

Software tool for brain structure - phenotype associations (D2.4.1 - SGA2)

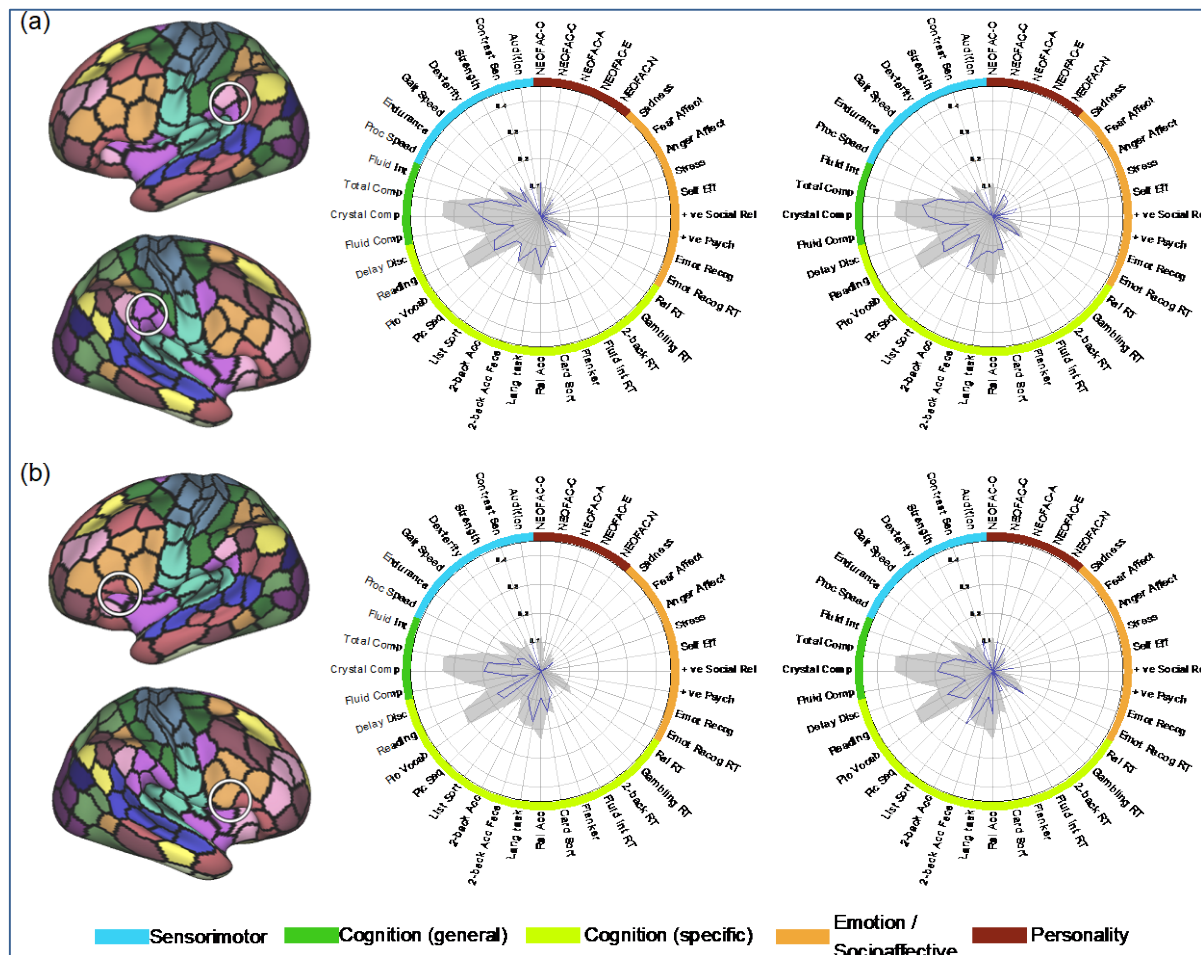


Figure 1: Parcel-wise connectivity-based psychometric prediction framework (CBPP).

Psychometric profiles for the pair of parcels in (a) Supramarginal gyrus (b) Broca region in left and right hemispheres respectively. Grey filled contour shows whole-brain prediction profile, while blue contour shows parcel-wise prediction profile (Components ID=C2312, C2313).

