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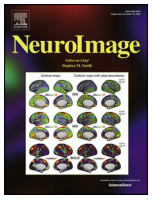

Combination of structural and functional connectivity explains unique variation in specific domains of cognitive function

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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 the fit of regression models of cognitive performance. Principal Component Analysis (PCA) was first applied to cognitive data from the Human Connectome Project to identify latent cognitive components: Executive Function, Self-regulation, Language, Encoding and Sequence Processing. A Principal Component Regression approach with embedded Step-Wise Regression (SWR-PCR) was then used to fit regression models of each cognitive domain based on structural (SC), functional (FC) or combined structural-functional (CC) connectivity. Executive Function was best explained by the CC model. Self-regulation was equally well explained by SC and FC. Language was equally well explained by CC and FC models. Encoding and Sequence Processing were best explained by SC. Evaluation of out-of-sample models' skill via cross-validation showed that SC, FC and CC produced generalisable models of Language performance. SC models performed most effectively at predicting Language performance in unseen sample. Executive Function was most effectively predicted by SC models, followed only by CC models. Self-regulation was only effectively predicted by CC models and Sequence Processing was only effectively predicted by FC models. The present study demonstrates that integrating structural and functional connectivity can help explaining cognitive performance, but that the added explanatory value (in-sample) may be domain-specific and can come at the expense of reduced generalisation performance (out-of-sample).

1. Introduction

Cognitive neuroscience generally seeks to develop an understanding of neural substrates of cognition and adaptive behaviour. One approach to the study of the brain is to characterise it as a network of brain regions and connections between them (Fornito et al., 2016; Sporns et al., 2005). Following this approach, structural connectivity (SC) of a brain network describes the patterns and the integrity of white matter connections between neural populations (Sporns et al., 2005), whereas functional connectivity (FC) of a brain network describes patterns and strength of temporal associations of activation patterns across remote brain regions (Bullmore & Sporns, 2009; Friston, 2002). In recent years, efforts have been made to investigate how SC and FC relate to each other and how this relationship may affect cognitive function and health (Bullmore & Sporns, 2009; Rykhlevskaia et al., 2008). A key question is whether SC and FC 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, SC and FC must be related to some degree. In support of this proposal, evidence demonstrates systematic coupling of lifespan changes in SC and FC (Baum et al., 2020; Romero-Garcia et al., 2014). Further, 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; Vázquez-Rodríguez et al., 2019). To elaborate, Johansen-Berg and colleagues (2004) have found that the SC 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 important features that characterise the brain's

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structure-function relationship. First, spatially organised neuronal populations determine where activation can occur. Evidence demonstrates that the degree of functional activation of a cortical area is influenced by the physical properties of the region, including cortical volume, thickness, surface area and curvature (Chen et al., 2018; Tillisch et al., 2017). Second, the amount of locally exchanged of cortical activity is influenced by local connection density (Bassett & Bullmore, 2017; Bullmore & Sporns, 2012; Cammoun et al., 2014; Powell et al., 2006). Third, exchange of activities across remote regions is more efficient when it is supported by long-range white matter tracts with excellent integrity (Bullmore & Sporns, 2012; Liu et al., 2017; Taubert et al., 2011).

The most direct evidence of structural influence on neural activation comes from neurostimulation studies. It has been shown 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 impact the strength of FC between select regions. On the other hand, it has been hypothesised that regions that fire together, will eventually wire together through plasticity mechanisms (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 can produce changes in cortical volume (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, prolonged pharmaceutical interventions targeting brain function can also impact the physical properties of the targeted neuronal populations. For example, in clinical settings, prolonged medication has induced functional and structural abnormality in regions that were previously functionally related to relevant healthy cognitive function (Fu et al., 2013; Thomaes et al., 2014). Perhaps the most striking illustration of the complex relationship between structure and function comes from administration of hormonal contraceptives to healthy adults. A recent systematic review demonstrates that such intervention results with changes to structural volume, to the intensity of neural activity and it results with affective and cognitive changes (Bronnick et al., 2020). Interestingly, most work has been focused on FC strength, but more recent evidence suggests that the topography of functional nodes is also important for cognition (Kong et al., 2019), which suggests that spatial constraints are also consequential for brain function. This evidence demonstrates that there is a diversity of (not mutually exclusive) potential brain mechanisms underlying these findings, and all are likely to be involved in the evolving neural instantiation of cognitive processing. This highlights the complexity of the pervasive interplay between brain structure and function and suggests a high degree of overlapping in their roles with regards to cognition.

Although there are patterns of overlap across SC and FC, substantial evidence demonstrates that each displays unique features that can be relevant to cognition and behaviour. For example, studies have demonstrated that regions that are not directly connected by white matter can show similar patterns of activity, which suggest that they are (indirectly) 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). Additionally, parcellations of the human brain produced based on combined structural-functional information only show approximately 30% of overlap with structurally defined parcels (Keyvanfard et al., 2020). In a more recent publication, Mansour et al. (2021) have demonstrated that FC fingerprints are more predictive of cognitive function, while SC ones are more able to differentiate identity of individuals. This evidence suggests that, alongside shared information, the SC and FC show unique features which can impact cognition in distinct ways. Therefore, we need to understand the potential benefits of using an integrative approach, and discover exactly how the two networks diverge.

The ultimate goal of understanding 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 between SC and FC. For example, high working memory performance has been associated with strong SC 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 SC and FC information improved the accuracy of linear models of fluid intelligence, composed of executive function, attention, picture sequence memory, working memory, and processing speed. Conversely, functional information alone best modelled crystallised intelligence composed of language. This suggests that the extent of the impact of the relationship between SC and FC on cognitive performance may depend on the cognitive domain that is being analysed. However, composite intelligence scores are theory-driven and do not necessarily reflect the underlying variance. This means that they serve as good summaries of cognitive performance but it may lose on important information about cognitive health (Barch & Ceaser, 2012; Covey et al., 2011; De Felice & Holland, 2018; Rivera-Fernández et al., 2021). Consequently, further investigations should explore how the relationship between structure and function impacts performance across individual cognitive domains.

The present research used diffusion Magnetic Resonance Imaging (dMRI), resting-state functional Magnetic Resonance Imaging (rs-fMRI) and cognitive data from the Human Connectome Project (HCP) to investigate how combining SC and FC (integrative approach) benefits the understanding of the neurobiological basis of cognitive function. To do this we carried out a model comparison analysis to arbitrate between competing regression models of specific cognitive domains. For each cognitive domain, the competing models differed in the type of connectivity data used to construct the models, namely: (i) SC, (ii) FC or (iii) Combined Connectivity (CC) which combined SC and FC. This model comparison approach allowed us to select the most effective domain-specific model, based on connectivity measures of structure and function. In doing so, we tested the hypothesis that, including information from both brain structure and function (i.e. CC) would improve modelling of performance in a cognitive domain over and above that provided by SC or FC in isolation.

2. Materials and methods

Codes used to implement the below analysis are available on GitHub (https://github.com/MCLit/SC-FC-CC).

2.1. 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).

2.1.1. 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). 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. 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 material 1 presents a table summary of each tasks' cognitive subdomain and a brief outline of its cognitive demands. The present work has used scores that were not adjusted by age, as the age range is narrow (22-35). 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 (Liesefeld & Janczyk, 2018). For the Delay Discounting task, the area under the curve was used from both $200 and $40 000 versions of the task.

2.1.2. Minimally processed 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 the 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. Additional processing of Neuroimaging data

2.2.1. Structural data and structural connectivity calculation

As additional steps to the minimal processing pipeline, the diffusion data was put through BEDPOSTX procedure in FSL, which runs Markov Chain 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 SC matrix between regions was constructed by first counting the number of streamlines originating from a seed region i that reached a target region j (M_{ij}). These counts are asymmetric since the count of streamlines from region i to j is not necessarily equal to the count of streamlines from region j to i ($M_{ij} \neq M_{ji}$), but they are highly correlated for all subjects (lowest Pearson's Correlation was 0.76, $p < 0.001$). Based on these counts, the weight W_{ij} (entries of the SC matrix) between any two pairs of regions i and j was defined as the ratio of the total streamline counts in both directions ($M_{ij} + M_{ji}$), to the maximum possible number of streamlines that can be shared between the two regions, which is $(N_i + N_j) * 5000$ (where N_i and N_j are the number of seed voxels in regions i and j, respectively):,

$$W_{ij} = \frac{\left(M_{ij} + M_{ji}\right)}{\left(N_i + N_j\right) * 5000}$$

Similar to previous studies, the weight W_{ij} can be interpreted as capturing the connection density (number of streamlines per unit surface) between nodes i and j, which accounts for possible bias due to different sizes of the seed regions (Friston et al., 2008; Ingalhalikar et al., 2013). Note that the SC matrix defined based on these weights is symmetric because swapping around the regions' indices does not change the result; and it is also normalised between 0 and 1, because the maximum value of the numerator can only be reached when all streamlines originating from each of region reach the other region, so that $M_{ij} = N_i * 5000$ and $M_{ji} = N_j * 5000$, which gives $W_{ij} = 1$. Evidence suggests that structural connectivity is most sensitive to individual differences with moderate-to-high thresholding (Buchanan et al., 2020) and produces least false positive and negative results (de Reus & van den Heuvel, 2013), therefore an 80% proportional threshold was applied. Supplementary material 6 presents the results of analysis conducted on dense connectivity.

