Title: Combination of structural and functional connectivity explains unique variation in specific domains of cognitive function.

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Declarations of interest: none

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Highlights:

- We assessed the relationship between cognitive domains and structural, functional and joint structural-functional connectivity.
- We found that Processing Speed and Self-regulation components were best predicted by joint models.
- Other, more regionally localised cognitive domains were best modelled by functional connectivity alone.
- Our findings provide insight into separable contributions of function and structure to different cognitive domains.

Abstract

The relationship between structural and functional brain networks has been characterised as complex: the two networks mirror each other and show mutual influence but they also diverge in their organisation. This work explored whether a combination of structural and functional connectivity can improve models of cognitive performance, and whether this differs by cognitive domain. Principal Component Analysis (PCA) was applied to cognitive data from the Human Connectome Project. Four components were obtained, reflecting Retention and Retrieval, Processing Speed, Self-regulation, and Encoding. The PCA-Regression approach was applied to predict cognitive performance using structural, functional and joint structural-functional components. Model quality was evaluated using model evidence, model fit and generalisability. Functional connectivity components produced the most effective models of Retention and Retrieval and Encoding, whereas joint structural-functional components produced most effective models of Processing Speed, and Self-regulation. The present study demonstrates that multimodal data fusion using structural and functional connectivity can help predict cognitive performance, but that the additional explanatory value (relative to overfitting) may depend on the specific selection of cognitive

domain. We discuss the implications of these results for studies of the brain basis of cognition in health and disease.

1. Introduction

Cognitive neuroscience generally seeks to uncover and understand neural substrates of cognitive processes and adaptive behaviour. They have done so by examining brain structure and function. Brain structure refers to the physical cells present in the brain and their interconnections. The research in this field has explored brain properties such as microstructure, volumes and inter-regional white matter connectivity (Rykhlevskaia et al., 2008). Meanwhile, brain function refers to the patterns of activity of neuronal populations observed during specific task performance or at rest (Rykhlevskaia et al., 2008) . This research typically uses inter-regional temporal correlations of the recorded activity as measure of functional connectivity. In recent years, efforts have been made to investigate how the structural and functional properties of the brain relate to each other and how this relationship may affect cognitive function and health (Bullmore & Sporns, 2009) . A key question is whether these separate modalities provide complementary or, alternatively, overlapping information for explaining cognition and behaviour (de Kwaasteniet et al., 2013; Guye et al., 2010; Hahn et al., 2013; Salami et al., 2014; van den Heuvel & Fornito, 2014; Wang et al., 2016).

In general, the research that relates brain structure and function is motivated by the fact that the human brain activates and operates on the scaffold of neurons and neuronal connections. Consequently, brain structure and function must be related to some degree. In support of this proposal, research has found striking similarity between white matter connectivity profiles and functionally meaningful parcellations of the cortex (Greicius et al., 2008; Johansen-Berg et al., 2004; Jung et al., 2017). To elaborate, Johansen-Berg and colleagues (2004) have found that the structural connectivity profile of human medial frontal cortex shows abrupt changes at boarders of functionally meaningful regions. Further yet, evidence demonstrates that the most central nodes of functional networks are directly and strongly connected by white matter tracts (Greicius et al., 2008). There are three mechanisms how brain structure may influence its function. First, neuronal populations determine where activation can occur. Evidence demonstrates that the degree of functional activation is influenced by the properties of cortical area, including cortical volume, thickness, surface area and curvature (Chen et al., 2018; Tillisch et al., 2017). Second, the amount of activation passed locally is influenced by the density of cortico-cortical connections (Bassett & Bullmore, 2017; Bullmore & Sporns, 2012; Cammoun et al., 2014; Powell et al., 2006). Third, activation can be more efficiently passed across remote areas via stronger long-range white matter pathways (Bullmore & Sporns, 2012; Liu et al., 2017; Taubert et al., 2011). The most convincing evidence of structural influence on neural activation comes from neurostimulation studies; it was found that the presence and integrity of direct white matter connections can modulate the impact of transcranial direct current stimulation on global patterns of neural function and cognitive outcomes (Li et al., 2019; Lin et al., 2017). These findings demonstrate that brain structure can directly influence patterns of brain function. On the other hand, it has been hypothesised that regions that fire together, will eventually wire together through mechanisms of grey matter growth and synaptic pruning (Draganski et al.,

2004; Gaser & Schlaug, 2003; Hölzel et al., 2011). In support of this hypothesis, studies have found that repeated engagement or suppression of brain activity in specific brain regions can result in corresponding anatomical changes. For example, in healthy populations extended behavioural training (Gu & Kanai, 2014; May, 2011) and environmental stressors (Czéh et al., 2006; Ortiz & Conrad, 2018; Radley et al., 2015) tend to repeatedly engage brain activity in specific brain regions and such prolonged activity results in corresponding cortical and structural connectivity changes. In clinical research, it has been found that therapy for developmental dyslexia results with cortical volume changes (Krafnick et al., 2011) and intense speech therapy for chronic stroke patients with Broca's aphasia result with strengthening of white matter connections (Wan et al., 2014). Similarly, pharmaceutical interventions generally target brain function, but prolonged use of medication also results in physical impacts on the targeted neuronal populations. For example, in clinical setting medication has induced [x] (Fu et al., 2013; Thomaes et al., 2014). It should be emphasised that none of these mechanisms are mutually exclusive, and all are likely to be involved in the evolving neural instantiation of cognitive processing, underlying the complexity of the pervasive interplay between brain structure and function. Perhaps the most striking illustration of this comes from administration of hormonal contraceptives to healthy adults. A recent systematic review demonstrates that such intervention results with a complex interplay of changes including affective and cognitive changes, as well as changes to structural volume and the intensity of neural activity (Bronnick et al., 2020). Thus, there is a wealth of potential mechanisms by which cognition, brain structure and function may mutually influence each other.

In favour of the integrative approach, substantial evidence demonstrates that neural structure and function also display unique physiological properties. For example, studies have demonstrated that regions that are not directly connected by white matter can show similar

patterns of activity, which implies that they interact with each other and they are functionally connected (Ashourvan et al., 2019; Friston, 2002; Hagmann et al., 2008; Honey et al., 2009; Honey et al., 2010; Liao et al., 2015; Røge et al., 2017; Sun et al., 2012; Thomas et al., 2009). In addition, parcellations of the human brain produced from joint information across brain structure and function only show approximately 30% of overlap with structurally defined parcels (Keyvanfard et al., 2020). This evidence suggests that, alongside shared information, the two networks show some unique patterns. In this case, we need to understand the potential benefits of using an integrative approach, and discover exactly how the two networks diverge.