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Description in GA:	Software tool for brain structure - phenotype associations implemented (T2.4.2); software available for usage		
Abstract:	<p>Our research aimed to provide a tool to characterise the behavioural profile of brain regions by mapping interindividual variability in local structure (grey matter volume and cortical thickness) to interindividual variability in psychometric data. Our exploratory study aimed to search correlations between psychometric data and grey matter volume in prior-defined right dorsal premotor regions. Contrary to our expectations, the correlations were generally low and unstable across resampling (see P1770). In contrast, several studies discussed the relation between local brain structure and inter-individual variability in behavioural phenotype (for a review see Kanai, 2011). Because of the unexpected results from our first study, we performed a second study, investigating the replicability of associations between local grey matter volume and psychological variables in healthy adults. Again, our results showed very low replicability rates for significant associations between local grey matter volume and psychological variables when using region-of-interest approach (P1777; see Figure 4).</p> <p>To better understand the interindividual variability in psychometric data, we are now developing a connectivity-based psychometric prediction framework (CBPP).</p>		
Keywords:	Replicability, good scientific practices, ethics		
Target Users/Readers:	clinicians, computational neuroscience community, computer scientists, consortium members, funders, general public, neuroscientific community, neuroscientists, students		

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1. The replicability of brain structure - phenotype association: empirical facts

1.1 Introduction

The goal of our work was to better understand behavioural functions, such as memory, attention, cognitive control, emotions, ... , associated with different brain regions. One line of research in this project was to identify associations between grey matter in some brain regions and performance across a range of psychological tests, measuring different aspects of human behaviour, such as personality traits, memory performance, intelligence etc. This idea was based on a vast amount of previous studies showing that certain type of behaviour, cognitive performance or intelligence are related to grey matter volume in some parts of the brain. The previous studies hence suggested that differences between people in aspects of behaviour such as extraversion, political orientation, social abilities, memory skills or intelligence could be related to differences between people in grey matter volume in some parts of the brain. The results of these studies have usually conveyed the idea that “we are different because our brains are structurally different”. However, when we started searching for associations between grey matter volume measured with an MRI scanner and measures of behaviour (such as personality or IQ) in large samples of healthy people, we found only a few associations that could be considered as statistically significant. When we then tried to replicate the associations found in one sample of healthy people (for example between perceptual IQ and grey matter volume in some brain regions) in another similar sample of healthy people, the replication attempts mostly failed. By using different estimates of grey matter, many different behavioural measures and different samples of participants, we confirmed that there is a general issue of replication for reports of associations between grey matter in some parts of the brain and behaviour. Thus, overall, these unexpected findings suggest that the results of previous studies should be seriously questioned, and more generally, that the common idea of “we are different because our brains are structurally different” seriously lacks reliable scientific evidence.

1.2 Scientific motivation

Our research aimed to provide a tool to characterise the behavioural profile of brain regions by mapping interindividual variability in local structure as measured with grey matter volume and cortical thickness to interindividual variability in psychometric data. In a first exploratory study we searched for correlations between grey matter volume regions within the dorsal premotor cortex and psychometric data within a cohort of healthy adults. Strikingly, we found that correlations between grey matter volume and psychometric data were generally low, unstable across resampling and, when a significant correlation was evidenced, it could not be replicated in a new sample. For example, we found that for the same test (TMT-A) a correlation with grey matter volume of the rostral PMd was found in one sample ($r = .32$, $p < .01$) but not in the other sample ($r = -.2$) (Figure 2). Moreover, when we examined the percentage of actually (nominally) significant correlation coefficients across subsamples, it was observed that the rates were mostly below 5% in very small samples (i.e. $n = 15$) and almost only bigger subsamples (i.e. $n = 30$) outperformed the rate of 5% (Figure 3). These preliminary findings have been published in an international peer-reviewed Journal (P1170 - SGA1 publication) and led us to conduct a systematic and extensive evaluation of the replicability of associations between local grey matter volume and psychological variables in healthy adults. By using several indices of replication, our results revealed that significant associations between local grey matter volume and psychological variable (such as perceptual IQ illustrated below) found with an exploratory approach showed very low replicability rates in healthy cohorts when using region-of-interest approach (P1777; see Figure 4) These results were unexpected, given the vast literature discussing the brain structural basis of interindividual variability in behavioural phenotype (for a review see Kanai, 2011) and rose serious concerns on the scientific validity of this literature.