2.2.2. Functional data and functional connectivity calculation

The minimally processed images were obtained for rs-fMRI to compute FC based on pair-wise correlations (Glasser et al., 2013). Next, the following steps were taken to further process data using the CONN Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) with use of the standard FC processing pipeline (Nieto-Castanon, 2020). Briefly, images were realigned, slice-timing correction was conducted, and outlier detection of functional images for scrubbing was performed with Artefact Detection Tools (ART, https://www.nitrc.org/projects/artifact_detect/). Grey matter, white matter, cerebrospinal fluid and non-brain tissues were then segmented. Images were normalized and smoothed with a 6 mm Full Width at Half Maximum Gaussian kernel. Next, the data was denoised with default Conn denoising options using the anatomical component-based noise correction procedure (Behzadi et al., 2007). This procedure removes artefactual components from the data, including noise components from cerebral white matter and cerebrospinal areas, subject-motion parameters (Friston et al., 1996), identified outlier scans (Power et al., 2014), and constant and first-order linear session effects (Whitfield-Gabrieli & Nieto-Castanon, 2012). Then standard denoising steps were applied including scrubbing, motion regression and application of high pass filter (0.01 Hz cut-off), and a low pass filter (0.10 Hz cut-off).

FC analysis was performed based on the same high-resolution brain parcellation used in the SC computations (Shen et al., 2013). The average blood oxygenation level-dependent signal in each ROI was obtained and the pairwise (ROI-to-ROI) correlation of the averaged signals was calculated. Since the CONN toolbox produces Fisher's Z-scores

(Fisher, 1915), a hyperbolic tangent function was used to reverse the Fisher's transformation, and obtain original correlation values ranging between -1 and 1. Negative correlations were transformed to positive by taking their absolute values and a proportional 80% FC threshold was then applied (Garrison et al., 2015; van den Heuvel et al., 2017). Thresholding procedure has been shown to produce more reliable components resulting from Principal Component Analysis (PCA) of functional connectivity than analysis of dense connectome (Hong et al., 2020). Supplementary material 6 presents the results of analysis conducted on dense connectivity and supplementary material 7 presents the results of preserving sign of negative correlations.

3. Data analysis

3.1. Behavioural data analysis

The HCP provides a wealth of behavioural data that assess a rich variety of cognitive tasks. Consequently, it is possible that different behavioural measures draw on shared cognitive processes. Principal Component Analysis (PCA) was used to estimate orthogonal rotated components (RC) each reflecting specific latent cognitive domains (Butler et al., 2014; Hoogendam et al., 2014; Levin et al., 2013; Schumacher et al., 2019). This PCA-based cognitive domain extraction was carried out on the cognitive data of 433 out of the total of 682 participants, by setting aside the 249 participants (for which the Neuroimaging data was available) used later for constructing the different models of cognition. Specifically, after standardising the data (z-score) the most stable number of PCA components with eigenvalues equal to or greater than 1 (Guttman-Kaiser rule) was estimated by randomly selecting 90% of the 433 participants for the PCA estimation and repeating the procedure 10000 times. An eigenvalue of 1 has been proposed as a reasonable lower bound for selecting PCA components in psychology research (usually leading to 80% of explained variance and interpretable components) and has been shown to have some optimal reliability properties, as being a necessary and sufficient condition for a principal component to have positive Kuder-Richardson reliability (Kaiser, 1960). The complementary stability analysis described above showed 5 to be the most stable number of components (occurring in 78.91% of cases), explaining 63.83% of the variance on average (standard deviation 3.45%). The estimated RCs were then used to compute RC scores of the remaining 249 subjects, which were taken as response variables for the subsequent model construction (see next section). Since the proposed model construction approach was embedded in a repeated k-fold cross-validation (CV) setting, estimating the cognitive components on the separate sample of 433 subjects, prevents data-leakage during the CV procedure. This is because the subsequent computation of the component scores of the remaining 249 subjects, is effectively independent of the CV procedure.

3.2. Model Construction and Model Comparisons

3.2.1. Overall approach

Model construction was based on a Principal Component Regression (PCR) approach, where separate linear regression models of individual cognitive domains (5 domains), were fit using SC, FC or CC. This resulted in a total of 15 models to be estimated (5 cognitive domains * 3 types of connectivity). The Bootstrap Bias Corrected Cross-Validation (BBC-CV) (Tsamardinos et al., 2018) was implemented to validate the PCR as a learning method. Finally, the model comparison analysis between the three types of connectivity models obtained for each cognitive construct was based on the Bayesian Information Criterion (BIC) (Schwarz, 1978). The BIC balances the goodness-of-fit of the model (model accuracy) against its complexity (the number of parameters included in the model), so that reduced BIC is associated with improved model quality.

3.2.2. Principal Component Regression with Step-Wise Regression (SWR-PCR)

The PCR method solves a regression problem of a response variable (here a cognitive RC score associated with a given cognitive construct) on multiple explanatory variables (here SC, FC or CC values) in three steps:

Step 1: the PCA of connectivity information is carried out to deal with multi-collinearity of connections and to reduce the dimensionality of the problem by obtaining the orthogonal principal components (PC);

Step 2: the obtained PC scores are used as new features to solve the regression problem in the reduced PCA space;

Step 3: the estimated regression coefficients in PCA space are projected back to the original connectivity space using the corresponding PC weights, to obtain one regression coefficient for each connection (network edge).

The SC and FC matrices were defined by first vectorising the elements of the lower triangle of the respective connectivity matrices of each subject to obtain one row connectivity vector per subject for each connectivity type. The connectivity vectors of all subjects, were then stacked row-wise for each connectivity type to obtain separate SC or FC matrices, each of dimension number of subjects (subjects' dimension) by number of connection edges (connectivity dimension). The matrix for the CC case was constructed by concatenated the SC and FC matrices column-wise. This means that in the case of the CC model, the PCA in step (i) of the PCR was applied to the concatenated SC and FC data across the connectivity dimension.

One possible limitation of PCR is that the PCA in step 1 favours components to be selected based on explained connectivity variance across subjects, even if those components do not make large contributions to the model skill. To address this, in the present work the regression problem in step 2 was solved using SWR, with any reduction in BIC as criterion for including or excluding a component in the regression ($\Delta BIC=0$) (Figure 1). BIC has been demonstrated to produce simpler models in general, and it has also been reported to be a preferable approach (less biased) in the small sample case (Hurvich & Tsai, 1989). This effectively amounts to a variable selection step, where a component is considered if its inclusion improves (i.e. reduces) the BIC of the model.

3.2.3. Bootstrap Bias Corrected Cross-Validation approach

To evaluate the generalisation (out-of-sample) performance of the models, we implemented the BBC-CV method proposed by Tsamardinos et al. (2018). BBC-CV combines (repeated) k-fold CV and bootstrap techniques in order to produce bias corrected estimates of the out of sample predictive performance of a learned model. In doing so, BBC-CV leverages the two techniques and provides unbiased (population) estimates of the expected out-of-sample performance metrics and their confidence intervals. In brief, BBC-CV bootstraps the out-of-sample predictions generated during the k-fold CV to compute the population of bootstrap estimates of the performance statistics. This population estimates are then used for both bias correction of performance due to hyperparameter tuning, as well as for computing confidence interval on the bias corrected estimates. Originally the BBC-CV was proposed as an efficient alternative to nested CV for bias correction during hyperparameter tuning. Although in the present paper no hyperparameter tuning is performed, we capitalise on BBC-CV to compute confidence intervals on the estimated out-of-sample performance statistics (Tsamardinos et al., 2018).

During this procedure, the SWR-PCR learning method was embedded in a randomised repeated (100 times) 5-fold CV using the 249 participants. Specifically, in each 5-fold CV split, 4 folds (199 participants out of the 249) were used to train each model (training set) using the SWR-PCR method; and 1 fold (50 participants) was used to evaluate the out-of-sample model performance (validation set). Prior to training and

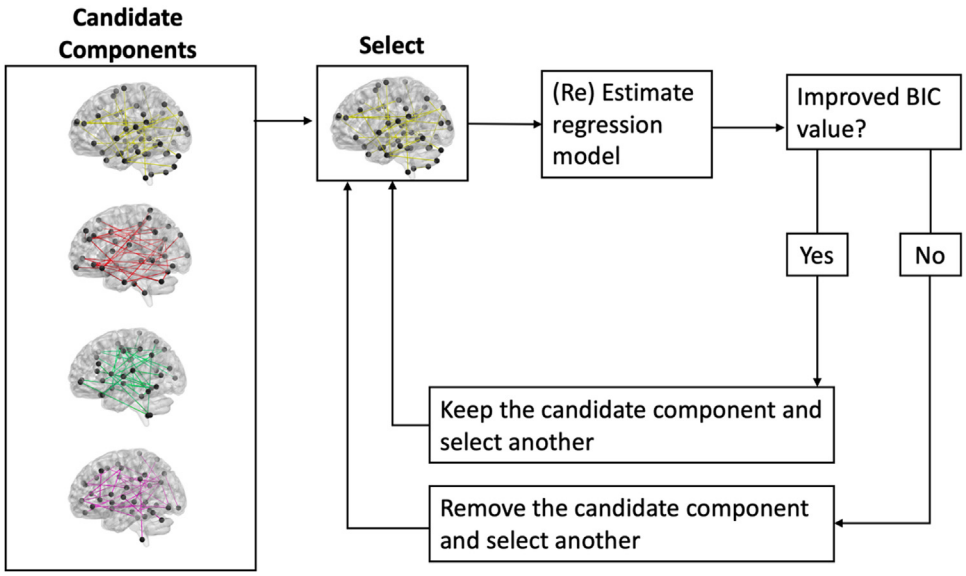

Fig. 1. A visual illustration of the stepwise regression method applied to the connectivity components. The process is repeated until BIC value cannot be improved (reduced) any further and all candidate components have been considered by the model.

