Predicting memory scores brain from resting state connectivity

Esra Freitag
Maastricht Centre for Systems Biology (MaCSBio), Department of Cognitive Neuroscience, Maastricht University, the Netherlands
e.freitag@student.maastrichtuniversity.nl

ABSTRACT

While decades of neuroscientific research has detailed the brain networks underlying memory, to date the neurobiology underlying interindividual memory differences in a healthy population is not known. Here we use the behavioral and resting state fMRI data from the Human Connectome Project (HCP), and predict subjects' scores on tests of working and episodic memory based on their whole brain functional connectivity significantly above chance. We observed that brain connectivity between regions determining differences between healthy subjects were different from those traditionally associated with memory. Results may ultimately be relevant to determine risk factors for the development of neurodegenerative disorders.

Keywords

Human Connectome Project, fMRI, episodic memory, working memory, regularized regression

INTRODUCTION

The study of memory has long been one of the cornerstones of cognitive psychology and neuroscience. Both episodic memory, the memory of personal events, and working memory, ensuring temporary availability of relevant information, are well characterized in terms of their underlying brain networks. Meta-analysis of neuroimaging and neuropsychological research points to the medial-temporal lobe as a hub of episodic memory encoding and retrieval [1, 2]. Within that region, especially the hippocampus has been studied extensively [3].The prefrontal cortex plays an important role in episodic memory functioning as well, as it has been implicated in structuring information for encoding and retrieval [4]. With regards to working memory, research points to a fronto-parietal network [4].

While previous studies help to identify brain networks that underlie memory function, much less is known about how brain connectivity determines inter-individual differences in memory performance. In the extreme case of Alzheimer's disease, where episodic memory and working memory are compromised, changes in large-scale connectivity [5] as well as networks associated with task performance becoming more similar to those associated with rest are observed. [5]

To date, an investigation of the differences in brain functional connectivity within a group of healthy subjects is lacking. One reason for this is the use of small sample sizes in neuroscientific studies that make detection of variability within healthy subjects difficult. The human connectome project [6] offers an opportunity to overcome this limitation. This large dataset has already been used to predict variables such as fluid intelligence [7].

Our study intends to further this line of research and use resting state connectivity and memory tests provided by the HCP to investigate if scores on the behavioural tests can be

predicted from brain functional connectivity. This analysis would help pinpoint specific connections in the brain that might give rise to differences in memory performance on an individual basis.

A similar analysis was done with the "HCP MegaTrawl" (https://db.humanconnectome.org/megatrawl/index.html). Their analysis, however, turned out non-significant. We intend to make use of an alternative parcellation as published by Glasser and Coalson[8] and Ridge Regression to improve on their work.

For two out of three variables that we are studying our results show a significant correlation between our predicted and observed scores.

METHODS

Data

Behavioural data. Behavioural measures relevant to the study at hand are the Picture-Sequence-Memory-Test (PSMT), for episodic memory, the Penn-Word-Memory-Test (IWRD), for verbal episodic memory and the List-Sorting working memory test. Both previously mentioned variables are available adjusted for age by linear regression and unadjusted.. This is scored by reaction time (RT) in milliseconds and by the total number of correct responses. All tests are part of the NIH toolbox.

Neuroimaging data. The HCP fMRI data was obtained using a Siemens 3T Skyra scanner modified with a Siemens SC72 gradient coil. [9] were collected in four runs of about 15 minutes, over two sessions with two runs each. (http://protocols.humanconnectome.org/HCP/3T/imaging-protocols.html;TR = 720 ms, TE = 33.1 ms, voxel size = 2.0 mm isotropic).

Subjects

Resting state measurements and behavioural data of 102 subjects are obtained from the human connectome database (53.47% female, mean age range = 26-30). All subjects are healthy and part of the young adult cohort of the HCP data releases.

Connectome Preparation and Parcellation

We summarized the full brain resting state data of each individual using the semi-automated parcellation proposed by Glasser and Coalson[8] (referred to as HCP-MMP1, figure 1). This serves to reduce the dimensionality of the raw fMRI data: Instead of producing a connectome (matrix of

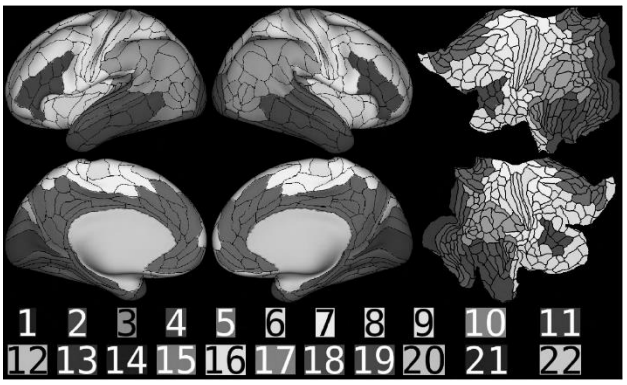

Figure 1: adapted from Glasser and Coalson[8], Neuranatomical Supplementary Results
180 areas per hemisphere are summarized into 22 broader regions. Within one region areas share similar functionality. The first column shows the left hemisphere, lateral and medial view. The second column shows the right hemisphere, lateral and medial view. The third column shows the left hemisphere on top and the right hemisphere at the bottom.