	Rostral_PMd	Caudal_PMd	Central_PMd	Ventral_PMd	Dorsal_PMd
FZJ					
Finger Tapping (Right)	0.05	-0.08	0.05	0.08	0.01
Finger Tapping (Left)	0.03	-0.01	0.02	0.12	0.06
Finger Tapping (Median)	0.05	-0.07	0.08	0.14	0.01
Hand-Arm Movements (Right)	0.05	-0.26	0.05	0.12	0.08
Hand-Arm Movements (Left)	0.00	-0.23	-0.12	0.24	-0.05
Hand-Arm Movements (Median)	0.13	-0.23	0.04	0.24	0.03
TMT-A	-0.20	-0.11	-0.05	-0.03	-0.03
TMT-B	-0.09	-0.12	-0.05	-0.12	0.08
Digit-Symbol Test	0.01	-0.10	-0.06	0.12	0.06
Digit Span Score (Forwards)	-0.07	-0.19	-0.16	0.00	-0.08
Digit Span Score (Backwards)	-0.02	-0.07	0.05	-0.01	0.04
Digit Span (Forwards)	-0.01	-0.18	-0.13	-0.07	-0.13
Digit Span (Backwards)	0.23	-0.22	0.13	0.13	0.01
Benton Test (Correct Items)	0.12	0.22	0.04	0.15	0.22
Benton Test (Errors)	0.21	0.03	0.09	0.13	0.02
Stroop Task (Reading)	-0.17	0.01	-0.03	-0.02	-0.02
Stroop Task (Naming)	-0.05	0.12	0.11	0.14	-0.11
Stroop Task (Color-Word Interference)	0.12	0.10	0.20	0.07	-0.02
Block Tapping (Forwards)	0.11	-0.09	0.17	0.10	-0.03
NKI					
ANT (Alert)	0.04	0.05	0.01	0.18	0.13
ANT (Orienting)	-0.02	0.16	0.00	-0.09	-0.11
ANT (Conflict)	-0.08	-0.04	-0.17	-0.14	0.07
TMT-A	0.32	-0.07	0.12	0.19	-0.05
TMT-B	-0.06	-0.23	-0.20	-0.08	-0.17
Card Sorting (Free Sorting)	0.16	0.00	0.06	0.05	-0.22
Card Sorting (Sort Recognition)	0.12	-0.05	0.10	0.03	-0.23
Verbal Fluency (Letter)	0.06	-0.08	-0.09	-0.08	-0.11
Verbal Fluency (Category)	0.04	0.07	-0.06	-0.03	-0.08
Verbal Fluency (Category Switching)	0.01	-0.02	-0.02	-0.03	-0.19
Design Fluency (Filled Dots)	0.10	-0.02	0.00	-0.01	-0.06
Design Fluency (Empty Dots)	-0.03	-0.07	-0.13	-0.16	-0.09
Design Fluency (Switching)	-0.07	-0.04	0.03	-0.15	-0.03
CWI (Color-Naming)	0.17	-0.15	-0.03	-0.04	-0.09
CWI (Word-Reading)	0.18	0.18	0.12	0.22	-0.10
CWI (Inhibition/Switching)	0.06	-0.09	-0.04	-0.08	0.02
20 Questions	-0.03	-0.05	-0.02	0.09	-0.11
Word Context	-0.08	-0.17	-0.12	-0.07	-0.24
Tower of London	0.01	-0.20	-0.14	-0.12	-0.01
Proverbs (Free Inquiry)	0.04	-0.11	0.00	0.05	-0.28
Proverbs (Multiple Choice)	0.02	0.04	-0.02	0.03	-0.22

Figure 2: Assessing correlations between grey matter volume and psychometric data.

Partial correlations between right dorsal premotor (PMd) cortex grey matter volume of interest (VOI-GM) and behavioural performance in the FZJ and NKI cohorts; colour coding: blue = negative, red = positive; significant correlation coefficients ($p \leq .05$, uncorrected for multiple testing) are highlighted with a bold font and square frame; TMT: Trail-Making Test, CWI: Colour Word Interference, ANT: Attention Network Test.