validation in each CV split, the mean and standard deviation of the training fold were calculated and used to standardise (centre and scale) both the training and the validation sets. This procedure ensures a consistent validation step because the same operations are applied to both training and validation sets, and results in standardised estimated regression coefficients. The predicted data of all validation sets across all repetitions were saved and used to provide unbiased model skill estimates and corresponding confidence intervals using bootstrap. That is, out-of-sample predictions and their corresponding observed outcomes in the validation sets were bootstrapped to obtain 10,000 bootstrap datasets (each of size = 249). The explained variation (coefficient of determination), accuracy (Pearson's R) and error (RMSE) were used as performance statistics (Li et al., 2019; Poldrack et al., 2020) and computed for each of the bootstrap datasets. The resultant population of bootstrapped statistics was used to produce performance estimates (median) and corresponding confidence intervals. As noted in Tsamardinos et al. (2018), since predictions for the same subject in different repeats are correlated (easy-to-predict subjects tend to produce small errors, while outliers tend to produce big errors), predictions on the same subject for different repeats were to all be included in a bootstrap sample. That is, the bootstrap data is created by resampling with replacement the indices of the subjects. We also note that, in the present analysis, individual variation in age, education and gender were treated as confounds and regressed out from each of the five cognitive components (Tian & Zalesky, 2021). In order to avoid data leakage, this confounds correction was embedded in the 5-fold CV procedure. That is, beta coefficients for the above confounds were estimated in the training set and then applied to the validation set. Finally, all models generated during CV were discarded and the final models reported were those trained on the full confound-corrected dataset.

3.2.4. Significance of models' predictive performance

Permutation (randomisation) test was used to assess how likely it is to get the observed models' performance by chance. Specifically, the saved predictions during the BBC-CV were randomised (sampled without replacement) 10,000 times and the models' performance statistics (coefficient of determination) were estimated for each randomisation. This null distribution was then used to assess the observed model performance statistics in the non-permuted data. (Tsamardinos et al., 2018). That is, a p-value for testing models' performance was determined by computing the proportion of resampled statistics at least as high or greater than the observed statistics.

As a complementary analysis, we used the non-parametric Wilcoxon rank sum tests for equal medians to assess the significance of difference in performance between different connectivity models. These comparisons were only done for models which performed better than chance, and the results based on Pearson's R and RMSE are reported in Supplementary Material 4.

3.2.5. Model comparison approach

The resultant SC, FC and CC models for each cognitive domain were compared using BIC-based model comparison with the CC as the reference model. That is, the BIC value of the CC model was first subtracted from the BIC of the other models. Results were then interpreted so that, given any two models M_1 and M_2, a positive difference ($\Delta BIC = BIC(M_1) - BIC(M2)$) is interpreted as weak (barely worth a mention) (1-3 units), positive (3-20 units) or strong (20-150 units) evidence in favour of M_2 (Kass & Raftery, 1995). To complement this analysis, models were further assessed in terms of their coefficients of determination in the sample of 249 participants (Poldrack et al., 2020). Fig. 2

3.3. Interpretation and visualisation

A specific regression coefficient in connectivity space is interpreted as the partial regression coefficient associated with a specific connection (edge). Therefore, in order to identify the connections that are significantly related to a cognitive domain, we tested the hypothesis of no linear association between each connection and the cognitive response variable. This was done by implementing a raw data permutation (randomisation) test (5,000 permutations) for partial regression coefficients (Anderson & Legendre, 1999; Manly, 2018). To account for multiple comparisons, the above permutation test was based on the "max statistic" method for adjusting the p-values of each variable (Groppe et al., 2011). Finally, those regression coefficients for which the null hypothesis was rejected (corrected p-value ≤ 0.05) were visualised with circlize package in R (Gu et al., 2014). However, since regression coefficients' values are not directly interpretable (Haufe et al., 2014), visualised coefficients were first Haufe-transformed to obtain interpretable edge weights as

$$\beta^{Haufe} = X^T \hat{y}$$

where X is the matrix of standardized connectivity predictors and $\hat{y}$ is the vector of predicted cognitive scores (Haufe et al., 2014; Tian & Zalesky, 2021). During visualisation, positive and negative weights were considered separately. To further facilitate interpretation and analysis of

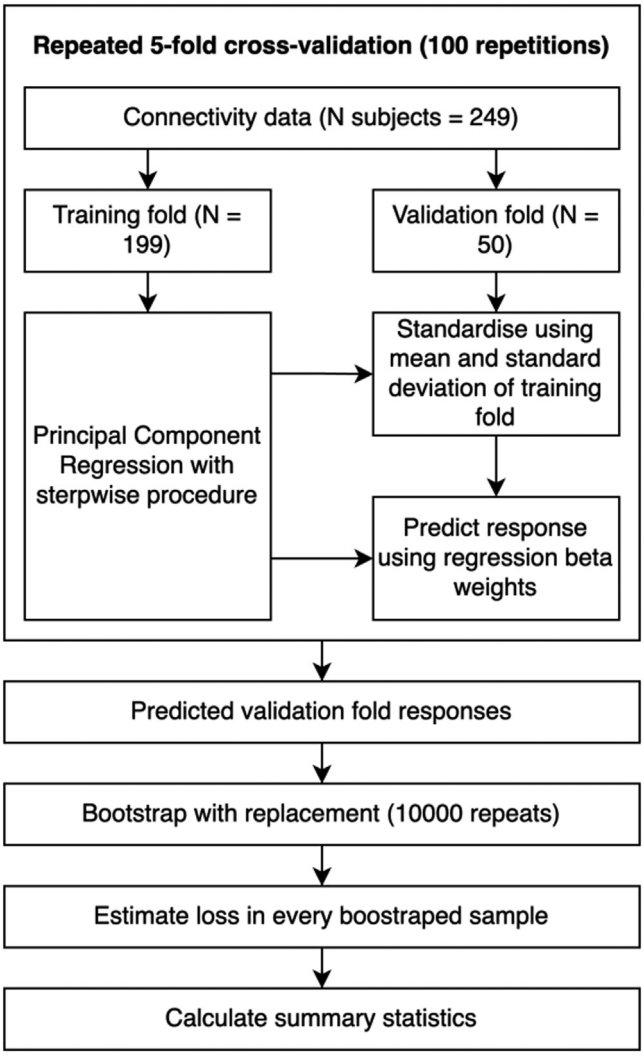

Fig. 2. A visual illustration of the Bootstrap Bias Corrected Cross-Validation approach.

results, weights were also averaged within the 7-network parcellation of resting state networks (Yeo et al., 2011). Cerebellum and subcortical regions were assigned with their respective networks. The weights of the resulting 9-nodes' networks connections were further scaled to range between 0 and 1.

4. Results

4.1. Cognitive components underlying behavioural data

The PCA of cognitive measures yielded a 5-component solution, which explained 62% of variance in the behavioural data. The rotated component solution was used to interpret the cognitive domains reflected by each component (Figure 3). The first component was primarily composed of Dimensional Change Card Sort, Flanker and Pattern Processing Speed tasks. The component also included a moderate negative loading from Variable Short Penn Line Orientation Test. Dimensional Change Card Sort and Flanker tasks dominated the solution with strongest loadings. Since these tests were designed to measure executive function the component will be referred to as such. The second component saw unique loading from Delay Discounting tasks, which measure impulsivity and self-control ability. Therefore, this component will be referred to as Self-regulation. The third component was dominated by Oral Reading Recognition and Picture Vocabulary tasks, as well as Penn's Progressive Matrices. Penn's Progressive Matrices reflect fluid intelligence rather than language ability. They are different domains supported by different neural systems (Woolgar et al., 2018), but both cognitive domains have been related in childhood development (De Stasio et al., 2014; Friesen et al., 2021; Gamaroff, 2012) and education (Kaufman et al., 2009). As the result of the dominance of language tasks on this component, we will now refer to this component as Language. The fourth component was made up of Short Penn Continuous Performance and Penn Word Memory tests, which both require effective encoding of information, therefore this component was called the 'Encoding' component (Cabeza et al., 2008; Ciaramelli et al., 2008). Finally, the fifth component had highest loadings associated with Picture Sequence Memory and List Sorting, both of which involve processing and reconstruction of sequences. Hence, this component will be referred to as Sequence Processing.