The ultimate goal of aiming to understand neural structure and function is to provide an account of human thought and behaviour. Although quantitative simultaneous consideration of neural structure and function is relatively rare in the imaging literature, a few recent investigations have demonstrated that cognition is supported by an interplay of structural and functional connectivity. For example, high working memory performance has been associated with strong white matter connectivity and increased competition between functional subnetworks (fronto-parietal and default mode) (Murphy et al., 2020). This illustrates that the previously proposed role of brain structure as a scaffolding for brain function can influence cognitive performance. In another study, (Dhamala et al., 2021) demonstrated that the integration of structural and functional information improved the accuracy of models of fluid intelligence, composed of executive function, attention, picture sequence memory, working memory, and processing speed but that crystallised intelligence was best predicted by functional information alone. This suggests that the extent of the impact of the relationship between brain structure and function may depend on the cognitive domain that is being analysed. Consequently, further investigations should explore how the

relationship between structure and function impacts performance across individual cognitive domains.

The present research investigated the benefits of combining structural and functional neuroimaging data to understand the neurobiological basis of cognitive function. For this, we used diffusion Magnetic Resonance Imaging (dMRI), resting-state functional Magnetic Resonance Imaging (rs-fMRI) and cognitive data from the Human Connectome Project (HCP). The cognitive data comprised of measures of verbal and non-verbal episodic memory, cognitive flexibility, inhibition, language, fluid intelligence, processing speed, impulsivity, spatial orientation, attention and working memory. We used Principal Component Analysis to extract orthogonal components reflecting specific cognitive domains (Butler et al., 2014; Hoogendam et al., 2014; Levin et al., 2013; Schumacher et al., 2019). Next, PCA was applied separately to structural connectivity, functional connectivity and then to joint structural and functional connectivity data. Similar joint decomposition approaches have been previously implemented with Independent Component Analysis (ICA) to fuse two or more neuroimaging modalities (Sui et al., 2012). Unlike ICA components, the components extracted with PCA are not constrained to be independent and non-Gaussian. PCA components are orthogonal and describe both unique and shared directions of variance in structural and functional connectivity. Regression models of cognition were constructed from PCA components of structural, functional and combined data. The benefit of the integrative approach was evaluated using model comparison based on the Akaike Information Criterion (AIC) (Akaike, 1974), which balances the explanatory power of the model (model accuracy) against the number of added parameters (model complexity). In doing so, we tested the hypothesis that for some cognitive domains, including a measure of the relationship between brain structure and function (i.e., joint connectivity) would improve prediction of

performance in some cognitive domains over and above that provided by structural and functional connectivity independently.

2. Material and methods

2.1.1. Participants

Behavioural data was obtained for 682 subjects from the 1200-subject release of HCP dataset (Van Essen et al., 2013). The sample of subjects for behavioural analysis was selected by only including those subjects who have complete behavioural data and neuroimaging data (i.e. at least one T1-weighted image, resting-state fMRI and diffusion MRI). The sample consisted of 370 females and 312 males. The subjects had age ranges of 22–25 years (N = 130), 26–30 (N = 315), 31–35 (N = 232), and 36-100 years (N = 5).

Neuroimaging data was obtained for 249 unrelated subjects from the 1200-subject HCP release. For consistent treatment of behavioural and neuroimaging subject selection, one subject was excluded from the neuroimaging analysis due to incomplete behavioural data. The sample consisted of 138 females and 111 males. The subjects had age ranges of 22–25 (N = 45), 26–30 (N = 105), 31–35 (N = 96), and 36-100 (N = 3).

2.1.2. Measures of cognition

The present study used all behavioural data from the domain of cognition (Barch et al., 2013) obtained with tasks from the Blueprint for Neuroscience Research–funded NIH Toolbox for Assessment of Neurological and Behavioral function (http://www.nihtoolbox.org) and tasks from the Penn computerized neurocognitive battery (Gur et al., 2010). Analysed tasks include: Picture Sequence Memory, Dimensional Change Card Sort, Flanker Inhibitory Control and Attention Task, Penn Progressive Matrices, Oral Reading Recognition, Picture Vocabulary, Pattern Comparison Processing Speed, Delay Discounting, Variable Short Penn Line Orientation Test, Short Penn Continuous Performance Test, Penn Word Memory Test, and List Sorting. Supplementary Table 1 has been produced

to describe each tasks' cognitive subdomain and to briefly outline their cognitive demands. The present work has used scores that were not adjusted by age. Participant performance was normalised using the NIH Toolbox Normative Sample (18 and older). Following normalisation, a score of 100 indicates average performance and a score of 115 or 85 indicates performance 1 SD above or below the national average respectively. For Penn Progressive Matrices, Penn Word Memory Test and Variable Short Penn Line Orientation Test the median reaction time for correct responses was divided by accuracy, to obtain a measure of overall efficiency of task performance. For the Delay Discounting task, area under the curve was used from both $200 and $40 000 versions of the task.

2.1.3. Neuroimaging data

The HCP provides minimally processed neuroimaging data that was used here, the data acquisition and processing pipeline has been discussed in detail by (Glasser et al., 2013). All neuroimaging data was collected with a 3T Siemens "Connectome Skyra" scanner that uses the Siemens 32-channel RF receive head coil and with SC72 gradient insert (Ugurbil et al., 2013). Here, we utilised Version 3 of minimal processing pipeline implemented with FSL 5.0.6 (Jenkinson et al., 2012) and FreeSurfer 5.3.0-HCP (Dale et al., 1999).

T1 weighted MR images were acquired with a 3D MPRAGE sequence (TR = 2400 ms, TE = 2.14, TI = 1000 ms, flip angle = 8°, FOV = 224 by 224 mm, voxel size = 0.7 mm isotropic). Rs-fMRI data was collected using the gradient-echo EPI (TR = 720 ms, TE = 33.1 ms, flip angle = 52°, FOV = 208 by 180 mm, 70 slices, thickness = 2.0 mm, size = 2.0 mm isotropic). Scans were collected in two sessions, each lasting approximately 15 minutes. The rs-fMRI data was collected both in left-to-right and right-to-left directions. In addition, in the original data, spin echo phase reversed images were acquired for registration with T1 images and the spin echo field maps were acquired for bias field correction. Diffusion weighted MR images

were acquired with spin-echo EPI sequence (TR = 5520 ms, TE = 89.5 ms, flip angle = 78°, refocusing flip angle = 160°, FOV = 210 by 180 mm, 111 slices, thickness = 1.25 mm, size = 1.25 mm isotropic). Each gradient consisted of 90 diffusion weighting directions plus 6 b=0 . There were 3 diffusion weighed shells of b=1000, 2000, and 3000 s/mm^2. SENSE1 multi-channel image reconstruction was used (Sotiropoulos et al., 2013).