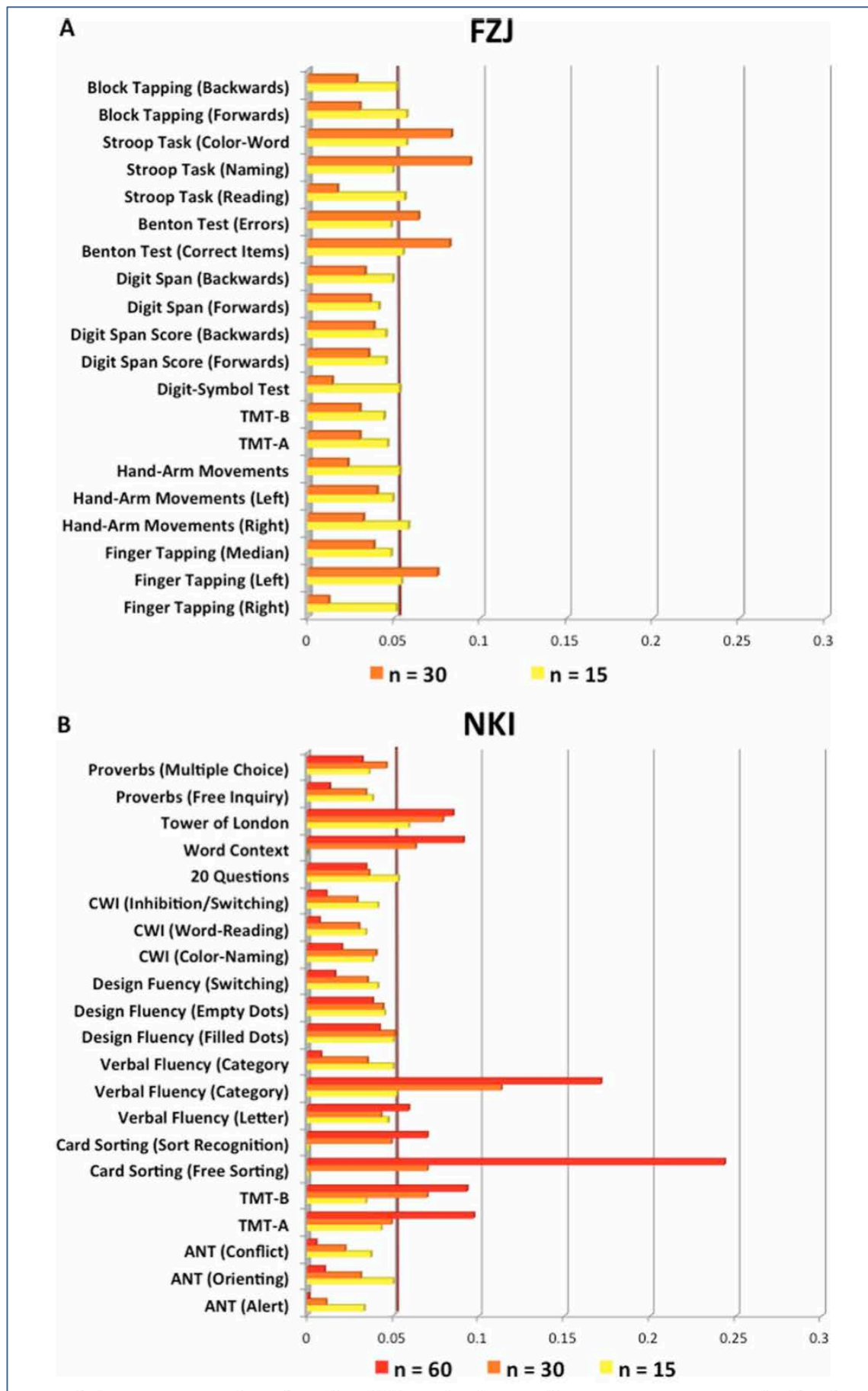


Figure 3: Examination of percentages of significant correlation coefficients across subsamples.

Percentage of significant correlations across 1000 random subsampling of different sizes ($n = 15$, yellow; $n = 30$, orange; $n = 60$, red) with replacements in FZJ cohort (A) and in NKI cohort (B).