Abbreviations and Numbering

1.V1	V1	12.IC, FOC	Insular Cortex, Frontal Opercular Cortex
2.early VC	early Visual Cortex	13.MTC	Medial Temporal Cortex
3.DSVC	Dorsal Stream Visual Cortex	14.LTC	Lateral Temporal Cortex
4.VSVC	Ventral Stream Visual Cortex	15.TPOJ	Temporo-Parieto-Occipital Junction
5.MT+, neighbours	MT+ complex and neighbouring visual areas	16.SPC	Superior Parietal Cortex
6.SSMC, MC	Somatosensory Cortex, Motor Cortex	17.IPC	Inferior Parietal Cortex
7.PCL, MCC	Paracentral Lobule, Mid Cingulate Cortex	18.PCC	Posterior Cingulate Cortex
8.PMC	Premotor Cortex	19.ACC, MPC	Anterior Cingulate Cortex, Medial Prefrontz
9.POC	Posterior Opercular Cortex	20.OFC, FPC	Orbital Frontal Cortex, Polar Frontal Cortex
10.early AC	early auditory Cortex	21.IFC	Inferior Frontal Cortex
11.AAC	Auditory Association Cortex	22.DLPFC	Dorsolateral Prefrontal Cortex

correlations) between all voxels the brain is separated into 180 areas per hemisphere, thus 360 areas relevant for analysis. This parcellation differs from most others in that it incorporates a neuroanatomical approach for areal delineation as well as an automated algorithmic approach. Further, most parcellations are based on one neurobiological property, e.g. architecture, function, connectivity or topography. HCP-MMP1 uses all four of those. Areas were first identified by an algorithm designed to detect region-to-region changes in those four properties in HCP fMRI data. The areas delineated by the algorithm were then interpreted by neuroanatomists consulting existing literature. In the third and last step of their approach, a machine learning classifier was trained to identify the 180 areas in new subjects. 96.6% of all areas turned out to be reproducible.

Regression

The regression analysis is performed in MATLAB R2016a. The data in its raw format would be very computationally intensive: Each subject is represented by a matrix $\mathbf{S}_{raw}$[parcel x parcel], with 360 parcels for the whole brain. We therefore perform principle component analysis before further processing. Sufficiently many PCA components were selected to explain approximately 70% of variance in the raw data so that for each subject:

$$\mathbf{S}_{PCA} = \mathbf{S}_{raw} V \quad (1)$$

Where $\mathbf{S}_{PCA}$ is a [P x K] matrix, with P (number of parcels) = 360 and K (number of components), and V is a [P x K] specifying the loading of each component. Each matrix $\mathbf{S}_{PCA}$ is then reshaped into a row vector and added to a Matrix $\mathbf{F}$[N x PK], where N (number of subjects) = 102 and PK (product of P and K).

Averaging over 20 repetitions, we use a 4-fold cross validation to model the score on each behavioural measure B_{train} [N_{train} x 1] as a combination of the functional connectivity matrix $\mathbf{F}_{train}$ [N_{train} x PK]

$$B_{train} = \mathbf{F}_{train} C \quad (2)$$

where N_{train} is the number of subjects in the training dataset per cross validation and C is a [PK x 1] vector of weights whose elements quantify the contribution of each region in the parcellation to the behavioural variable. In order to avoid overfitting, the solution to Equation 2 is computed using Ridge Regression with regularization parameter lambda = 1 x 10^4.

Performance is evaluated on the testing data B_{test} [N_{test} x 1] based on the obtained regression weights C. The predicted scores are modelled as:

$$\hat{B}_{test} = \mathbf{F}_{test} C \quad (3)$$

where N_{test} is the number of subjects in the testing dataset per cross validation. We quantify performance by computing the Pearson-correlation between $\hat{B}_{test}$ and B_{test}, where B_{test} represents the actual score of the subject on the respective behavioural measure.

To test for significance we employ 1000-fold permutation testing at lambda = 1 x 10^4. Here B_{train} and B_{test} are randomized before being fed through the Ridge Regression script.