2.2. Neuroimaging data pre-processing

2.2.1 Structural data

As additional steps to the minimal processing pipeline, HCP has provided diffusion data that was put through BEDPOSTX procedure in FSL, which runs MarkovChain Monte Carlo sampling to estimate probability distributions on diffusion parameters at each voxel. This information was used in the FDT module of FSL to run ROI-to-ROI probabilistic tractography with ProbtrackX. Tractography was run between parcels obtained with a high resolution functionally defined brain parcellation with 278 parcels (Shen et al., 2013). During tractography, 5000 streamlines were initiated from each voxel with step length of 0.5 mm (Behrens et al., 2007; Behrens et al., 2003; Jenkinson et al., 2012). Streamlines were constrained with curvature threshold of 0.2, maximum of 2000 steps per streamline and volume fraction threshold of subsidiary fiber orientations of 0.01. A structural connectivity matrix was constructed by counting streamlines that successfully connected pairs of regions. This produced an asymmetric matrix because the count of streamlines from region i to j is not necessarily equal to the count of streamlines from region j to i. To address this, a correlation analysis between vectorised upper and lower off-diagonal elements of the matrix was first run to confirm that they were not significantly different from each other. The lowest Pearson's R correlation coefficient across subjects was equal to 0.76. The streamline count was normalised by the size of origin and target ROIs in the following manner: first the number of voxels in the origin and target masks were averaged and multiplied by the number of

streamlines initiated from the original voxels (i.e. 5000), then each element of structural connectivity matrix was divided by corresponding value [citation]. Subsequently, the structural matrix was symmetrised by adding it to the transposed version of itself. This process ensured that the SC matrix ranged between 0 and 1. In the same manner as FC matrix, a threshold was applied where 80% of weakest connections were set to 0.

2.2.2. Functional data

The minimally processed images were obtained for rs-fMRI to compute functional connectivity. Next, the following steps were taken to further process data using the CONN Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) with use of the standard functional connectivity processing pipeline (Nieto-Castanon, 2020). Briefly, the tissues were segmented into separate parcels, corresponding to grey matter, white matter, cerebrospinal fluid and non-brain tissues. Outlier detection of functional images for scrubbing was performed with Artifact Detection Tools (ART, https://www.nitrc.org/projects/artifact_detect/). Images were smoothed with a 6 mm Full Width at Half Maximum Gaussian kernel. The data was then put though a high pass filter (0.01 Hz), and a low pass filter (0.10 Hz). Finally, an anatomical component-based noise correction procedure (Behzadi et al., 2007) was conducted to remove the following noise components from the data: noise components from cerebral white matter and cerebrospinal areas, subject-motion parameters (Friston et al., 1996), identified outlier scans (Power et al., 2014), constant and first-order linear session effects (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Functional connectivity analysis was performed on the same high resolution brain parcellation used in the anatomical connectivity computations (Shen et al., 2013). The average blood oxygenation level-dependent signal in each ROI was obtained. Next, ROI-to-ROI correlation was calculated and the toolbox produced Fisher's Z-scores (Fisher, 1915). A hyperbolic tangent function was applied to reverse the Fisher's transformation, which

resulted with scores that range between -1 and 1. An absolute functional connectivity matrix was constructed from these values, each of its entries representing the connection between one pair of regions. Finally, a threshold was applied where 80% of lowest values were set to 0 (Garrison et al., 2015; van den Heuvel et al., 2017).

3. Data analysis

3.1. Behavioural data analysis

The HCP provides a wealth of behavioural data that assesses a rich variety of cognitive tasks. Consequently, it is possible that measures draw on shared cognitive processes. To address this, a Principal Component Analysis (PCA) (SPSS 20.0) of the cognitive measures of the full set of 682 subjects was conducted to extract a reduced number of orthogonal latent factors (components) underlying the data. Factors were calculated based on the covariance matrix of the measures. Factors with eigenvalues greater than 1.0 were extracted and varimax rotation was conducted to facilitate interpretation. Participants' cognitive abilities were scored on each PCA factor, and the scores corresponding to the subset of 249 subjects for which the Neuroimaging data was available, were saved and used as response variables in the subsequent regression analysis (see next section). The use of a larger population sample to conduct PCA analysis was done to yield a generalisable and stable analysis (Halai et al., 2020). To ensure that the selection of the subset had not introduced collinearity to the subject scores, a Pearson's R correlation was conducted. The maximum correlation coefficient was 0.083 ($p = 0.193$).

3.2. Analysis of the relationship between neuroimaging data and cognitive performance

For each participant, the lower diagonal elements of structural and functional connectivity matrices were obtained and vectorised. Joint connectivity was constructed by concatenating the structural and functional vectors for each subject, as illustrated in Figure 1.

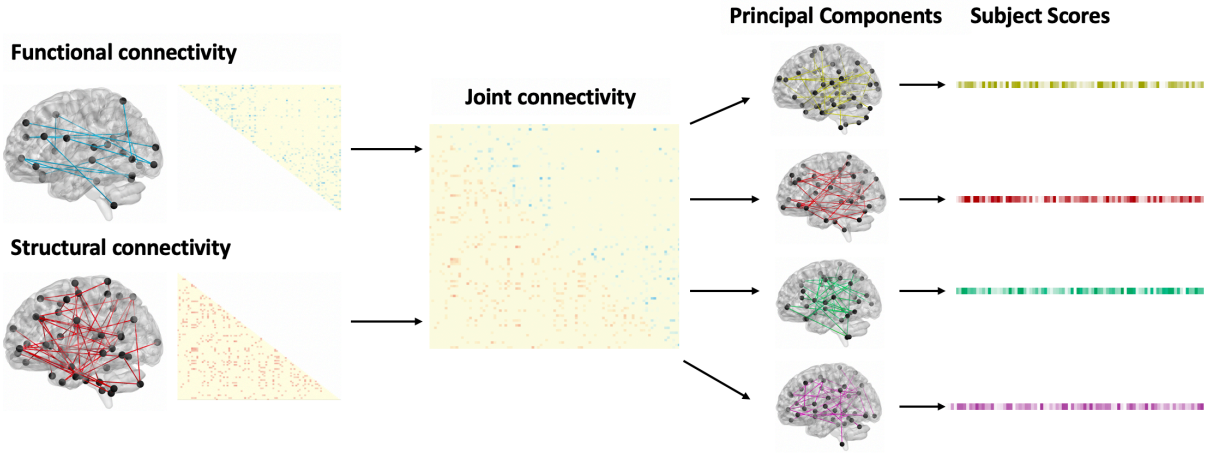

Figure 1 A visual illustration of joining structural and functional connectivity. First, the lower diagonal of structural and functional connectivity matrices is extracted. Then each participant's structural vector was combined with their functional vector. This produced a joint connectivity matrix that was carried to further analysis.