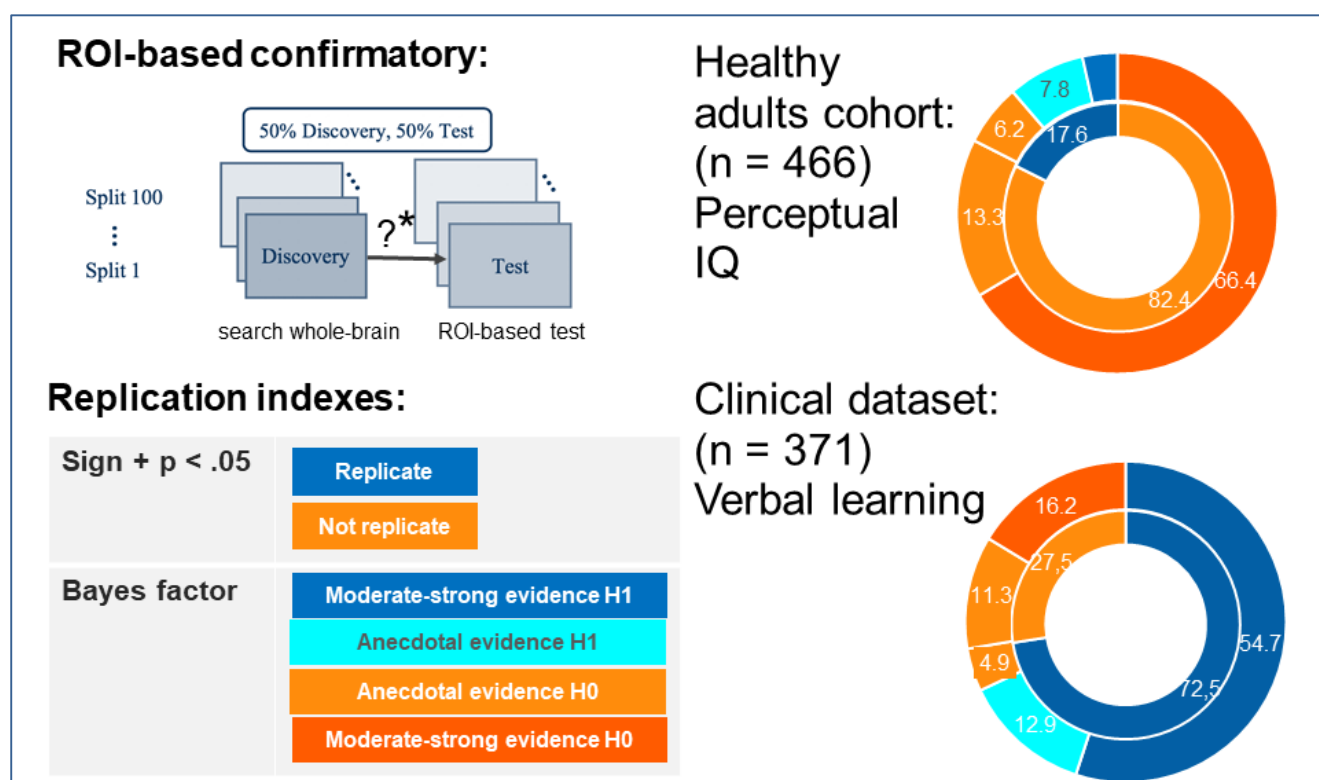


Figure 4: Associations replicability between grey matter volume and psychometric data.

Summary of the main methods and findings of Kharabian *et al.* (2019, P1777) in which the replicability of associations between local grey matter volume and psychometric data was systematically evaluated. The upper left panel illustrates the replicability procedure by splitting the datasets into discovery and test samples. The bottom left panel summarises the indices used to quantify replication success. The top and bottom right panels depicts the results obtained in a large cohort of healthy adults and in a cohort of patients with dementia, respectively. The inner ring and the outer ring of the donut plots shows the replication rates based on Bayes factor and based on significance indices, respectively.

Our results were published (P1777) and received a lot of interest and comments from the scientific community. One argument that was brought in the following scientific discussion with our peers was the limitations of grey matter volume as an MRI measure of brain grey matter structure. To address this point, we recently performed an evaluation of the replicability of the associations between local variation in cortical thickness and psychometric data. Our recent results revealed similar alarming low rates of replicability for associations between cortical thickness and psychological variables, found using an exploratory approach. These results have been submitted for publication. In conclusion, for our second line of research, the results of the three studies that we perform go in the same direction, seriously questioning the replicability and hence, the scientific validity of associations between local brain structure and psychometric data in the healthy adults' population. The reports of such associations are often disseminated outside the scientific community, they influence the public mind about the structural basis of individual behaviour, and contribute to inaccurate beliefs and stereotypes. Therefore, we aimed to increase awareness about the replicability issues of these associations and promote good scientific practices in the field. Additionally, to deconstruct the potentially harmful common beliefs fed by unreplicable studies of the bases of interindividual variability in behaviour, we have now developed a new line of research investigating the replicability of heritability of interindividual variability in brain and behaviour.

