signals (D’Esposito et al., 2003; West et al., 2019) may have contributed to our findings. Hence, the relationship between RSFC and cognition in aging definitively demands further investigation with the aim of precise predictions on a single-subject level. One of the highlights is the use of the RVM, which offers the advantage of a better localization and interpretability of connections that mainly drove the predictions by providing considerably sparse solutions with superior generalizability (Tipping, 2001; Y. Wang et al., 2010). Therefore, a more detailed evaluation of the neural mechanisms driving the predictions can be achieved.

Compared to previous studies addressing such age-related brain-behavior relationships in a data-driven way (Charroud et al., 2016; Wang et al., 2013), our approach offers the chance to improve our understanding of how and to what degree individual differences in particular cognitive functions (here: working memory) are represented and potentially implemented by particular features (here: RSFC) of a priori defined functional networks. Using meta-analytically derived functional networks in combination with performance prediction, we can evaluate whether particular features of networks known to be involved in certain cognitive functions do in fact contribute to inter-individual behavioral variation in this function, and how this is affected by age. As we have shown, individual RSFC patterns do

not always translate into individual performance levels (here: WMC), and the average level of predictability per group also seems to be related to the specificity of the predictability across networks: With both overall low predictability (in young adults) and overall rather high predictability (in older adults), specificity is low, which appears like floor and ceiling effects, respectively.

Although our data and analyses do not reveal the specific mechanisms underlying the generally better WMC predictability in advanced age, the network-specific analyses allowed us to reveal that normal aging is linked to a non-specific (i.e., network-independent) pattern of RSFC–performance relationships that spans across rather distinct networks. This would not have been possible with previous approaches based on the whole-brain connectome, which even in young samples often yielded patterns of RSFC among widely distributed and (seemingly) unrelated brain regions to be predictive of a given behavioral or cognitive feature (Finn et al., 2015; Rosenberg et al., 2016). Overall, the present study may answer as many questions as it raises new ones, but we hope that this will spur future research to unravel the neural mechanisms driving these predictions and their age-related differences. We argue that our approach of combining meta-analytically defined functional networks with multivariate pattern-regression using a robust cross-validation scheme provided new insights into aging-related brain reorganization by linking WMC to brain network integrity.

5. Conclusion

We investigated whether and to what degree the RSFC patterns of eight functional brain networks and a connectome-wide network predict individual WMC in young and old adults. By using ML-based regression modeling in a robust cross-validation scheme, age differences in predictability were examined. The comparison of prediction performance in young and old participants revealed differences in brain–behavior associations.

While a general unpredictability of the networks' connectivity patterns was observed in young adults, each network predicted WMC in older adults, suggesting neurobiological adaptation related to WM task demands predictable from resting-state interregional coupling. In advanced age, a similar degree of predictive power across diverse networks suggests different possibilities or combinations of neural-level reorganization such as a decreased segregation of functional networks, brain-wide alterations in network integrity and/or compensatory connectivity changes as common factors underlying inter-individual variation in WMC. Our results thus offer novel insights into age-related reorganization of functional brain networks linked to low and high WMC. Finally, our study underlines the value of RSFC as a marker for individual WMC in advanced age and potentially as a source for examining neural mechanisms linked to cognitive deterioration by using ML-based prediction.

Transparency and openness promotion (TOP) guidelines

Our participants did not consent to sharing their data with any third party for re-use; therefore, the conditions of our ethical approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact the author Robert Langner. Data can and will only be released to researchers who agree to collaborate with the

principal investigators, e.g., through a formal collaboration agreement. Thus, data are not generally available to individuals for the purposes of independent analysis and verification. Access can be granted only in accordance with ethical procedures governing the reuse of sensitive data, which would involve requesting permission to share the study data from the local ethics committee of the RWTH Aachen University Hospital, Aachen, Germany. Further, if permission is granted, each participant would need to retrospectively approve the data transfer to third parties.

We did not use experimental stimuli or presentation code in the resting-state fMRI study setting. We have deposited the analysis code under <https://osf.io/wru83>.