The remainder of the analysis pipeline consisted of a PCA-Regression analysis illustrated in Figure 2. Prior to regression analysis, group-level PCA was applied separately to the structural, functional and joint data (Figure 1), which allowed for dimension reduction and whitening (orthogonalisation) of the datasets. The participants were treated as observations and the connections were treated as variables. The first 120 components for structural data and 167 components for functional data were carried to further analysis. These components explained 80% of the variance within each connectivity.

Stepwise regression analysis (Figure 2) was performed separately for each cognitive component (response variables) and separately for structural, functional and joint components (explanatory variables or regressors). This resulted in 12 regression models in total. Features were added to the model if they significantly reduced (improved) the Akaike Information Criterion (AIC) of the model by at least 2 (Burnham & Anderson, 2016). All the analyses were done in MatLab 2018a (The MathWorks, Inc.).

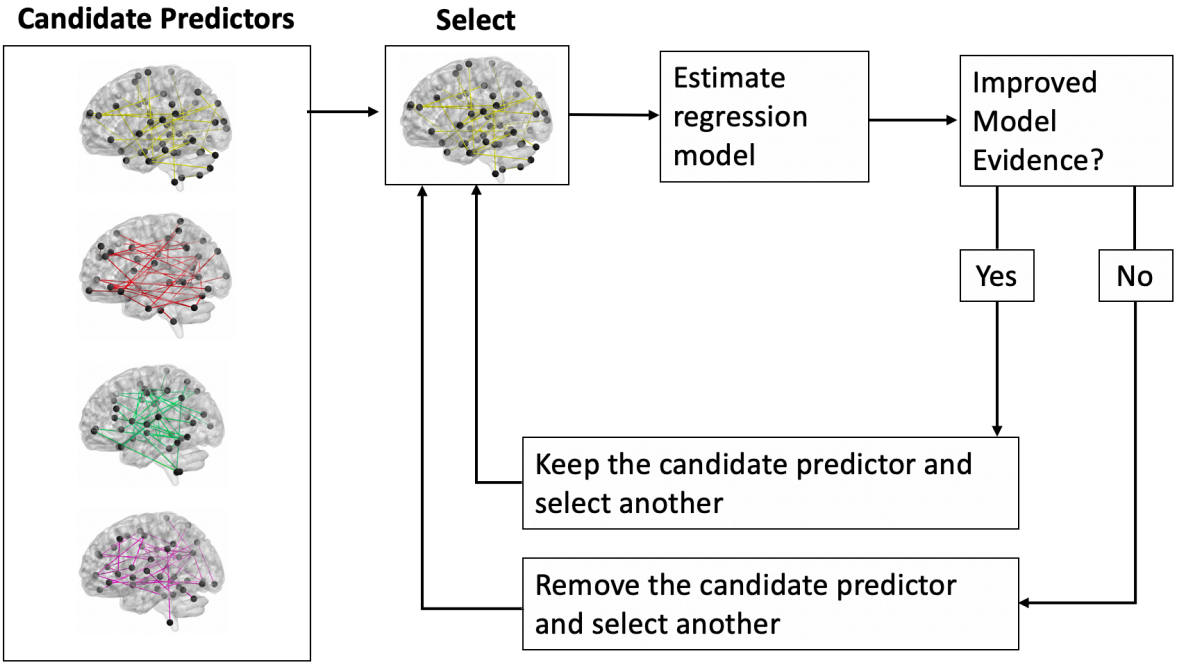

Figure 2 A visual illustration of the stepwise regression process applied to the connectivity matrices. The process is repeated until model evidence cannot be improved any further and all candidate predictors have been considered by the model.

The relative performance of the optimal functional, structural and joint models was evaluated using AIC-based model comparison with the joint model as the reference model. That is, the AIC value of the joint model was subtracted from the AIC of the other models. A positive difference is interpreted as small (2-4 units), moderate (4-7 units) or strong (7-10+ units) evidence in favour of the reference (joint) model (Arnold, 2010; Burnham & Anderson, 2016). To complement this analysis, models were further assessed in terms of their explained variance (Ordinary R-squared), model Root Mean Squared Error (RMSE) and generalisation power estimated with Mean Squared Error (MSE) generated during leave-one-out cross validation.

3.3. Model projections

3.3.1. Connectome space

The beta values of each regression predictor were multiplied by the component coefficients. The resulting vector of connections was then normalised to have mean of 0 and standard deviation of 1. A threshold was applied where 1% of positive and 1% of negative connections were maintained using Brain Connectivity Toolbox (https://brain-connectivity-toolbox.net) (Rubinov & Sporns, 2010). Next, Neurosynth (https://neurosynth.org/) (Yarkoni et al., 2011) was searched for the following terms: "Retention" and "Retrieval" corresponding to Retention and Retrieval Component, "Reaction" and "Executive" corresponding to Processing Speed Component, "Reward" and "Inhibitory Control" corresponding to Self-regulation Component, and "Encoding" corresponding to Encoding Component (see section 4.1 for component results). The resulting association test images were saved from Neurosynth. Term "Retention" on Nueorsynth yields large clusters, therefore the Shen et al. (2013) parcels overlapped by less than 5% with the clusters yielded by Neurosynth, then connections were masked prior to projection in BrainNet Viewer (http://www.nitrc.org/projects/bnv/) (Xia et al., 2013). For all other components, this threshold was reduced to 1%.

3.3.2. Resting-state network space

The beta values of each regression predictor were multiplied by the component coefficients. The resulting vector was then normalised to have mean of 0 and standard deviation of 1. Each Shen et al. (2013) parcel was assigned with the label of greatest overlapping network from the 17 resting-state networks (Yeo et al., 2011). The average connection strength was calculated for each network.