Since it was not possible to replicate brain structure - phenotype associations, we wanted to investigate brain function - phenotype associations. To better understand the relationships between interindividual variability in brain regions' connectivity and behavioural phenotypes, we are now developing a connectivity-based psychometric prediction framework (CBPP). Preliminary to the development of this region-wise machine learning approach, we performed an extensive assessment of the general connectivity-based psychometric prediction (CBPP) framework based on whole-brain connectivity information. Because a systematic evaluation of different parameters was lacking from previous literature, we evaluated several approaches pertaining to the different steps of a CBPP study. We hence tested 72 different approach combinations (3 types of preprocessing x 4 parcellation

granularity x 2 connectivity methods x 3 regression methods = 72 combinations) in a cohort of over 900 healthy adults across 98 psychometric variables (Figure 5, Table 1). Overall, our extensive evaluation combined to an innovative region-wise machine learning approach offer a framework that optimises both, prediction performance and neurobiological validity (and hence interpretability) for studying brain-behaviour relationships. We uploaded this tool to the Software Catalogue of the HBP Collab: <https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=software,CBPP> (Figure 1)

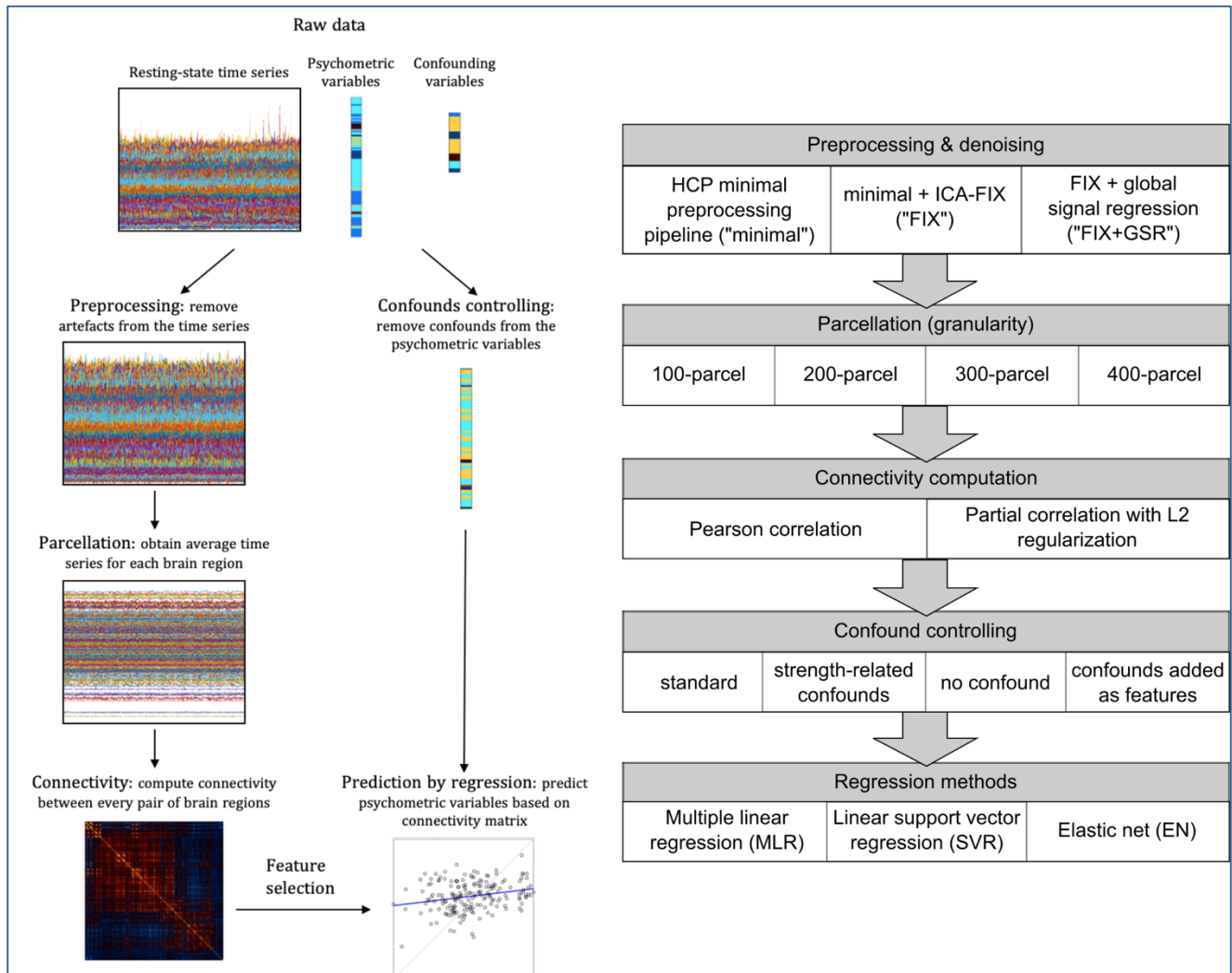


Figure 5: The connectivity-based psychometric prediction (CBPP) framework.