No part of the study procedures and analyses were preregistered in a time-stamped, institutional registry prior to the research being conducted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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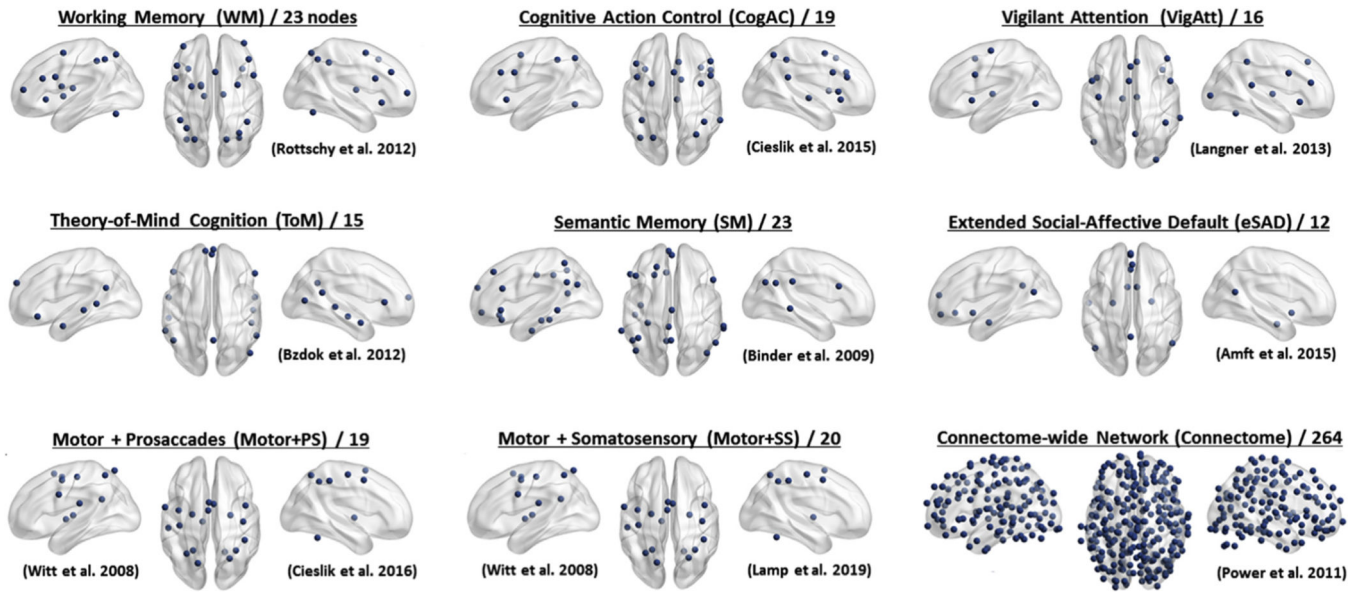


Fig. 1 –
Nodes of meta-analytically defined networks.