4.2. Connectivity-based models of cognition

4.2.1. BIC model comparison

Comparison of BIC values demonstrated moderate evidence that Executive Function was better explained by CC model, followed by FC model. CC model of Self-regulation was moderately outperformed by SC and FC models, but there was no appreciable difference between BIC values for SC and FC models. FC and CC models of Language have moderately outperformed SC model, but there was no appreciable difference between their BIC values. Encoding and Sequence Processing have demonstrated the same model preference, such that SC models were moderately favoured relative to FC, and FC models were moderately favoured relative to CC models. Fig. 4

4.2.2. Cross-validation based model comparison

Figure 5 illustrates the results of the BBC-CV procedure, as measured by coefficient of determination. Filled boxes illustrate greater than chance prediction skill and unfilled boxes illustrate not greater than chance prediction skill. Only results for models that predict greater than chance will be considered further. SC and CC models of Executive Function have explained more variation in validation sample than chance. SC models (mean = 0.03, SD = 0.02) have explained more variation in Executive Function than CC models (mean = 0.02, SD = 0.02). A Wilcoxon rank sum test found this difference to be significant ($Z = 41.08$, $p < .001$). Next, all models of Language have explained more variation in validation sample than chance. CC models (mean = 0.05, SD = 0.02) have explained more variation than FC models (mean = 0.02, SD = 0.02), and this difference was significant ($Z = 101.06$, $p < .001$). Next, SC models have explained most variation in Language (mean = 0.06, SD = 0.02), and they explained significantly more variation than CC models ($Z = 21.46$, $p < .001$).

4.2.3. Estimated models in network space

Projection of models' edge weights in network space demonstrated that for unimodal results, FC yields more connections associated with all cognitive domains than SC. In addition, there was no overlap between SC and FC connections supporting cognitive constructs. Compared to unimodal models, CC models yielded more structural and functional connections associated with cognition. In CC models, more functional connections were associated with cognition than structural. At most 0.002% of surviving connections overlapped across structural and functional parts of the CC models of Self-regulation. Figures 6-10 summarise projections of SC and FC model edge weights values in 7-resting state network space (Yeo et al. 2011). Supplementary material 5 presents CC model in the same space.

5. Discussion

In this study we examined whether cognitive performance in specific cognitive domains was best explained by models based on SC, FC

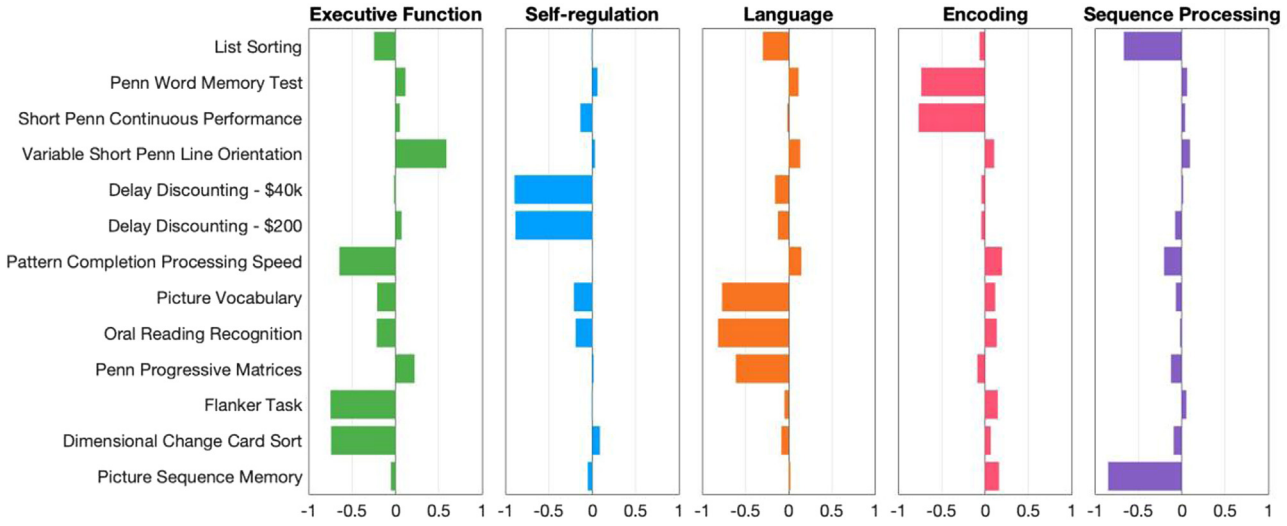

Fig. 3. Rotated Principal Component loadings illustrated in the form of a bar graph.

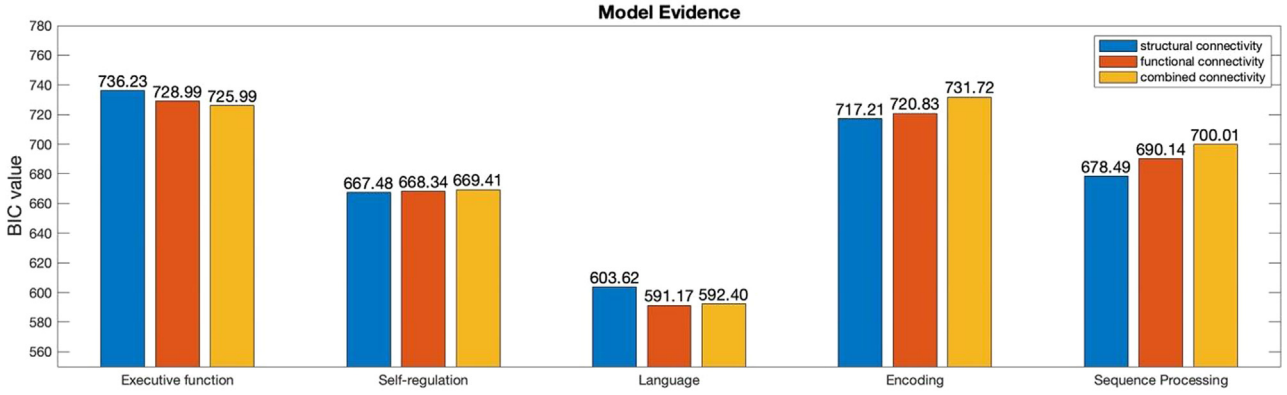

Fig. 4. BIC model evidence for SC, FC and CC models of each cognitive domain. Models with lower BIC values are favoured.

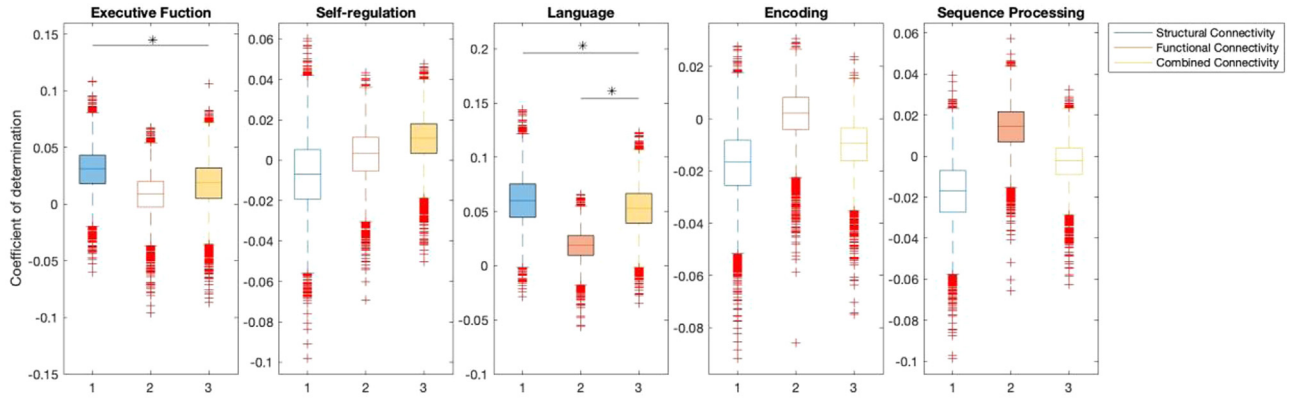

Fig. 5. Results of BBC-CV as measured by coefficient of determination. The solid lines show the median scores, the boxes show the interquartile range (IQR), and ticks outside of whiskers indicate outlier scores across all bootstrap samples. Filled boxes illustrate greater than chance prediction and unfilled boxes illustrate not greater than chance prediction. The asterisks indicate significant differences ($p < .001$) between model coefficients of determination observed for models that perform significantly better than chance.

or CC (i.e. combined SC and FC). First, we derived five distinct cognitive components from the HCP cognitive dataset: Executive Function, Self-regulation, Language, Encoding and Sequence Processing. It was found that the performance of SC, FC, and CC models depended on the cognitive domain. Comparison of model's BIC values demonstrated that Executive Function was best explained by the CC model. Self-regulation was better explained by SC and FC. Language was equally well explained by CC and FC models. Encoding and Sequence Processing were best explained by SC. Every cognitive domain was supported by a pattern of connections that was largely unique to structural and functional networks. SC model of Executive Function had better generalisation performance than the CC model. SC model of Language had better generalisation performance than the CC model and FC model. Only CC model of Self-regulation and FC model of Sequence Processing have performed