Visualization

For the purpose of interpretation, C is projected into the original space becoming a [P x P] matrix. This matrix is multiplied with a binarized average connectivity matrix, where all positive connections are equal to 1 and all negative connections are equal to -1. Hereby we ensure that the directionality of the relation of each weight and the behavioural score is clear, as e.g. a negative weight on an inhibitory connection would otherwise be positively related to the modelled behavioural measure. To visualize the results C is further summarized into 22 broader regions per hemisphere as defined by Glasser and Coalson [8].We create two matrices **Pos** and **Neg** with dimensions [44 x 44], where **Pos** shows positive connections and **Neg** shows negative connections, by adding up the weights of all areas within one region. These matrices are thresholded to only keep the strongest 5% its respective connections and set the rest to 0.

RESULTS

Picture Sequence Memory Test (PSMT)

PSMT scores, reflecting their episodic memory, were predicted above chance level. Adjustment for age made no difference leading to a correlation of r = 0.21. (P < 0.001). The strongest connections predictive of PSMT measurements are all positive. **Pos** for this variable shows little hemispheric dominance. Most connections that remain after thresholding are interhemispheric connections between the Dorsolateral Prefrontal Cortex (DLPFC); Orbital Frontal Cortex, Polar Frontal Cortex (OFC, FPC); Anterior Cingulate Cortex , Medial Prefrontal Cortex (ACC, MPC) Posterior Cingulate Cortex (PCC); Inferior Parietal Cortex (IPC) and Superior Parietal Cortex (SPC). The right hemisphere further shows fairly strong intrahemispheric connectivity within the aforementioned six regions. The strongest weights overall are on connections between DLPFC and ACC, MPC as well as connections between DLPFC(RH, LH) . There is interhemispheric connectivity between left-hemisphere DLPFC, OFC, FPC, ACC, PCC, IPC and SPC, respectively, and regions around MT+, as well as the dorsal stream visual cortex of the right hemisphere. There is a single connection between SPC(LH) and IC, FOC(RH). Lastly the Premotor Cortex(RH) connections to DLPFC, ACC, MPC(LH) and DLPFC(RH) are still visible after thresholding.

Neg for this variable shows one strong hub in the lateral temporal cortex (LTC) of the right hemisphere. Its connections to various frontal areas of the left hemisphere as well as LTC and AAC of the left hemisphere have the strongest weights in this matrix. However, connections between LTC(RH) and almost all areas of the left hemisphere are visible (excluding V1 and early visual cortex). Within the right hemisphere, weights on the connections between IC, FOC and DSVC and PCC are notable. MTC also has widespread negatively weighted connections but these are weak compared to LTC.

Penn-Word-Memory-Test (IWRD)

We could not successfully predict correct responses or reaction time scores on the IWRD task, which was the second episodic memory task that we included (r_{total} = -0.1061, r_{RT} = -0.1451).

List-Sorting

Regression. The List-Sorting Test is supposed to reflect a subjects working memory capacity. We were able to predict scores that correlate positively with the observations obtained for this variable. Results differ only very slightly between adjusted and unadjusted scores ($r_{unadjusted}$ = 0.2145 and $r_{adjusted}$ = 0.2269). Both are significant as no permutations reach a correlation greater than or equal to that of the unpermuted data when averaged over four cross-validations and 20 repetitions (P < 0.001). *Visualization.* In general, positive connections have stronger weights than negative connections. **Pos** for this variable shows few weights on intrahemispheric connections. The strongest weighted interhemispheric connections are between the regions around MT+(LH) and the Dorsal Stream Visual Cortex (DSVC) of the right hemisphere, further between IC, FOC (RH) and left hemisphere frontal regions(DLFPC; OFC, FPC; IC, FOC) and parietal regions(IPC, SPC), as well as between the superior parietal cortices of both hemispheres.

Neg for this variable is strongly lateralized in the right hemisphere. Connections are widespread and involve all areas except for V1 and early VC. However, connections between MT+ and its surrounding areas and DLPFC; OFC, FPC and ACC, MPC are more pronounced. The same is true for connections between SPC and these three frontal regions (DLPFC; OFC, FPC; ACC, MPC).

DISCUSSION

In this study, we sought to predict behavioural memory scores with individual resting state connectomes. Specifically, we were interested in episodic and working memory. For episodic memory connections between bilateral DLPFC and ACC, MPC were most predictive. Instead for working memory connections between IC, FOC as well as other frontal and parietal regions were most predictive for memory differences between individuals.