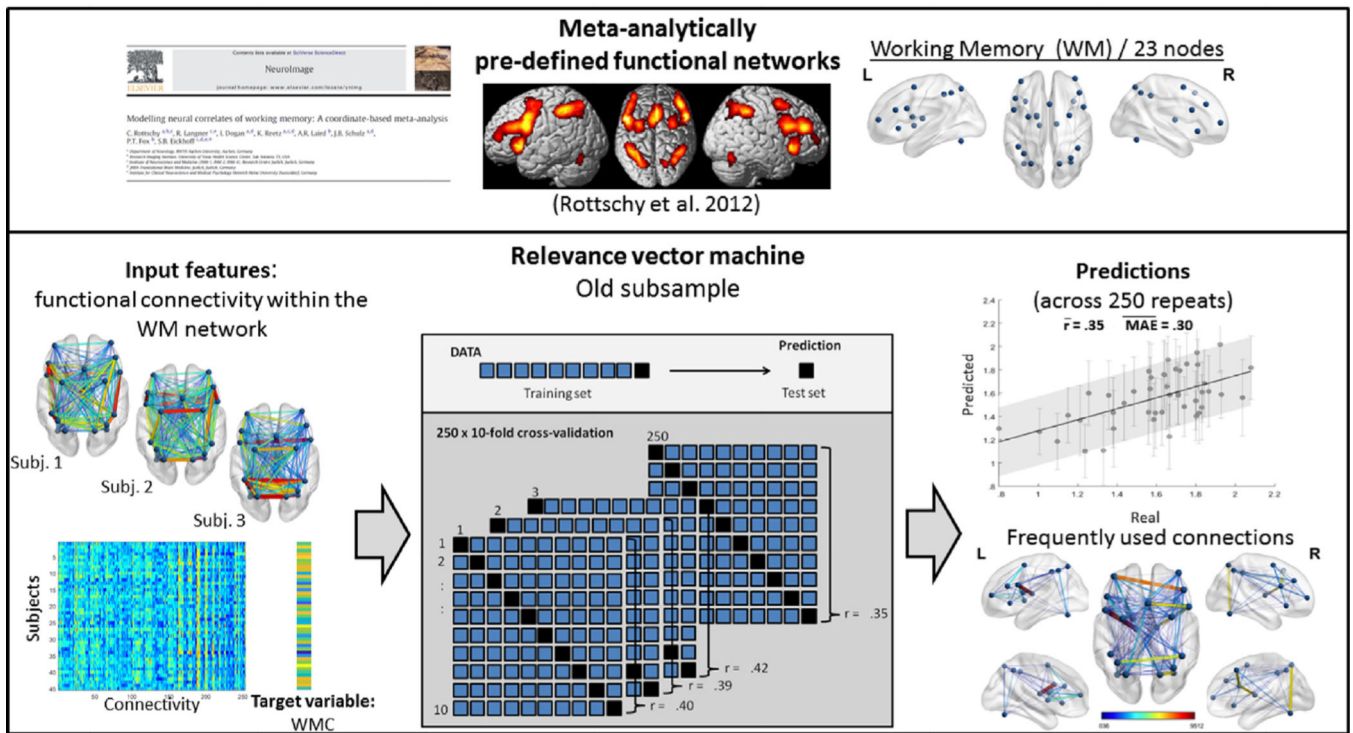


Fig. 2 –.
 Schematic exemplary analysis workflow: Working memory capacity (WMC) is predicted from resting-state functional connectivity in the WM network in the old sample. \bar{r}/\overline{MAE} : mean Pearson correlation coefficient/mean absolute error between real and predicted scores across 250 cross-validation repeats.

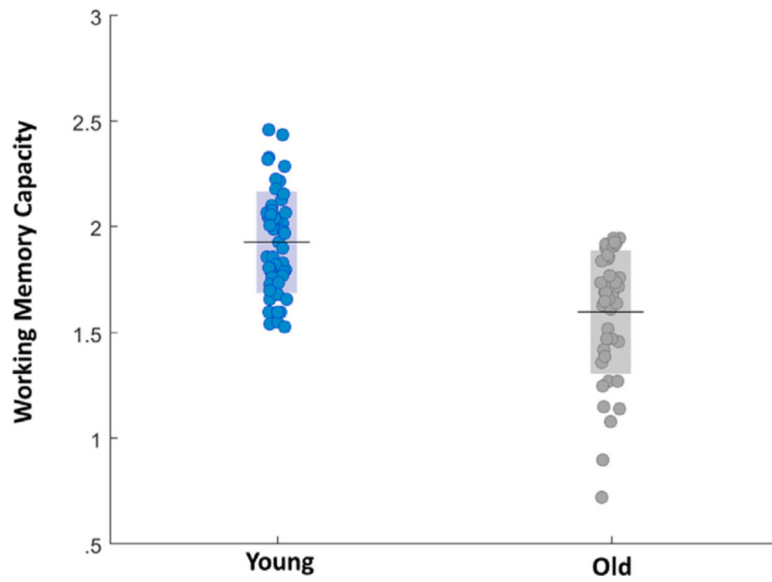


Fig. 3 –. Working memory capacity (WMC) plotted against age for young (in blue) and old (in gray) participants. Mean WMC (horizontal line) \pm SD (bounded box) for the young sample was $1.93 \pm .24$ and for the old one: $1.60 \pm .29$.