Left: general workflow of a connectivity-based psychometric prediction (CBPP) framework. Right: Approaches considered for each step in the CBPP framework.

Table 1: The 98 selected psychometric variables.

Domain	Subdomain/ Task	Psychometric Variable (HCP Column Header)	
Cognition	Episodic Memory	PicSeq_Unadj	PicSeq_AgeAdj
	Executive Function / Cognitive Flexibility	CardSort_Unadj	CardSort_AgeAdj
	Executive Function / Inhibition	Flanker_Unadj	Flanker_AgeAdj
	Fluid Intelligence	PMAT25_A_CR	PMAT24_A_RTCT
	Language / Reading Decoding	ReadEng_Unadj	ReadEng_AgeAdj

	Language / Vocabulary Comprehension	PicVocab_Unadj	PicVocab_AgeAdj
	Processing Speed	ProcSpeed_Unadj	ProcSpeed_AgeAdj
	Self-regulation / Impulsivity	DDisc_AUC_200	DDisc_AUC_40k
	Spatial Orientation	VSLOT_CRTE	
	Sustained Attention	SCPT_TRRT	SCPT_SEN
		SCPT_SPEC	SCPT_LRN
	Verbal Episodic Memory	IWRD_TOT	IWRD_RTC
	Working Memory	ListSort_Unadj	ListSort_AgeAdj
	Cognition Composite Scores	CogFluidComp_Unadj	CogFluidComp_AgeAdj
		CogTotalComp_Unadj	CogTotalComp_AgeAdj
		CogCrystalComp_Unadj	CogCrystalComp_AgeAdj
Emotion	Emotion Recognition	ER40_CR	ER40_CRT
		ER40ANG	ER40FEAR
		ER40NOE	ER40SAD
	Negative Affect	AngAffect_Unadj	AngHostil_Unadj
		AngAggr_Unadj	Sadness_Unadj
		FearAffect_Unadj	FearSomat_Unadj
	Psychological Well-being	LifeSatisf_Unadj	MeanPurp_Unadj
		PosAffect_Unadj	
	Social Relationships	Friendship_Unadj	Loneliness_Unadj
		PercHostil_Unadj	PercReject_Unadj
		EmotSupp_Unadj	InstruSupp_Unadj
	Stress and Self-efficacy	PercStress_Unadj	SelfEff_Unadj
Motor	Endurance	Endurance_Unadj	Endurance_AgeAdj
	Locomotion	GaitSpeed_Comp	
	Dexterity	Dexterity_Unadj	Dexterity_AgeAdj
	Strength	Strength_Unadj	Strength_AgeAdj
Personality	Five Factor Model (NEO-FFI)	NEOFAC_A	NEOFAC_O
		NEOFAC_C	NEOFAC_N
		NEOFAC_E	
Sensory	Audition	Noise_Comp	
	Olfaction	Odor_Unadj	Odor_AgeAdj
	Taste	Taste_Unadj	Taste_AgeAdj
	Contrast Sensitivity	Mars_Log_Score	Mars_Final
In-scanner Task	Gambling	Gambling_Task_Median_RT_Larger	Gambling_Task_Median_RT_Smaller
		Gambling_Task_Reward_Median_RT_Larger	Gambling_Task_Reward_Median_RT_Smaller
		Gambling_Task_Punish_Median_RT_Larger	Gambling_Task_Punish_Median_RT_Smaller
	Language	Language_Task_Acc	Language_Task_Story_Acc
		Language_Task_Math_Acc	Relational_Task_Median_RT_Median_RT

	Relational Processing	Relational_Task_Acc	Relational_Task_Median_RT
		Relational_Task_Match_Acc	Relational_Task_Match_Median_RT
		Relational_Task_Rel_Acc	Relational_Task_Rel_Median_RT
	Working Memory	WM_Task_2bk_Acc	WM_Task_2bk_Median_RT
		WM_Task_2bk_Body_Acc	WM_Task_2bk_Face_Acc
		WM_Task_2bk_Place_Acc	WM_Task_2bk_Tool_Acc
		WM_Task_2bk_Body_Median_RT	WM_Task_2bk_Face_Median_RT
		WM_Task_2bk_Place_Median_RT	WM_Task_2bk_Tool_Median_RT

1.3 Data types, methods and tools

To perform the above-mentioned analyses, we used T1-weighted MRIs collected from a large cohort of individuals. The T1-weighted scan of each individual was then pre-processed using common neuroimaging packages (CAT: for grey matter associations; FreeSurfer: for cortical thickness associations). The pre-processed images were then registered to a common template and smoothed to increase cross-subject correspondence.