4. Results

4.1. Cognitive components underlying behavioural data

The PCA of cognitive measures yielded a 4-component solution (Table 2), which altogether accounted for 55.04% of variance in the data. The rotated component solution was

used to interpret the cognitive constructs reflected by each component. The first component was primarily composed of List Sorting, Oral Reading Recognition, Picture Vocabulary, and Picture Sequence Memory (Table 2), with a moderate negative loading from Variable Short Penn Line Orientation Test. The elements that loaded positively with this component engaged working memory processes (Acheson & MacDonald, 2009; Schwering & MacDonald, 2020), while the negative loading was only composed of the single visuo-spatial test (Dubois et al., 2018). Across these measures retention and retrieval was the common process and this component will be referred to as such. The second component was composed of executive function tasks including Dimensional Change Card Sorting and Flanker task, as well as Pattern Completion Processing Speed. Previously, the relationship between Card Sorting task, Flanker task and Pattern Completion have been attributed to the construct of processing speed and hereinafter this factor will be referred to as the 'Processing Speed' (Dubois et al., 2018). The third component was made up of the Delay Discounting task, which is referred to by the NIH toolbox as a self-regulation task. This component also saw some weak loading from Penn's Progressive Matrices that, like Delay Discounting, relies on decision-making and comparison of choices. From now on this third factor will be referred to as the 'Self-regulation'. Finally, the fourth factor was made up of Short Penn Continuous Performance and Penn Word Memory tests, which both require effective encoding of information , therefore the final factor was called the 'Encoding' component (Cabeza et al., 2008; Ciaramelli et al., 2008).

Table 2. The rotated component solution of PCA conducted on cognitive measures from HCP for 682 subjects. The measures have been sorted by their loading with each component in ascending order. Measures with loading above .5 have been presented in bold font.

Measure	Component 1 Loading	Component 2 Loading	Component 3 Loading	Component 4 Loading
Working Memory (List Sorting)	**.729**	.114	-.075	.098
Language/Vocabulary Comprehension (Picture Vocabulary)	**.684**	-.029	.343	-.270
Language/Reading Decoding (Oral Reading Recognition)	**.680**	-.020	.342	-.299
Episodic Memory (Picture Sequence Memory)	**.524**	.192	-.118	.060
Spatial Orientation (Variable Short Penn Line Orientation Test)	-.479	-.222	-.071	.044
Executive Function/Cognitive Flexibility (Dimensional Change Card Sort)	.158	**.772**	-.001	-.107
Executive Function/Inhibition (Flanker Task)	.103	**.758**	.066	-.148

Processing Speed (Pattern Completion Processing Speed)	.137	**.717**	-.067	-.085
Self-regulation/Impulsivity (Delay Discounting - $40k)	.101	.069	**.875**	.025
Self-regulation/Impulsivity (Delay Discounting - $200)	.108	.037	**.850**	.083
Fluid Intelligence (Penn Progressive Matrices)	-.070	-.267	.330	-.028
Sustained Attention (Short Penn Continuous Performance Test)	.117	-.161	.115	**.770**
Verbal Episodic Memory (Penn Word Memory Test)	-.215	-.121	-.033	**.667**

4.2. Regression models

Appendix (A2) provides a table containing all the statistics for each model, including its AIC value, explained variance, accuracy, RMSE and cross-validation MSE.

4.2.1. Model quality

AIC differences across models are illustrated in Figure 3. Across all cognitive domains, there was strong preference for functional models relative to structural models (Retention and Retrieval ΔAIC = 26.42, Processing Speed ΔAIC = 34.44, Self-Regulation ΔAIC = 31.24, Encoding ΔAIC = 25.40). Compared to structural models, there was strong evidence in favour of joint model of Retention and Retrieval (ΔAIC = 10.88), Processing Speed (ΔAIC = 46.84) and Self-regulation (ΔAIC = 35.22) but only moderate evidence in favour of the joint model of Encoding (ΔAIC = 6.72). Compared to functional models, there was strong to strong evidence in favour of joint models for Processing Speed (ΔAIC = 12.40), and moderate evidence for Self-regulation (ΔAIC = 19.64). However, model evidence strongly favoured functional models of Retention and Retrieval (ΔAIC = -15.55) and Encoding (ΔAIC = -18.68).

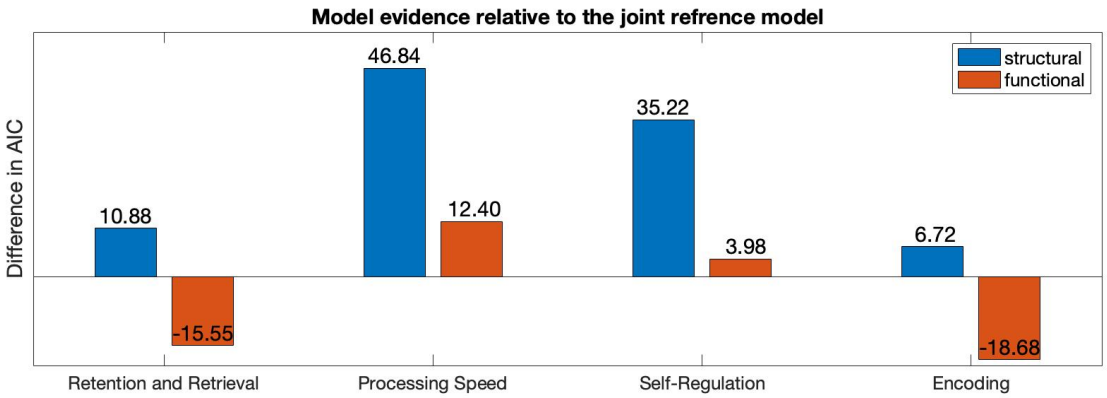

Figure 3 AIC-based Model Comparison for each cognitive component. The joint model was used as the reference model for model comparison. Bars with positive values indicate preference for the reference model.

4.2.2. Model Fit

Figure (4) shows the explained variance of the models under consideration. Across domains and neural modalities, models achieved moderate accuracy in prediction of cognitive data (R-Squared > 0.4). The functional regression model produced best fit and

generalisation of Working Memory and Attention, whereas, for Processing Speed and Self-Regulation, best fit and generalisation were achieved with joint models.