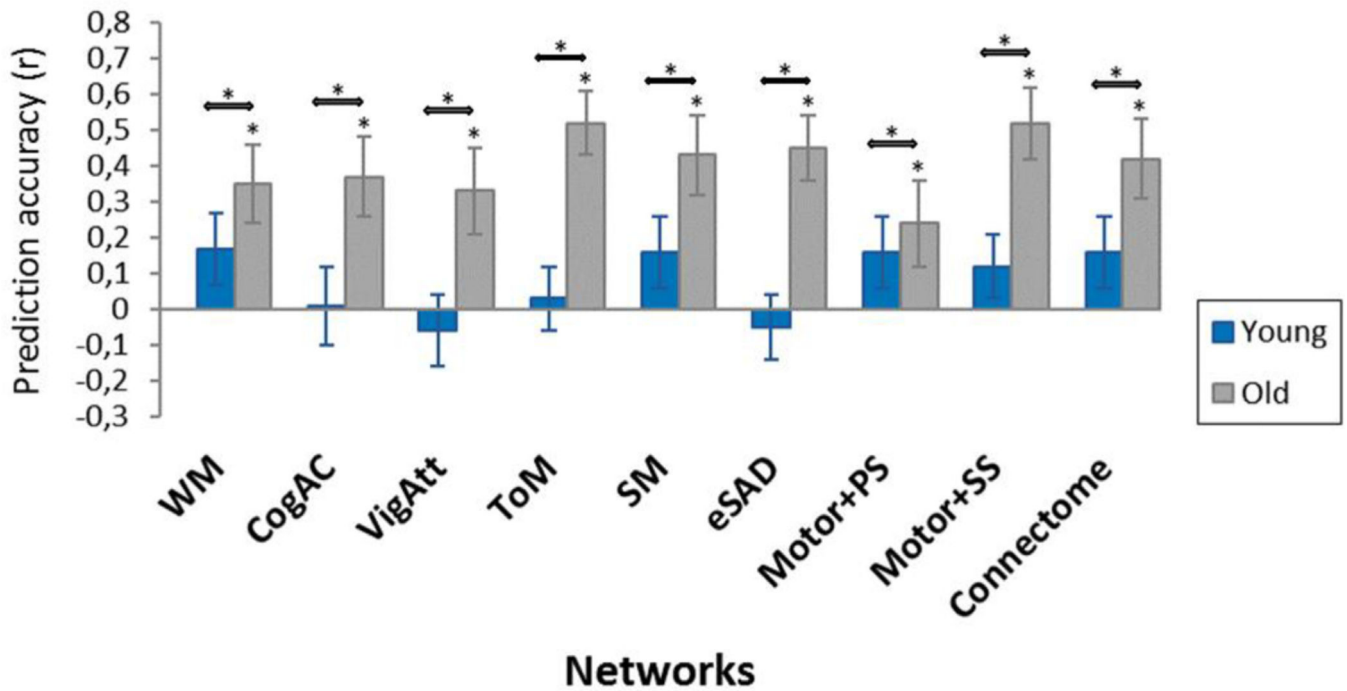
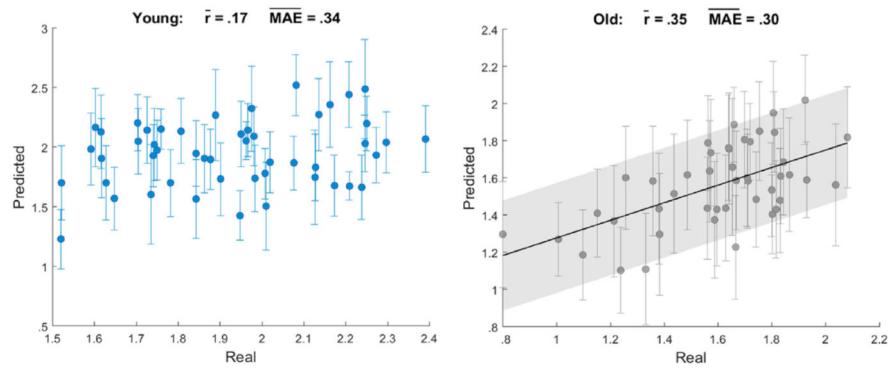


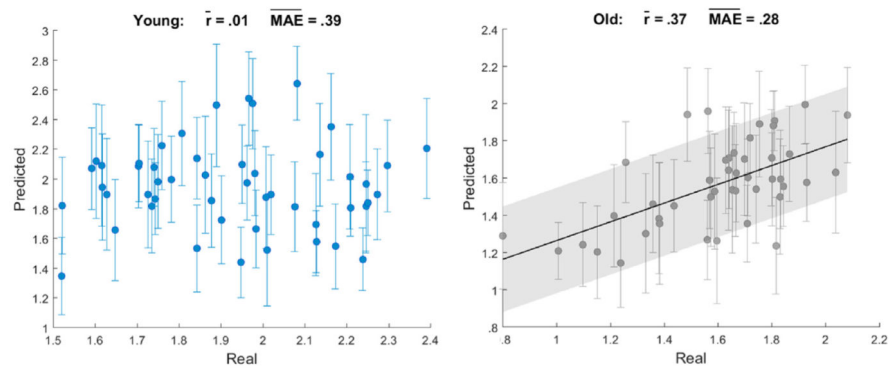
Fig. 4 –.