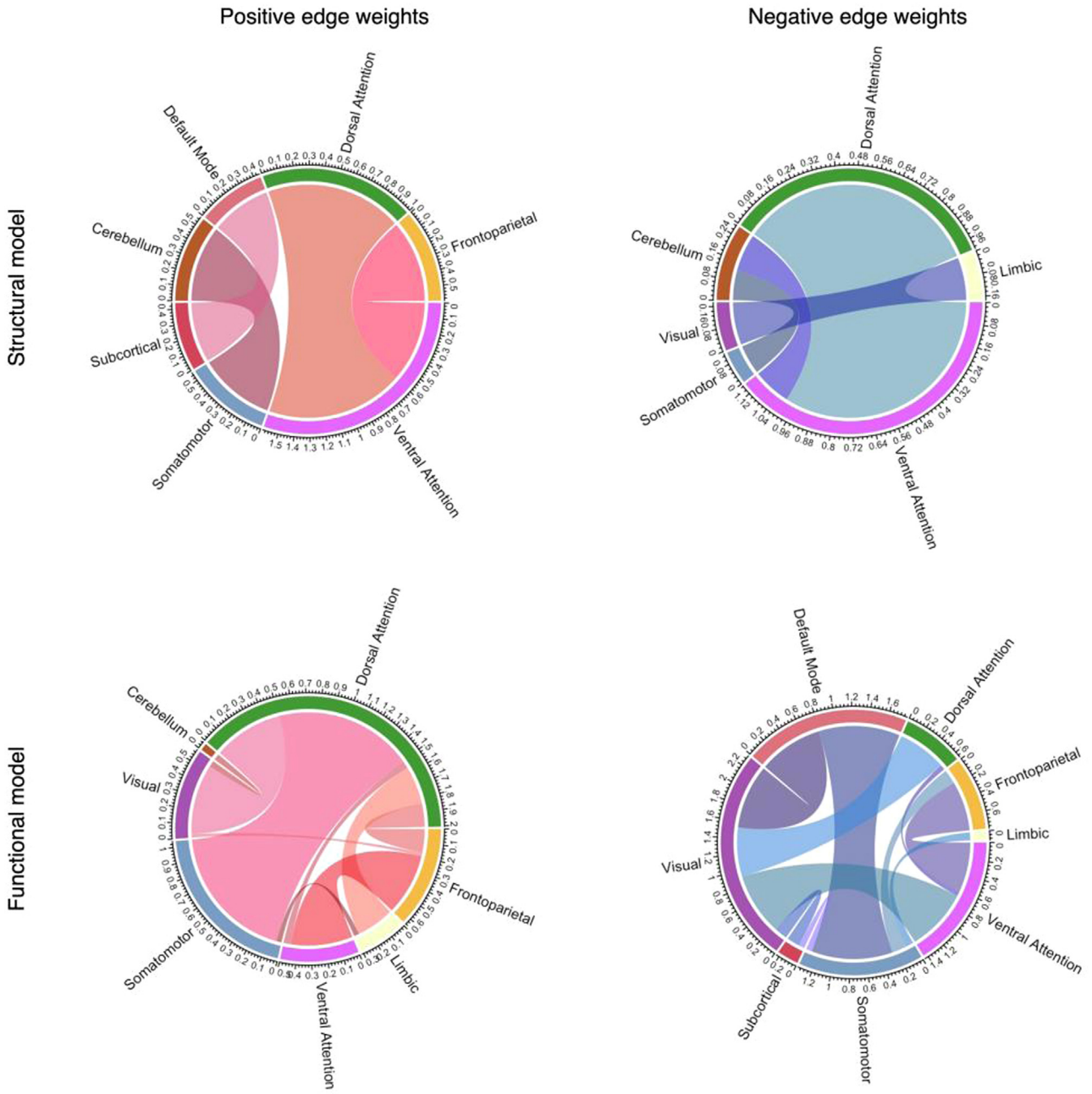

Fig. 6. Chord plots depict projections of SC and FC model edge weights (following significance testing) in 7-resting state network space (Yeo et al. 2011) for models of Executive Function. Link width around outer rim of each diagram reflects normalised average edge weight (connection importance) for each network. The weight values have been separately scaled for positive and negative weights to range between 0 and 1 prior to p-value based masking (p-value =< 0.05). Red links present positive edge weights and blue links present negative edge weights. Outer rim colour scheme corresponds to colours utilised by Yeo et al. (2011), such that it is possible to compare across different panels to identify the variations in networks involved by considering the proportion of the rim taken up by each network

above chance level. All models of Encoding performed bellow chance level. The following sections discuss the cognitive PCA analysis, the relative explanatory (in-sample) power of each regression model, their (out-of-sample) predictive performance and caveats of this work.

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; Robinson et al., 2021; 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 covariance. 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 demen-

tia (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 five components underpinning performance on these cognitive tasks: Executive Function, Self-regulation, Language, Encoding and Sequence Processing.

5.2. Models of cognition

It has been proposed that every neuroimaging modality measures specific biological properties and in doing so it presents some unique information about the characteristics of the brain (Eickhoff et al., 2018). Consequently, combining information across modalities should result in a more complete representation of the state of the system. Here, we explored if combination of SC and FC benefits explanation of performance on specific cognitive domains. We constructed regression models of cognitive performance with SC, FC and CC. To compare model quality, we assessed difference between candidate model BIC values, which allowed us to select the best performing model based on a balance between model accuracy and complexity.

SC models of Encoding and Sequence Processing were favoured above FC models. Within the original HCP dataset, the behavioural measures that load with Language and Sequence Processing are summarised by a single composite score known as crystallised intelligence. These measures commonly reflect person's ability to retrieve knowledge, experience, and skills (Heaton et al., 2014). Consequently, it was surprising to find that Language and Sequence Processing would be most effectively explained by different models. Generally, learning and experience have been found to lead to systematic structural changes in the brain across lifespan (Douaud et al., 2014; Zatorre et al., 2012). This suggests that SC is especially useful for understanding of Sequence Processing due environmental pressures and experience. In addition, we observe that different structural connections were associated with Language and Sequence Processing abilities (Figure 7). This demonstrates that it is important to study and understand unique associations between brain networks and individual cognitive domains, rather than composite scores.

Next, comparison of BIC values demonstrated that Executive Function was best modelled by CC. BIC evidence demonstrated that Language is equally well modelled by CC and FC, although CC model appeared to explain more variation than FC model (Supplementary Figure 1). The finding that joint consideration of SC and FC provides unique contribution to models of specific cognitive domains replicates previous findings from Rasero et al. (2021). More specifically, Rasero et al. (2021) have found that the more abstract cognitive domains were best modelled by combined features of the brain. Their finding could be explained by hierarchical cortical organisation of behavioural tasks, as demonstrated by Taylor et al. (2015). Taylor and colleagues found that concrete cognitive tasks require engagement of sensory connections. However, deeper and more distant connections are also engaged as tasks become more complex and abstract. In reference to this finding, Rasero et al. (2021) have argued that due to hierarchical cortical organisation of behavioural tasks there is a benefit to combining information about different features of the brain. Similarly, we found that highly abstract cognitive domains of Executive Function was best modelled by CC, whereas CC model of Language was contested by FC model. Meanwhile Encoding and Sequence Processing require more concrete memory processes. Consequently, we found that according to BIC evidence these two domains were best modelled by SC and FC alone. Thus, our findings are consistent with the argument presented by Rasero et al. (2021) that benefit of combining multimodal information in regression modelling is related to hierarchical cortical organisation of behavioural tasks.

Further, Rasero et al. (2021) have argued that combining information about different features of the brain benefits modelling of abstract behavioural tasks. However, we propose further that the more abstract domains may especially depend on the relationship between structural and functional inter-regional connections. Taylor and colleagues (2015) have demonstrated that more abstract tasks require sensory inputs but their processing requires additional engagement of cortical connections that progress deeper into the cortex. With this finding in mind, we propose that highly abstract cognitive domains benefited from combined SC and FC because any disruption to the structural integrity of inter-regional connections impacts the speed and efficiency of signal transmission. Consequently, deeper cortical connections would accentuate the impact of structural features on highly abstract cognitive domains. This effectively explains that CC will be effective at modelling of those domains that require deeper cortical processing because the strength of structural connections impacts the strength of functional connections.

Finally, model projections in brain space have demonstrated that fewer structural connections were associated with cognition than functional connections. This pattern was observed for both unimodal models and for combined models. This pattern of results replicates findings from Zimmermann et al. (2018). One explanation of these findings is that SC is generally sparser than FC, because FC includes indirect connectivity, observed when two remote brain regions are functionally connected without direct structural connections (Deligianni et al., 2011; Honey et al., 2009; Røge et al., 2017). Thus, SC generally presents less information about the state of the system. In support of this proposal, Zimmermann and colleagues (2018) have repeated their analysis with correction for connectome sparsity and still found that fewer structural connections supported cognition. In addition, we have found that despite joined consideration of SC and FC in CC models and despite application of PCA to CC, unique structural connections are associated with cognitive performance. This result replicates the findings of Zimmermann et al. (2018) and Dhamala et al. (2021). This pattern was observed for every cognitive domain, which suggests that unique features of SC may support cognitive performance. Taken together, these results demonstrate that study of both SC and FC is important for a complete understanding of cognition.

5.3. Predictive performance

To assess the predictive performance of models generated by the model training pipeline, BBC-CV approach was implemented (Tsamardinos et al., 2018). This revealed that in validation sample SC, FC and CC produced generalisable models of Language performance. SC models performed most effectively at predicting Language performance in unseen sample. Next, Executive Function was most effectively predicted by SC models, followed by CC models. Self-regulation was only effectively predicted by CC models and Sequence Processing was only effectively predicted by FC models.