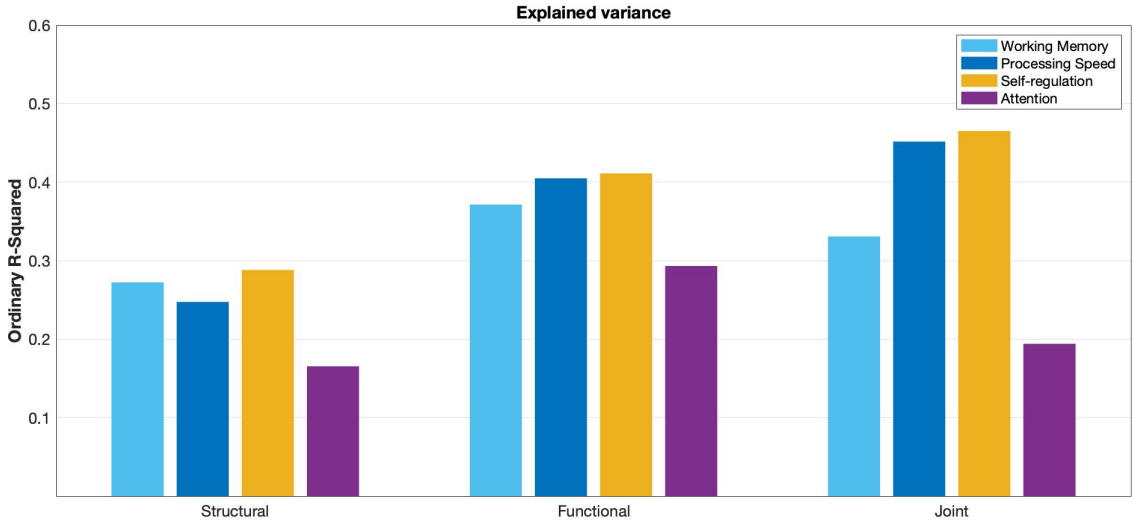

Figure 4 Bar graphs illustrate the explained variance structural, functional and joint models of cognitive components.

4.2.3. Regression model in connectome space

Across all cognitive components, projection of just 1% of connections in glass brain yields a rich network of connections across regions involved with related cognitive processing (Figure 5). Complete visual illustration of regression models in connectome space has been provided in Appendix 3 (A3).

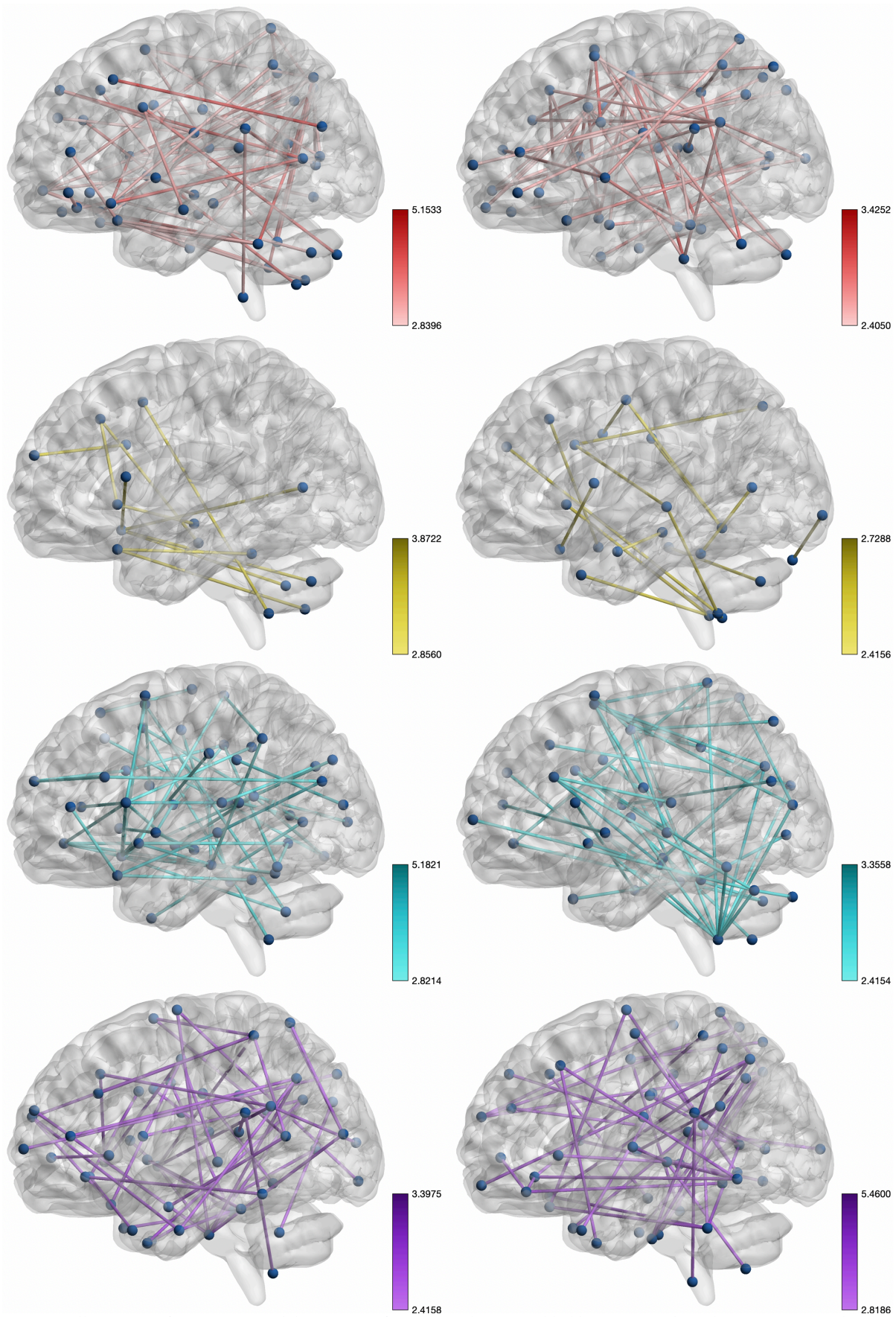

Figure 5 Illustration of regression models in space of cognitive clusters yielded by Neurosynth. Only connections with positive association with cognition were projected for sparsity. Left column presents projection of structural regression

models, whereas left column presents projection of functional regression models. Red connectomes represent models of Retention and Retrieval, yellow represent Processing Speed, teal represent Self-regulation, purple represent Encoding.