Bar plot of prediction accuracies expressed as mean (error bars: SD) Pearson correlations (r) between real and mean predicted working memory capacity (WMC) scores across 250 cross-validation repeats for the young (in blue) and old (in gray) sample. * significant ($p < .001$) predictions/group differences. WM, working memory; CogAC, cognitive action control; VigAtt, vigilant attention; ToM, theory-of-mind cognition; SM, semantic memory; eSAD, extended social-affective default; Motor + PS, motor + prosaccades; Motor + SS, motor + somatosensory.

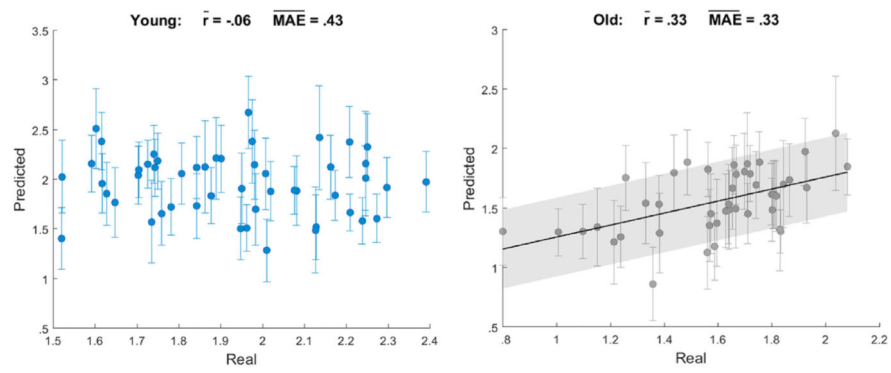
Working Memory Network



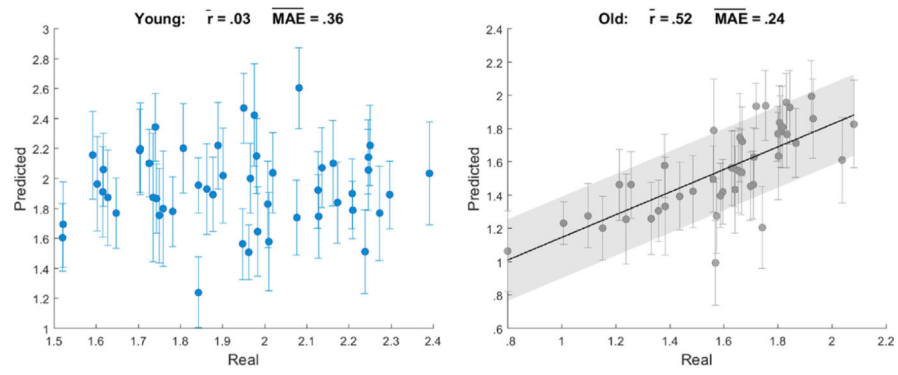
Cognitive Action Control Network



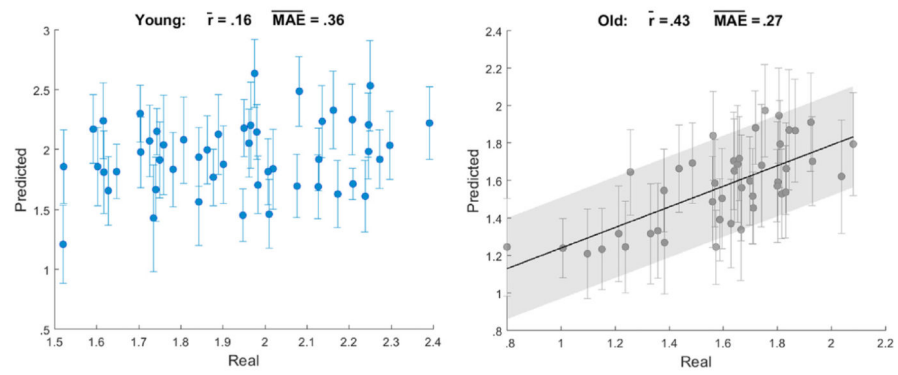
Vigilant Attention Network



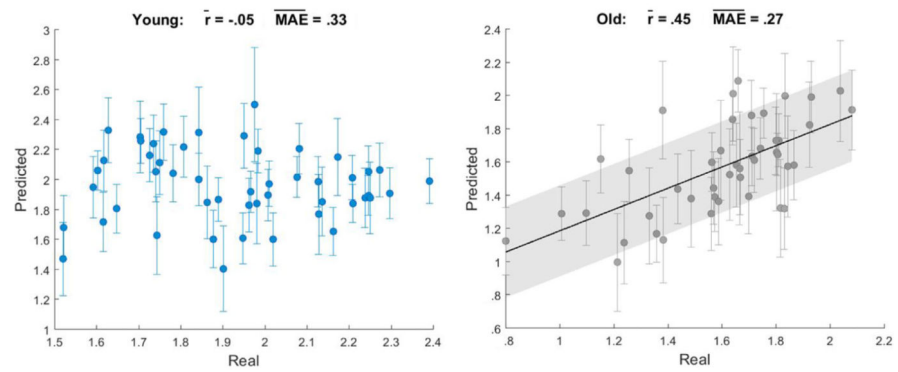
Theory-of-Mind Cognition Network



Semantic Memory Network



Extended Social-Affective Default Network



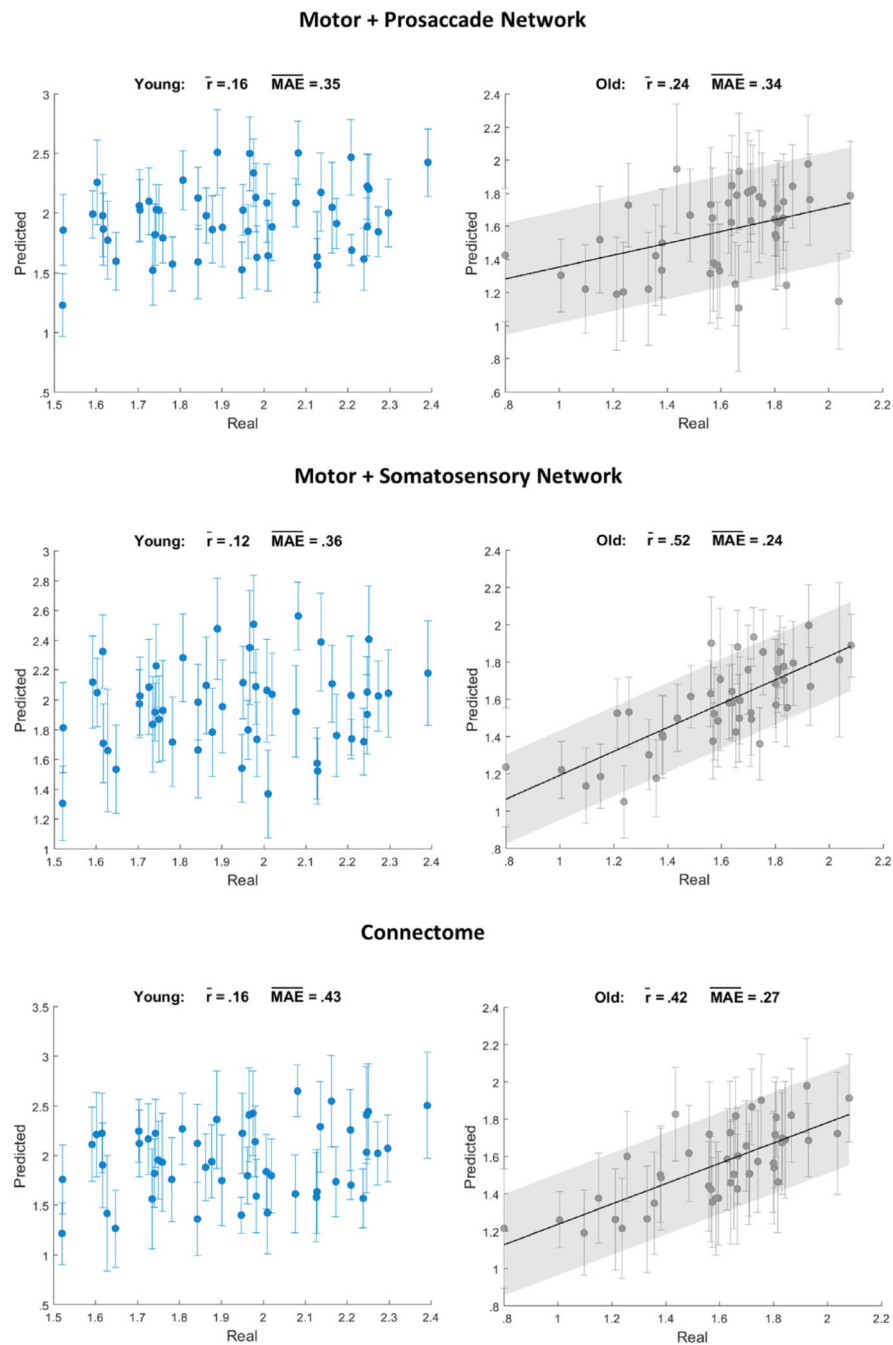