Out of all cognitive domains, Language was most effectively predicted by the SWR-PCR pipeline. There are three explanations that may account for this finding. First, language is a learned skill that relies on retrieval of learnt knowledge, therefore it may be less impacted by temporary conditions such as sleep and stress than fluid abilities like executive function and self-regulation (Hofmann et al., 2012; Nilsson et al., 2005; O'Neill et al., 2020). Second, comprehension and production of language has been extensively and thoroughly related to specific structural and functional networks (Friederici & Gierhan, 2013). Consequently, the fact that language relies on stable patterns of connectivity be the reason why Language itself may constitutes an effective target domain for predictive modelling. Third, acquired skills and environmental pressures and their impact on the plasticity of the brain may contribute to the generalisability of Language models. Language abilities are acquired during childhood and a shared relationship has been demonstrated between education, socioeconomic status and neural connectivity (Dunbar, 2008; Merz et al., 2019; Monzalvo & Dehaene-Lambertz, 2013). Language itself has been related to systematic life-span changes in SC and FC (Diaz et al., 2016; Shafto & Tyler, 2014; Wlotko et al., 2010). Thus, the relationship between neural plasticity and language may be the rea-

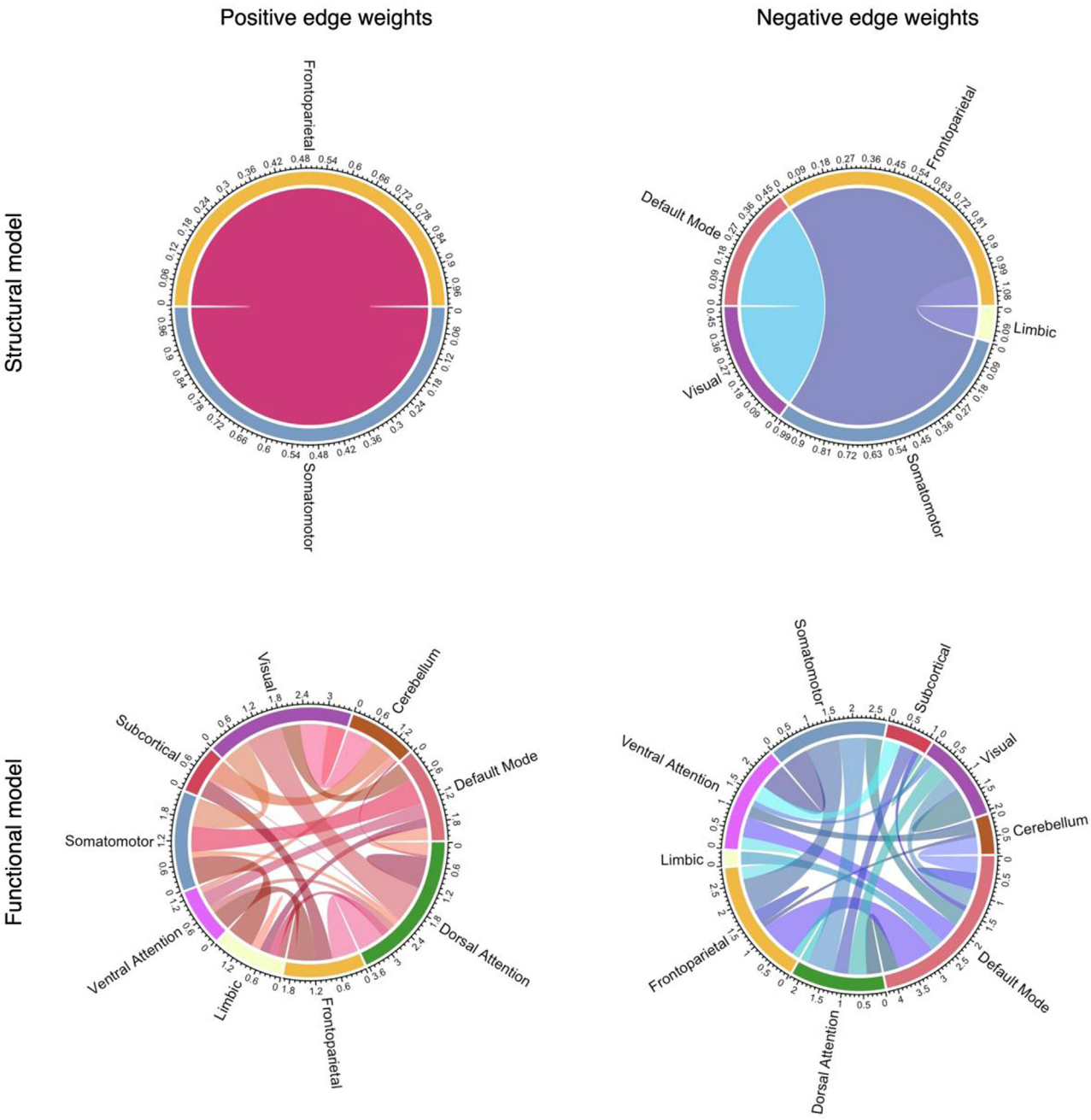

Fig. 7. Chord plots depict projections of SC and FC model edge weights (following significance testing) in 7-resting state network space (Yeo et al. 2011) for models of Self-regulation. Link width around outer rim of each diagram reflects normalised average edge weight (connection importance) for each network. The weight values have been separately scaled for positive and negative weights to range between 0 and 1 prior to p-value based masking (p-value =< 0.05). Red links present positive edge weights and blue links present negative edge weights. Outer rim colour scheme corresponds to colours utilised by Yeo et al. (2011), such that it is possible to compare across different panels to identify the variations in networks involved by considering the proportion of the rim taken up by each network

son why Language models were generalisable. If this is the case, then not only language abilities, but also other learnt abilities such as long-term memories and proficiency in learnt skills may constitute cognitive domains that can be more effectively predicted from connectivity and particularly the relationship between SC and FC.

In addition, we found a divergent result that SC produced most generalisable model of Language, whereas FC produced the only generalisable model of Sequence Processing. As previously discussed in section 5.2, the behavioural measures that load with Language and Sequence Processing have been summarised by a single composite score known as crystallised intelligence (Heaton et al., 2014). Previous work has demonstrated that that unseen crystallised intelligence scores were best predicted using FC (Dhamala et al., 2021; Mansour et al., 2021). Here, SC outperformed FC at predicting Language abilities in unseen sample and FC produced the only generalisable model of Sequence Processing. This discrepancy of the results suggests that effectiveness of SC at modelling of cognition may have been previously obscured by use of composite intelligence scores due to conflicting directions of variance in cognition. Alternatively, the we may also explain these results by methodological differences between previous and present research. Here, we applied PCA to connectivity matrices prior to regression. PCA generally aims to identify the orthogonal components that describe the