To assess the replicability of the behavioural associations with either of the brain phenotypic measures, we performed exploratory analyses within randomly-chosen subgroups of individuals from the main cohort. The exploratory analyses assessed associations between each behavioural score and brain morphology within each voxel/vertex. Significance of the found associations within each subgroup were then assessed using non-parametric methods with a family-wise error corrected p-value below 0.05.

Spatial overlap of the found significant associations was then assessed across multiple rounds of randomly-drawn subgroups of individuals.

The replicability of the found exploratory association within each subgroup was then assessed in a demographically matched subsample of the remaining participants from the main cohort, using a confirmatory pipeline. In the confirmation pipeline, mean brain morphometry (grey matter volume / cortical thickness) is defined within significant clusters of exploratory analyses and the associations between behavioural measure and brain morphometry are defined within the matching subsample.

1.4 Impact and exploitation for the scientific community

Across this project, we encountered unexpected issues regarding the replicability of associations between MRI-based estimates of local structure and psychological variables in healthy adults. Across three independent studies, we ruled out the influence of several potential biases and developed a framework to evaluate the replicability of associations between behavioural phenotype and local brain structure. This framework can now be used by the scientific community to systematically evaluate the replicability of associations in many different populations and context such as children, aging people and clinical studies (<https://github.com/inm7/cbpp/>).

1.5 Publications:

- Kharabian Masouleh, S., Eickhoff, S., Hoffstaedter, F., & Genon, S. (2019). Empirical examination of the replicability of associations between brain structure and psychological variables. *eLife*, 13(8) (P1777).

- Genon, S., Wensing, T., Reid, A., Hoffstaedter, F., Caspers, S., Grefkes, C., Nickl-Jockschat, T., & Eickhoff, S. B. (2017 – SGA1 publication). Searching for behavior relating to grey matter volume in a-priori defined right dorsal premotor regions: lessons learned. *NeuroImage*, 157, 144-156 (P1170).

1.6 Disseminations:

1.6.1 *Talks at international conferences*

- Kharabian Masouleh S. (10 Oct 2019). Factors influencing replicability of associations between psychological variables and brain structure. 6th Iranian Human Brain Mapping Program (IHBM 2019), Tehran, Iran (E1467).
- Genon, S. (10 Oct 2019). Linking brain to behavior with bottom-up approaches: opportunities and challenges. 6th Iranian Human Brain Mapping Program (IHBM 2019), Tehran, Iran (E1456).
- Genon, S. (23 May 2019). Linking brain to behavior with bottom-up approaches: opportunities and challenges. AISC midterm conference 2019, Lucca, Italy (E1458).
- Kharabian Masouleh S. (20 Sep 2018). Empirical evaluation of replicability of associations between psychological variables and brain structure. 5th Iranian Human Brain Mapping Program (IHBM 2018), Tehran, Iran (E1468).

1.6.2 *Talks at universities and research centres*

- | | |
|-------------|---|
| 13 Apr 2018 | Genon, S. Decoding human brain organization and function with multi-modal parcellation and behavioral profiling. Institut du Cerveau et de la Moelle Epinière, Paris, France (Y1E0438). |
| 17 Mai 2018 | Genon, S. A shift for cognitive neuroscience: from model-based data to data-driven models. Invited participant at the research seminar of cognitive neurosciences. Eberhard Karls Universität, Tübingen, Germany (Y1E0440). |
| 16 Aug 2018 | Genon, S. Decoding cognitive information processing with multi-modal parcellation and behavioral profiling. Psychiatric And Developmental Imaging Laboratory, University of Pennsylvania, Philadelphia, United States of America (Y1E0441). |
| 23 Aug 2018 | Genon, S. Decoding cognitive information processing with multi-modal parcellation and behavioral profiling. Department of Radiology & Biomedical Imaging, Yale University, New Haven, United States of America (Y1E0442). |
| 27 Aug 2018 | Genon, S. Decoding cognitive information processing with multi-modal parcellation and behavioral profiling. Laboratory For the Study of the Brain Basis of Individual Differences, Athinoula A. Martinos Center for Biomedical Imaging, Boston, United States of America (Y1E0443). |

1.6.3 *Public Dissemination*

Schnack H. (2019). Brain and Behavior: Assessing reproducibility in. association studies, *Elife*.8.