Fig. 5 –. Predictability of individual working memory capacity (WMC) based on functional connectivity patterns in nine brain networks. Scatter plots show real against mean predicted WMC scores across 250 cross-validation repeats (error bars: SDs) for young (denoted in blue) and old (denoted in gray) participants. For significant prediction accuracies (r): Pearson correlations between real and predicted scores), a linear regression line and a gray bounded line indicating the mean absolute error (\overline{MAE}) were added.

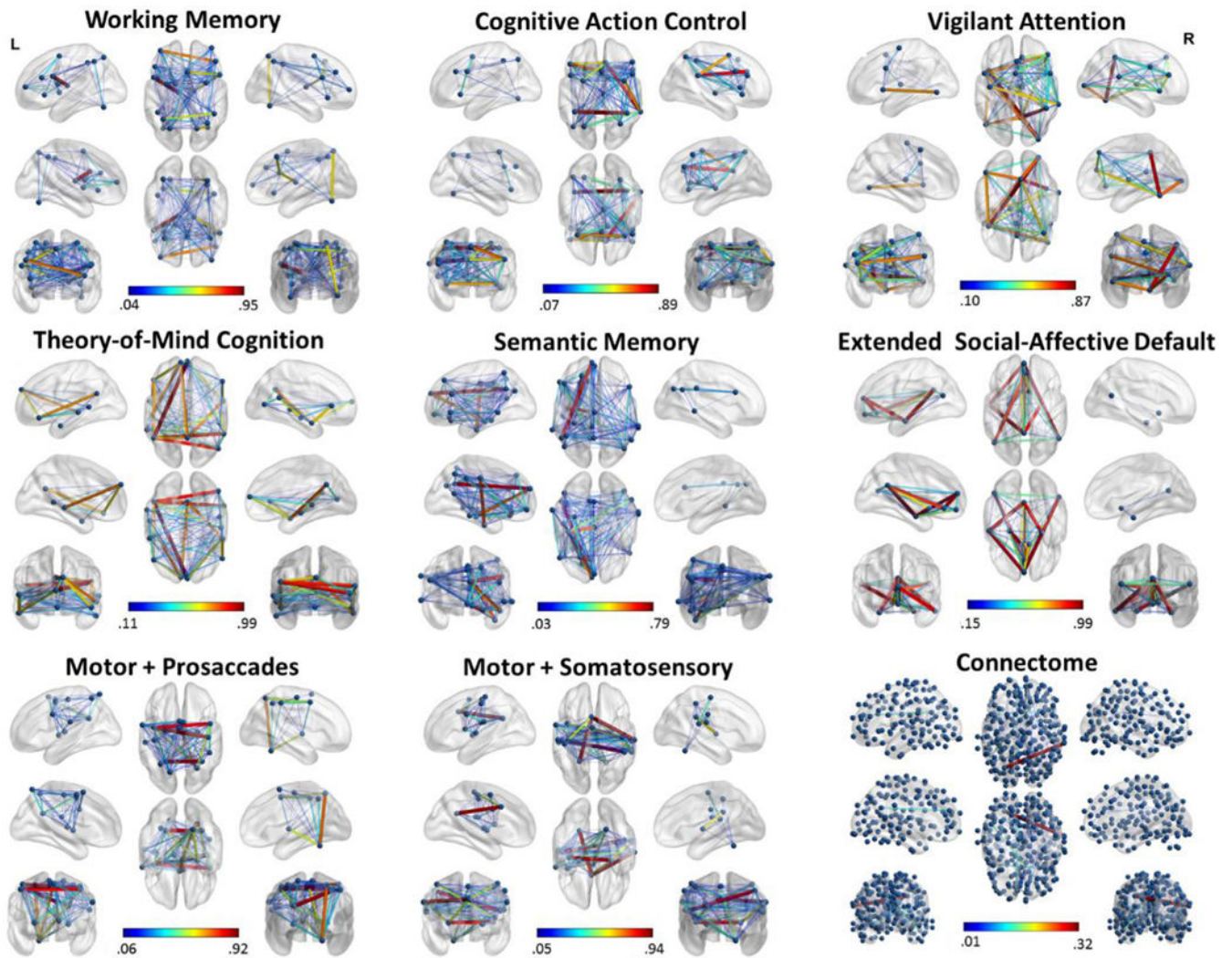


Fig. 6 –.