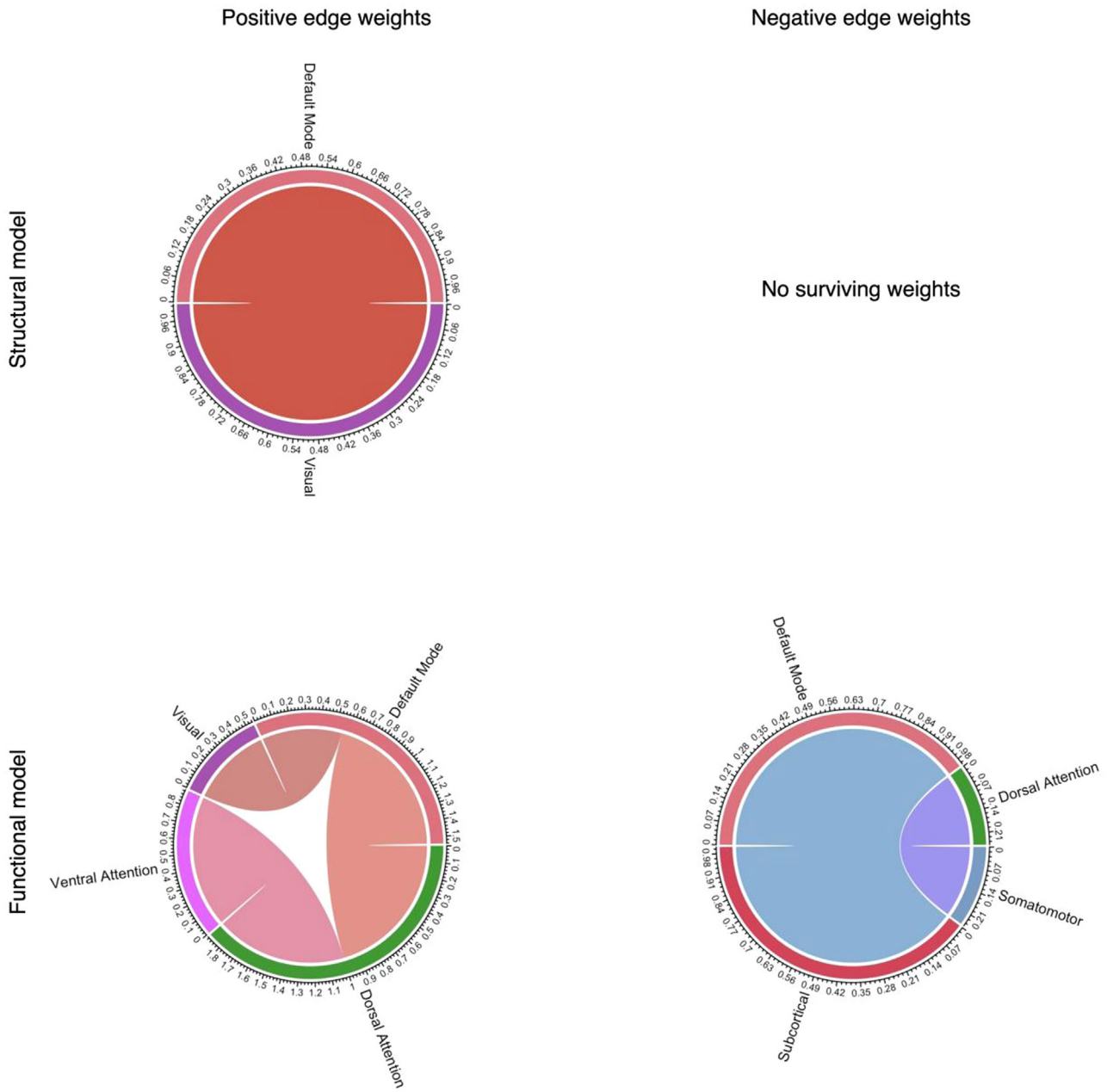

Fig. 8. Chord plots depict projections of SC and FC model edge weights (following significance testing) in 7-resting state network space (Yeo et al. 2011) for models of Language. Link width around outer rim of each diagram reflects normalised average edge weight (connection importance) for each network. The weight values have been separately scaled for positive and negative weights to range between 0 and 1 prior to p-value based masking (p-value =< 0.05). Red links present positive edge weights and blue links present negative edge weights. Outer rim colour scheme corresponds to colours utilised by Yeo et al. (2011), such that it is possible to compare across different panels to identify the variations in networks involved by considering the proportion of the rim taken up by each network

directions of greatest variance. Implementation of PCA may result with a more pronounced relationship between connectivity and cognitive performance, and this process may aid generalisability of models constructed with SC that was previously not seen.

However, our pipeline did not succeed at producing generalisable models of Encoding. This suggests that the generalisability of SWR-PCR may be lower for specific cognitive domains. For such domains, SWR-PCR identifies feature weights that are specific to the sample that they are trained on. This finding is not unheard of; previous work demonstrates that feature selection is unstable across training samples (Nogueira et al., 2017). Further, feature weights are unreliable even in massive samples of 400+ participants (Tian & Zalesky, 2021). Consequently, it is important to consider the caveat that model fit alone is not necessarily a good criterion of model quality if the intended purpose is making prediction.

The pipeline implemented here utilised BIC value as a feature selection criterion, which balances model fit with its complexity by introducing a penalty term for addition of features to the model. This means that strong associations with cognition are necessary for connectivity components to survive the penalty for model complexity. Consequently, sparse parsimonious models are constructed. However, these parsimonious models did not produce accurate predictions for Encoding performance and individual models from Executive Function, Self-regulation and Sequence Processing were also specific to the sample they were trained on. This suggests that the regression models produced for most cognitive domains are related to strong individual differences. In

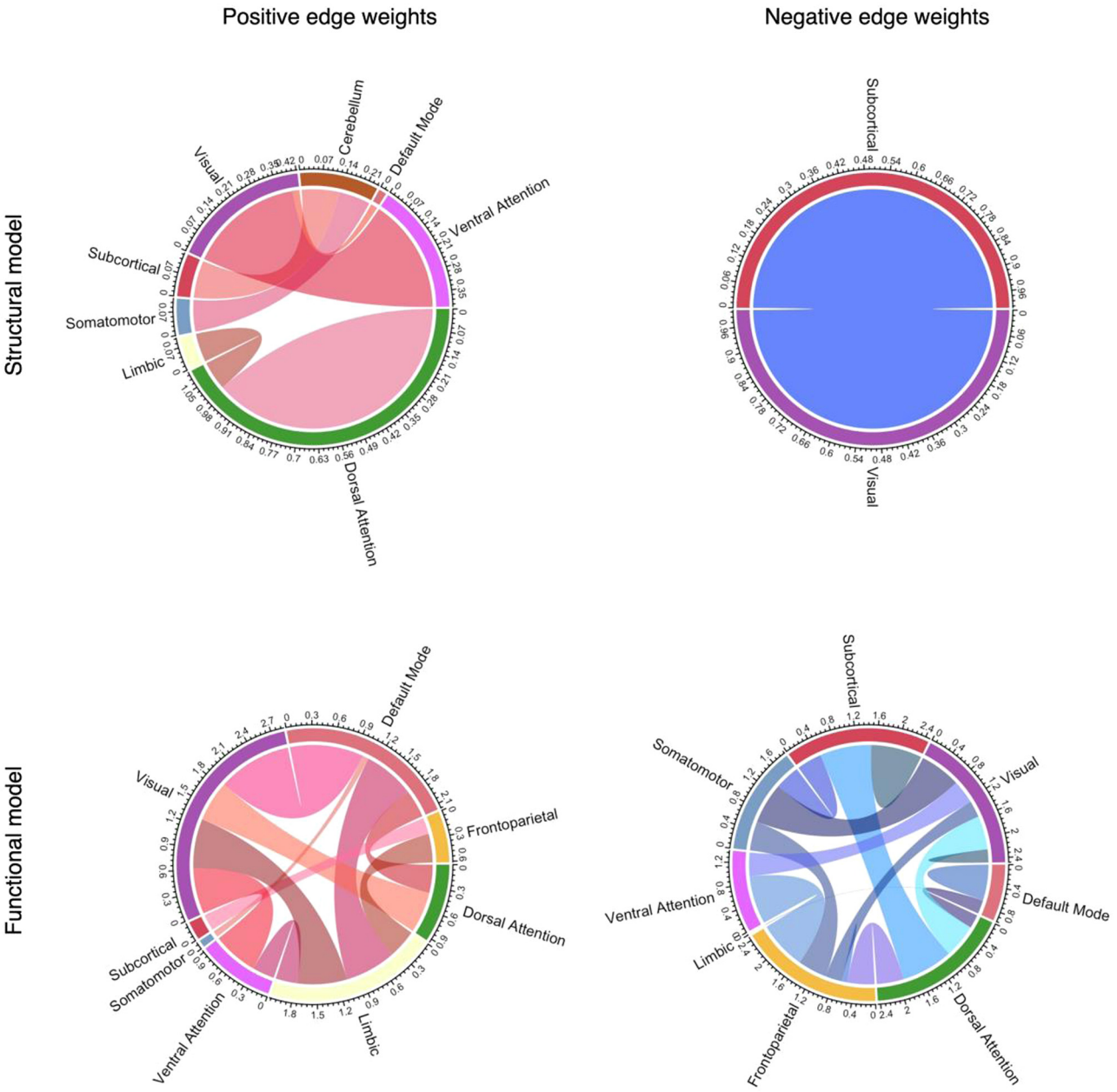

Fig. 9. Chord plots depict projections of SC and FC model edge weights (following significance testing) in 7-resting state network space (Yeo et al. 2011) for models of Encoding. Link width around outer rim of each diagram reflects normalised average edge weight (connection importance) for each network. The weight values have been separately scaled for positive and negative weights to range between 0 and 1 prior to p-value based masking (p-value =< 0.05). Red links present positive edge weights and blue links present negative edge weights. Outer rim colour scheme corresponds to colours utilised by Yeo et al. (2011), such that it is possible to compare across different panels to identify the variations in networks involved by considering the proportion of the rim taken up by each network

other words, the relationship between brain connectivity and cognitive performance presented in many of our models reflects strong, sample-specific characteristics. Previous work demonstrates that accurate behaviour prediction in unseen sample is not necessarily related to reliable networks (Byrge & Kennedy, 2020; J. Liu et al., 2017; Noble et al., 2017). Understanding how individual differences impact the relationship between individual cognitive domains and patterns of brain connectivity will be critical for a more effective machine modelling in the future.

5.4. Methodological caveats and future directions

Our work has aimed to explore how effective SC, FC and CC are at modelling of cognition. We produced models of individual cognitive domains using SC and FC alone or a combination of the two (CC). Thus, this work is the first to compare performance of SC, FC and CC with an information theory-driven method of constructing and selecting across candidate models. In addition, here for the first time, PCA was applied to structural and functional connectivity as a dimension reduction method. Components resulting from this reflect common and unique directions of variance between brain structure and function. Future work will have to explicitly address how the two modalities interact, and what contributions cross-modal interactions and higher order terms make to models of cognition. However, the combined 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 specific cognitive domains.