Episodic Memory

The first thing that is noticeable when looking at our episodic memory data, is that the medial temporal lobe seems to have little predictive value in determining inter-individual differences. This is surprising, as the hippocampus and its surrounding areas are firmly established as a hub for memory formation and retrieval [1-4]. Our data suggest that even though this region is central to memory function, it does not determine differences in performance as strongly as other regions like the prefrontal cortex, which is visible in our positive network. The PFC itself has been strongly implicated in memory retrieval and encoding[4] and most connections with stronger weights in our analysis also involve subdivisions of this region. Considering the general implication of for example the DLPFC in working memory and cognitive control, this might hint at differences in performance on the PSMT being due to differences efficiency of organizing information.

Another important region according to our data is the lateral temporal lobe of the right hemisphere. Its widespread connectivity with the left hemisphere appears to be negatively related with memory performance. Note that MTC shows a similar pattern, albeit weaker. LTC is not often talked about as a central region to memory function, rather authors tend to discuss its function in concordance with MTC. Moscovitch and Nadel[10] point out that if lesions to the temporal lobe encompass both medial and lateral temporal lobe, retrograde amnesia becomes temporally ungraded and extends further back in time. This adds an interesting facet to our picture of episodic memory: It seems temporal lobe structures send out an array of connections that are not beneficial to memory performance.

Working Memory

The first thing to notice when looking at the positive working memory network is the relatively small role the DLPFC seems to play. While our results do show a fronto-parietal network [11], the DLPFC is not the most well-connected region and only shows one strongly weighted connection to the insular and frontal opercular cortex. This is puzzling, as the DLPFC is the most well established neural correlate of working memory . The insular and frontal opercular cortex of the right hemisphere stand out in our visualization's positive network. According to Sridharan, Levitin [12] the frontal insular cortex of the right hemisphere plays a central role in switching between default mode and central executive network. This work has been replicated by Goulden, Khusnulina [13]. Applying this line of thought to our results, a possible conclusion is that a strong determinant of inter-individual differences in working memory performance is a person's ability to suppress default mode network activity and more so to activate the central executive network, as the IC, FOC region has strong connections to the right DLPFC, IPC and SPC.

Surprisingly, sensory areas and connections between them are also implicated in our positive connectivity matrix. The general theory of working posits that it operates on existing LTM and perceptual representations by biasing accessibility [14]. Connections among sensory regions might point to an importance of these representations themselves rather than how the prefrontal cortex biases their accessibility.

The negative network is strongly lateralized in the right hemisphere, while the positive network consists primarily of interhemispheric connections. However, the negative network does show some overlap with the positive network. Interestingly, MT+ and surrounding areas are implicated again, with their connections to three frontal areas (DLPFC; OFC, FPC; ACC, MPC). The Superior Parietal Cortex' connections to the same set of areas is also negatively weighted.. It might be that

essentially the same regions' interconnections are responsible for improved as well as diminished performance levels and that specifics depend on a higher level of detail.

General conclusions and future research

When reading the previous sections it might seem like our results are quite contradictory to what is current consensus in neuroscience. It is crucial to consider that Ridge Regression typically selects very distributed models. Therefore, the weights that are not present after thresholding still play an important role in prediction. It is certainly interesting to observe atypical connections accounting for more variance than connections between common ROIs, but common ROIs are by no means irrelevant for our predictive model. Additionally, we sum our results onto a 22 region parcellation that obscures potentially important details of the original model.

Naturally, some additional steps need to be taken, before our results can be fully interpreted. First, appropriate permutation testing must be done on our current results and the presence of siblings must be controlled for. Assuming the results hold up, it is of interest if a more sparse analysis method like Elastic Net Regression produces a similar model to our thresholding. Alternatively, Connectome Based Predictive Modelling (CPM) [15] could be used to this end as well, as individual edges can be subjected to significance testing.

Further, it is customary for any regularized regression script to employ model selection for optimizing the parameter lambda. We were not able to do this because of a lack of time. Instead, we consulted an expert, who was able to discern a lambda value that produced positive results. This analysis should therefore be repeated with proper model selection.

Nonetheless, our study is evidence for a number of unexpected connections contributing to inter-individual differences in episodic and working memory performance and shows improvements compared to the HCP MegaTrawl (https://db.humanconnectome.org/megatrawl/index.html). Though we cannot clearly attribute this improvement to the parcellation or regression method because both differ between analyses.

ROLE OF THE STUDENT (MANDATORY)

Esra Freitag, an undergraduate Psychology student performed this project under supervision of Michelle Moerel (Maastricht Center for Systems Biology, Maastricht University). The topic was proposed by the supervisor. The analysis, interpretation of the results, and writing was performed by the student

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