Figure 6 illustrates network-level associations with performance on Retention and Retrieval. All models have been fully illustrated in Appendix 4 (A4) and Appendix 5 (A5). Briefly, it was found that, each cognitive component showed unique structural and functional connectivity fingerprint that differed from other cognitive components. In addition, different connectivity fingerprints were observed across structural and functional regression models (Figure 6, top row). For example, the strongest positive association between Retention and Retrieval and structural connectivity was found across Limbic A network (comprised of nodes located in the temporal poles) and Default Mode C network (comprised of retrosplenial and parahippocampal cortices), whereas for functional connectivity the strongest positive association was found within Limbic B network (comprised of orbital frontal cortex). Furthermore, when functional and structural connectivity were joined, the structural and functional connectivity fingerprints were changed (Figure 6, bottom row). For example, positive association between structural connectivity and Retention and Retrieval was shifted to connections within Default Mode C network, whereas positive associations of functional connectivity was shifted to connectivity across peripheral visual network (comprised striate calcarine, extra-striate inferior and extra-striate superior cortices) and somatomotor B network (comprised of secondary somatosensory cortex, auditory cortex and insula).

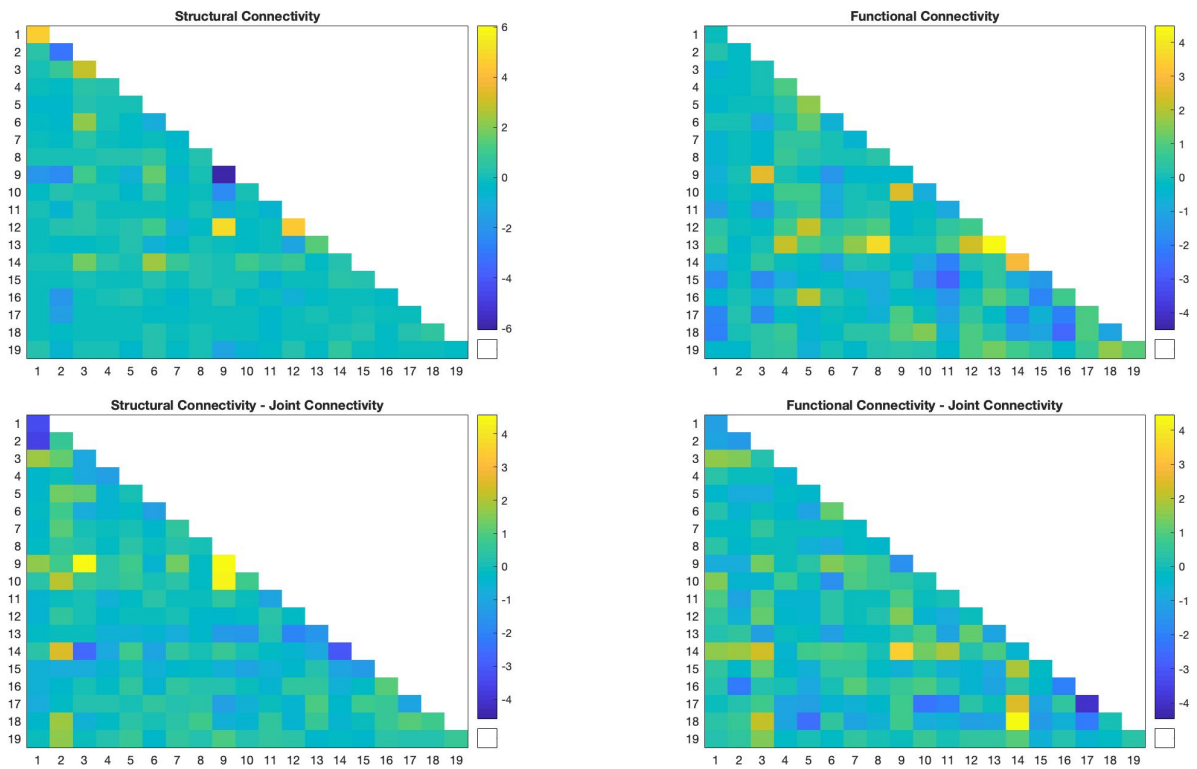

Figure 6 Projection of regression models of Retention and Retrieval in resting-state network space. In each heatmap, rows and columns present 17 resting state networks (Yeo et al. 2011) plus cerebellar and subcortical networks. Top two heatmaps present structural and functional connectivity models, when related to cognition separately. Bottom heatmaps present structural and functional connectivity models, when related to cognition in joined connectivity.

5. Discussion

In this study we examined whether cognitive performance was best predicted by models based on brain structure alone, brain function alone or combined information concerning the relationship between structure and function. We derived four distinct cognitive components from the HCP cognitive dataset: Retention and Retrieval, Processing Speed, Self-regulation and Encoding. For all cognitive domains, models based on functional connectivity were better at explaining performance than models based on structural connectivity. Further, we demonstrated that joint models combining structural and functional connectivity were better at explaining cognitive performance and improved predictions of Processing Speed and Self-regulation, but did not outperform functional models of Retention and Retrieval or Encoding. We consider the implications of these findings below.

5.1. Cognitive domains

In order to develop an effective understanding of the brain bases of cognition we need to quantify the relevant abilities through optimising the combination of multiple behavioural measures. Previously, researchers have combined functional and structural brain measures with summary measures of intelligence from the NIH toolbox measures, including crystallised, fluid and total intelligence, as well as 'early' cognition (Dhamala et al., 2021; Dubois et al., 2018; Prabhakaran et al., 1997; Seidlitz et al., 2018; van den Heuvel et al., 2009; Zimmermann et al., 2018). However, these summary measures are combined based on theoretical principles, not based on shared co-variance. Consequently, they risk masking relevant variation in performance across the relevant domains. In contrast, approaches that explore individual cognitive domains have great potential to improve our understanding and prediction of cognitive health and pathology (Barch & Ceaser, 2012; Covey et al., 2011; Rivera-Fernández et al., 2021), and have been effectively applied to predict performance in various populations, including dementia (Hackett et al., 2018; Rivera-Fernández et al., 2021) stroke aphasia (Butler et al., 2014; Mirman et al., 2019) and healthy aging (Reddy et al., 2015). We therefore considered a wide range of behavioural measures from the HCP dataset, and PCA analysis revealed four components underpinning performance on these cognitive tasks: retention and retrieval, processing speed, self-regulation, and encoding processes.