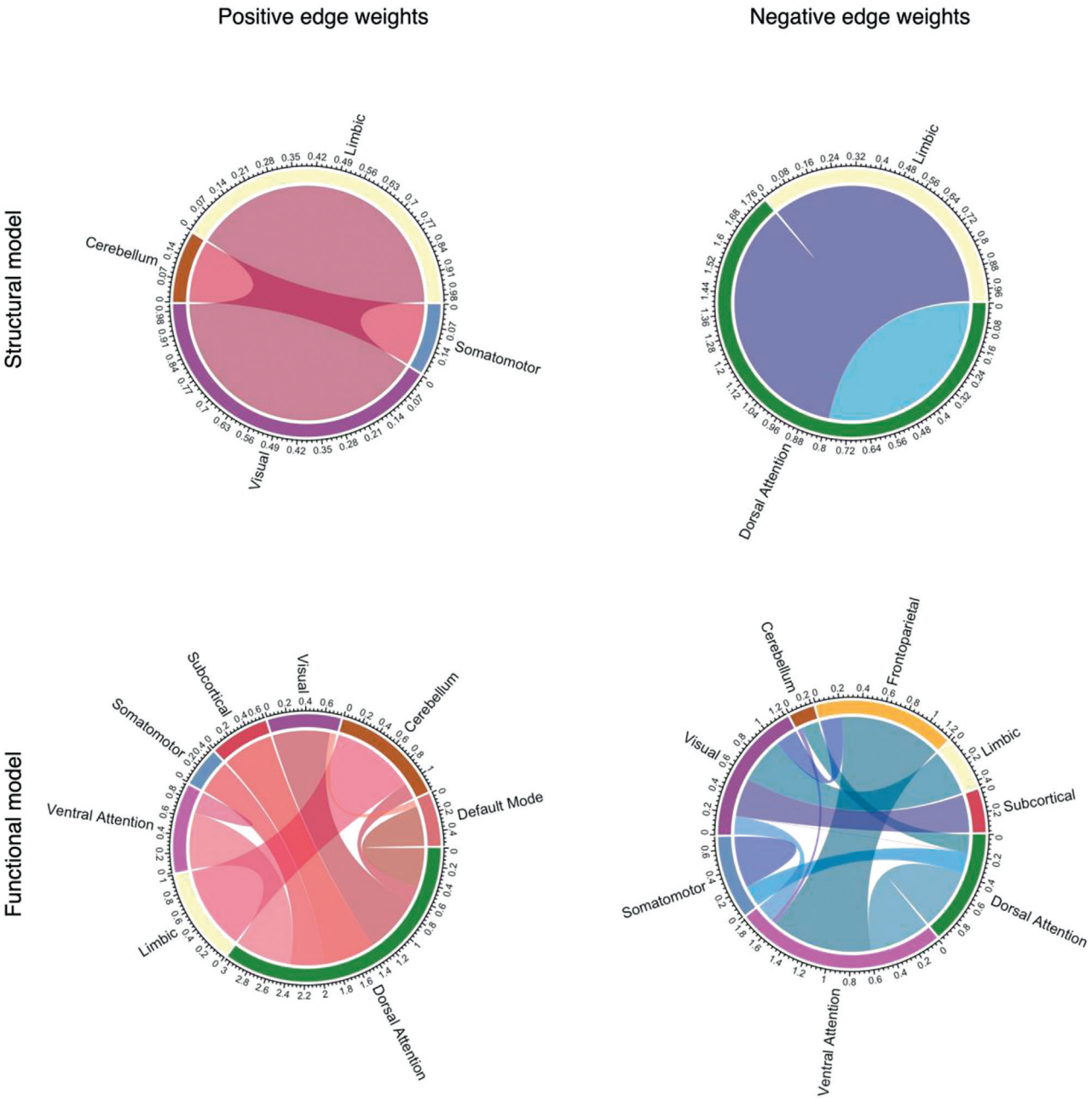

Fig. 10. Chord plots depict projections of SC and FC model edge weights (following significance testing) in 7-resting state network space (Yeo et al. 2011) for models of Sequence Processing. Link width around outer rim of each diagram reflects normalised average edge weight (connection importance) for each network. The weight values have been separately scaled for positive and negative weights to range between 0 and 1 prior to p-value based masking (p-value =< 0.05). Red links present positive edge weights and blue links present negative edge weights. Outer rim colour scheme corresponds to colours utilised by Yeo et al. (2011), such that it is possible to compare across different panels to identify the variations in networks involved by considering the proportion of the rim taken up by each network

There are specific processing decisions that must be kept in mind when assessing the patterns of these results. The results presented in the main body of this manuscript focus on patterns of thresholded SC and FC. The procedure of thresholding has been demonstrated to generate more stable and accurate connectomes (de Reus & van den Heuvel, 2013; Hong et al., 2020). Comparison of explained variation in thresholded and dense connectomes (Supplementary Material 6 and 7) demonstrates that thresholding improved the effectiveness of modelling with CC for cognitive domains of Executive Function, Self-regulation and Language but not Encoding or Sequence Processing. To understand why such effect was observed, it is important to discuss what information is conveyed by the removed weak connections. Weaker connections may convey meaningful information about individual differences (Santarnecchi et al., 2014) but they may also be more prone to inclusion of noise due to error of white matter tracking algorithms (Roberts et al., 2017; Thomas et al., 2014; Zalesky et al., 2010), and due to presence of weak and unstable functional signal (Fornito, 2010; Garrison et al., 2015; Simpson et al., 2013; Wang et al., 2017). It is also possible that weak connections are associated with negative functional associations between pairs of regions or functional connections in the absence of direct structural connections (Wang et al., 2016). The role of these unique features of FC in CC and their relation to cognition will constitute an interesting avenue for future research.

Further, here we analysed absolute FC, focusing on the structural-functional associations in strength of connectivity. This was done with the goal to include some reflection of negative functional associations between nodes, because evidence suggests that negative connections reflect meaningful information about the state of the system (Fox et al. 2009; Chen et al. 2011). However, because structural-functional associations should remain related regardless of the sign of connectivity. Consequently, it is unclear what would be the interpretation of seeing the impact of direction of functional connectivity on its relationship with structural connectivity, and so this work focused on absolute FC. Supplementary Material 7 demonstrates that some FC and CC models benefited from inclusion of sign of FC, but the benefit observed for models of FC was never shared with CC. This suggests that sign of FC may impact PCA solution of CC and this may sometimes hinder the association of CC with cognition. Thus, the differences between main manuscript results and supplementary material open another avenue for investigations.

Next, when assessing multimodal results, it is important to consider that that the parcellation of the brain impacts the relationship between brain structure and function and cognition (Dhamala et al., 2021; Messé, 2019). Here, we used a high-resolution brain atlas from Shen et al. (2013). High atlas resolution has been found to benefit investigations of the relationship between brain structure and function (Diez et al., 2015). Consequently, different model preference may be found using atlases with lower spatial resolution. In addition, previous work demonstrates that the topography of functional parcellation can contribute to the efficiency of its explanation of cognition (Kong et al., 2019). In the present work, we have used a functional atlas defined during resting state connectivity. Thus, it is likely that use of an atlas defined with cytoarchitectural information would also change the pattern of results. However, atlas use is a subject to wide debate as every atlas will focus on specific features of the brain (Eickhoff et al., 2018). For example, the atlas defined by Shen and colleagues (2013) is a whole brain atlas that jointly optimises subject and group level parcellation under constraint of local functional homogeneity. This means that the signal contained within each parcel is stable and less likely to include interfering signals across several parcels. In comparison, other research groups, like Bellec et al. (2010), have prioritised parcels that are stable at subject and group level, rather than locally homogenous parcels. Thus, it is clear that use of specific atlases will influence what information is prioritised by the models. The question is, however, why such information would change the patterns of results, and future work should carefully investigate how network characteristics differ across parcellations. For example, are specific atlases more sensitive to network modularity than others and does that sensitivity improve modelling of specific cognitive domains using structural, functional or joint connectivity.

6. Conclusion

The present work has illustrated, for the first time, that the 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 Executive Function. In addition, function alone and combination of structure and function produced effective models of Language. Conversely, structure alone produced most effective models of Self-regulation, Encoding and Sequence Processing. However, model fit often came at the expense of model generalisability. This demonstrates that our use of combined structural-functional connectivity provides new insights concerning the different neural mechanisms involved in distinct cognitive domains. We have proposed that hierarchical cognitive organisation and interplay between direct and indirect functional connectivity is what drives the model preference in our research.

Author statement

Marta Czime Litwinczuk: Conception and design, Data processing and analysis, Visualisation and writing of manuscript. **Nelson Trujillo-Barreto**: Conception and design, Data processing and analysis, Visualisation and writing of manuscript. **Nils Muhlert**: Data processing and analysis, Visualisation and writing of manuscript. **Lauren Cloutman**: Funding acquisition, Conception and design. **Anna Woollams**: Funding acquisition, Conception and design, Data processing and analysis, Visualisation and writing of manuscript.

Data/code availability

Data is openly available as part of the WU-Minn HCP 1200 Subjects Data Release of HCP Young Adult study, part of the Human Connectome Project (https://www.humanconnectome.org/study/hcp-young-adult/). Codes for data analysis are available at https://github.com/MCLit/SC-FC-CC.

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Ethics

Ethical approval has been provided by the University of Manchester (grant reference: BB/M011208/1). The HCP is an open dataset and Open Access Data agreement was signed for use of the data.

Declaration of Competing Interest

None.

Data Availability

Data is openly available as part of the WU-Minn HCP 1200 Subjects Data Release of HCP Young Adult study, part of the Human Connectome Project (https://www.humanconnectome.org/study/hcp-young-adult/).

Acknowledgements

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119531.

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