Illustration of the frequency with which connections were used in each of the nine functional brain networks for predicting working memory capacity (WMC) in the old sample.

Displayed are only nodes with a “relevant” connectivity (edge) value attached to them. Color indicates the percentage of use across 2500 cross-validation repeats per network (ranges are indicated with the color bars).

Table 1 –

Sample characteristics.

Normal Aging Sample	N (males)	Age (years)	Head Movement (DVARs)	DemTect	BDI-II	WMC
Young	50 (27)	26 ± 3	1.25 ± .25	–	6 ± 5	1.93 ± .24
Old	45 (24)	62 ± 5	1.57 ± .41 *	16 ± 2	5 ± 5	1.60 ± .29 *
WMC Low	24 (9)	61 ± 5	1.51 ± .46	16 ± 2	6 ± 5	1.40 ± .26
WMC High	21 (15)	62 ± 6	1.63 ± .34	17 ± 2	4 ± 5	1.82 ± .09 *

Note. All values (except *n*) represent mean ± SD.

DVARs, derivative of root mean squared variance over voxels (head movement parameter).

DemTect, Mild Cognitive Impairment and Early Dementia Detection; BDI-II, Beck Depression Inventory II.

WMC, working memory capacity score.

* Significantly different between groups at $p < .05$.

Table 2 –

Predictability of individual working memory capacity based on functional connectivity in nine brain networks.

	Networks								
	WM	CogAC	VigAtt	ToM	SM	eSAD	Motor + PS	Motor + SS	Connectome
\bar{r} young	.17	.01	-.06	.03	.16	-.05	.16	.12	.16
\bar{r} old	.35*	.37*	.33*	.52*	.43*	.45*	.24*	.52*	.42*
Cohen's q	.19	.38	.40	.55	.30	.54	.08	.46	.29

Pearson correlations between real and predicted working memory capacity (WMC) scores in the young \bar{r} young and old \bar{r} old sample, Cohen's q : effect size of age group differences in correlations (<.1: no effect; .1 – .3: small effect; .3 – .5: medium effect; >.5: large effect).

* Significant ($p < .001$) predictions with at least medium effect size ($\bar{r} \geq .24$, corresponding to Cohen's $d = .5$).

Predictability of individual working memory capacity based on functional connectivity in nine brain networks - global signal regression.

Table 3 –

	Networks								
	WM	CogAC	VigAtt	ToM	SM	eSAD	Motor + PS	Motor + SS	Connectome
\bar{r}_{young}	.12	0	.06	.09	.18	-.19	.11	.16	.20
\bar{r}_{old}	.40*	.27*	.26*	.42*	.33*	.32*	.39*	.36*	.43*
Cohen's q	.30	.28	.21	.36	.16	.52	.30	.22	.26

Pearson correlations between real and predicted working memory capacity (WMC) scores in the young \bar{r}_{young} and old \bar{r}_{old} sample.

* Significant ($p < .001$) predictions with at least medium effect size ($\bar{r} \geq .24$, corresponding to Cohen's $d = .5$).

Predictability of individual working memory capacity based on functional connectivity in nine brain networks in low- and high-WMC older adults.

Table 4 –

	Networks								
	WM	CogAC	VigAtt	ToM	SM	eSAD	Motor + PS	Motor + SS	Connectome
$\bar{r}_{\text{old low}}$ (n = 24)	.33*	.34*	.25*	.37*	.41*	.42*	.28*	.45*	.35*
$\bar{r}_{\text{old high}}$ (n = 21)	.08	.12	.23	.33*	.21	.18	-.02	.31*	.26v
Cohen's <i>q</i>	.26	.23	.02	.05	.22	.27	.31	.16	.10

Pearson correlations between real and predicted working memory capacity (WMC) scores in the old sample with low ($\bar{r}_{\text{old low}}$) and high ($\bar{r}_{\text{old high}}$) WMC. Cohen's *q*: effect size of differences in correlations between networks in low and high WMC older adults (<.1: no effect; .1 – .3: small effect; .3 – .5: medium effect; >.5: large effect).

* Significant ($p < .001$) predictions with at least medium effect size ($\bar{r} \geq .24$, corresponding to Cohen's *d* .5).