5.2. Models of cognitive components

The present work has used PCA components of structural, functional and joint connectivity to predict cognitive performance. We found that information about functional connectivity was more useful at modelling cognition than structural connectivity when each source of information was considered independently, replicating the findings of Dhamala et al. (2021). One reason for this may be that the structural connectivity in those studies and in

our current investigation was sparser than functional connectivity. Consequently, structural connectivity expresses less information about the state of the system and variance across subjects. Alternatively, our findings may be influenced by the atlas we used to parcellate the brain. We used a high-resolution brain atlas, defined using resting-state functional connectivity. Previous work suggests that the parcellation of the brain impacts the relationship between brain structure and function and cognition (Dhamala et al., 2021; Messé, 2019). However, it remains unclear to what extent parcellation choice may influence the quality of the models of individual cognitive domains.

The rich connectome resulting from the projection of the regression model in the glass brain demonstrates relevance of the regression models constructed here to the regions involved with related cognitive processing. When brain structure and function were considered separately, their connectivity profiles were different. In addition, each cognitive component had a different connectivity profile. This finding replicates the findings from Zimmermann et al. (2018) and Dhamala et al. (2021), as using different regression methods they have found that unique structural and functional connections predict cognition. We have further advanced this finding by demonstrating that structural and functional connectivity changes when joint connectivity is considered. However, even in the joint model unique structural and functional connections relate to cognition. This suggests that joint PCA was not merely re-describing shared information, but it has revealed information about the relationship between brain structure and function.

It has been proposed that each brain modality measures specific biological properties and in doing so it presents some unique information about the operation of the brain (Eickhoff et al., 2018). It follows that joining information across structural and functional modalities should result in a more complete representation of the state of the system. Our work aimed to compare how much the use of variables capturing the relationship between

structural and functional connectivity can benefit modelling of cognitive domains. Here for the first time, PCA was applied to structural and functional connectivity as a dimension reduction method, referred to by us as joint PCA. Components of this analysis reflect common and unique directions of variance between brain structure and function. It is not clear from the present analysis whether components reflect unique information reflecting the interaction between brain structure and function or whether they reflect a weighted average of the two modalities. When we examined the extent to which the joint PCA components identified as relevant to each cognitive domain correlated with the components from the separate structural and functional data from that domain, we found that there were very few significant correlations (Retention and Retrieval: structural 4.3%, functional 4%; Processing Speed: structural 1.6%, functional 2.6%; Self-regulation: structural 2.5%, functional 2.7%; Encoding: structural 1.1%, functional 1.8%). Future work will have to explicitly address how the two modalities interact and what contributions cross-modal interactions make to models of cognition. However, the joint PCA approach presented here has produced novel insights by establish that information concerning the relationship between brain structure and function and is differentially related to performance across distinct cognitive domains.

In this work, regression models obtained from joint PCA have explained more variance in Processing Speed and Self-regulation than the models that utilised unimodal information. However, the most effective models of Retention and Retrieval, and Encoding were produced with functional information alone. This demonstrates that the added benefit of studying relationship between brain structure and function depends on specific cognitive domains.

A key question is why Processing Speed and Self-regulation are more sensitive to complementary information from altered structural connectivity than Retention and Retrieval and Encoding. Specific cognitive constructs, like Processing Speed, may depend more

heavily on a distributed network of brain regions with long-distance connections (Küchenhoff et al., 2021; Penke et al., 2012; Penke et al., 2010; Zink et al., 2021). There is evidence to suggest this may be the case. Processing Speed in healthy participants has been associated with microstructural features within long white matter tracts connecting bilateral parietal and temporal lobe as well as the left superior lobe and cerebellum (Turken et al., 2008). Also in clinical conditions, such as multiple sclerosis, cognitive deterioration (of which processing speed is primarily affected) is more sensitive to pathology in long-range connections than shorter connections such as U-shaped fibres (Meijer et al., 2020). Thus, changes to microstructural features may easily disrupt information transmission across long distances. In contrast, Retention and Retrieval, and Encoding have been associated with more localised neural regions and so performance on these forms of cognition may be more fully captured by functional connectivity alone. Our Retention and Retrieval component reflected language tasks, typically localised to left hemisphere's temporal regions and inferior frontal gyrus (Bookheimer, 2002; Hill et al., 2019). In addition, verbal and non-verbal sequence processing, such as required by list sorting and picture sequence memory, have been specifically localised to Broca's area (Fiebach & Schubotz, 2006; Sahin et al., 2009). Attentional processes during uncued memory retrieval have been found to engage more posterior regions such as temporoparietal junction and regions specific to the stimuli (Burianova et al., 2012; Uncapher et al., 2011). Processing Speed may therefore benefit from joint PCA because the relationship between brain structure and function as expressed as patterns of convergence and divergence are more impactful on processes that involve more long-range connections. Other cognitive constructs, like Self-regulation, depend more on feedback loops between regions. This is important because any disruption of structural integrity could then specially impact the speed and efficiency of signal transmission, and with every loop the impact of the divergence would be accentuated. In support of this argument,

effective self-regulation in healthy young and old adults is associated on frontostriatal feedback loops involved with evaluation of value and adjustment of outputs (Frost & McNaughton, 2017; Hanggi et al., 2016). This could particularly explain why this would impact performance on tasks that rely on 'on the fly' adjustments of motivation and responses and repeatedly update information and behavioural outputs.

It is also important to note that a divergence across brain structure and function may be observed if two regions are functionally connected by indirect structural connections (Deligianni et al., 2011; Honey et al., 2009; Røge et al., 2017). With this scenario, the functional signal would need to travel though several regions. This is important because any disruption of structural integrity could then specially impact the speed of signal transmission, and with every "junction" or indirect connection, the impact of the divergence would be accentuated. This could particularly explain why this would impact performance on tasks that are sensitive to reaction time and efficient information exchange.

Conclusion

The present work has illustrated, for the first time, that the quantitative combination of information from structural and functional neural connectivity allows explanation of unique variation in performance in some, but not all, cognitive domains. The combination of structure and function produced a superior model of the neural bases of performance for the domains of Processing Speed and Self-regulation, while for the domains of Retention and Retrieval and Attention, models based purely on functional connectivity were sufficient. This difference in the importance of joint structural-functional connectivity across cognitive domains demonstrates that our novel use of combined structural-functional connectivity provides new insights concerning the different neural mechanisms involved in distinct cognitive domains. The limited correspondence between the joint structural-functional

components and those from each modality considered independently suggests that our approach captures information specific to the relationship between them, but this is a hypothesis that must be addressed in future research directed to elucidating the nature of the interaction between brain structure and function in the service of cognition.

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