From the Institute for Systems Neuroscience
At the Heinrich-Heine-University Düsseldorf

Multivariate Associations Relating Brain Structure to Behavior and Physical Health

Dissertation

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I Zusammenfassung

Das Verständnis des Zusammenhangs zwischen der Hirnstruktur sowie dem Verhalten und der körperlichen Gesundheit ist entscheidend für den Fortschritt im Gesundheitswesen. In den letzten Jahren wurden jedoch zunehmend Bedenken hinsichtlich der Reproduzierbarkeit veröffentlichter Studien zu diesem Thema geäußert. Dies erfordert eine systematische Untersuchung der Reproduzierbarkeit von Befunden in der strukturellen Neurobildgebung. Dementsprechend sollten Methoden gefördert werden, die die Reproduzierbarkeit und Generalisierbarkeit von Ergebnissen verbessern, wie zum Beispiel, die Anwendung von maschinellem Lernen (ML), größere Stichproben und multivariate Verfahren. Dies würde die Identifikation robuster Zusammenhänge zwischen Hirnstruktur sowie Verhalten und körperlicher Gesundheit ermöglichen, die anschließend als potenzielle Biomarker in der Medizin weiter untersucht werden könnten. Diese Arbeit untersuchte die Reproduzierbarkeit von Zusammenhängen zwischen Hirnstruktur und Verhalten. Darüber hinaus wurden in dieser Arbeit robuste Methoden eingesetzt, um replizierbaren und generalisierbaren Zusammenhängen zwischen Hirnstruktur sowie Verhalten und körperlicher Gesundheit zu identifizieren. Als Ausgangspunkt bewertete Studie 1 die Replizierbarkeit von Zusammenhängen zwischen Hirnstruktur und Verhalten, wenn diese mit Standardmethoden von univariate bzw. bivariate Assoziationen untersucht werden. Die Studie zeigte, dass signifikante univariate bzw. bivariate Assoziationen zwischen kortikaler Dicke und Verhalten höchst unwahrscheinlich sind und dass selbst wenn signifikante Zusammenhänge gefunden wurden, diese in der Regel nicht replizierbar waren. Als Nächstes wurden in Studie 2 ML und ein multivariater Ansatz (regulierte kanonische Korrelationsanalyse, RKKA) angewendet, um reproduzierbare und generalisierbare Zusammenhänge zwischen Hirnstruktur (kortikale Dicke, Oberfläche und Volumen der grauen Substanz) und einer Vielzahl verhaltensbezogene Merkmale (Wachsamkeit, Emotion und Kognition) zu untersuchen. Diese Studie identifizierte eine latente Dimension, die Hirnstruktur und Verhalten miteinander verknüpft. Besonders wichtig ist, dass die Ergebnisse in einer unabhängigen Stichprobe reproduziert werden konnten. Außerdem teilten diese hirnstrukturellen und verhaltensbezogenen Muster gemeinsame genetische Mechanismen. In ähnlicher Weise wurden in Studie 3 ML und RKKA eingesetzt, um reproduzierbare und generalisierbare Zusammenhänge zwischen Hirnstruktur (kortikale Dicke und Volumen der grauen Substanz) und einer Vielzahl von Risikofaktoren für

nichtübertragbare Erkrankungen (u. a. Körpermorphologie und -zusammensetzung, Blutdruck, Ernährung) aufzudecken. Diese Studie fand zwei latente Dimensionen, die verschiedene Muster der Hirnstruktur mit einer Achse der kardiometabolischen Gesundheit und einer Achse der körperlichen Robustheit verbinden. Insgesamt heben diese Befunde die geringe Reproduzierbarkeit von univariate Gehirn-Verhalten Assoziationen hervor. Im Gegensatz zeigen die Ergebnisse, dass der Einsatz von ML, großen Stichproben und multivariaten Methoden diese Einschränkungen mindert und die Identifizierung reproduzierbarer und generalisierbarer Zusammenhänge zwischen Hirnstruktur sowie Verhalten und körperlicher Gesundheit ermöglicht.

II Summary

Understanding the link between brain structure and both, behavior and physical health, is imperative to advance healthcare. However, in the last years, concerns have been raised regarding the replicability of published studies on that topic. This calls for systematic evaluations of the replicability of findings in structural neuroimaging. Accordingly, methods that improve the replicability and generalizability of findings should be promoted, like machine learning (ML), big sample sizes, and multivariate methods. This would enable the identification of robust associations between brain structure and both, behavior and physical health, that could be further examined as potential biomarkers in medicine. The present work studied the replicability of associations between brain structure and behavior. In addition, this work used robust methods to search for replicable and generalizable associations linking brain structure with both, behavior and physical health. As a starting point, in Study 1 we evaluated the replicability of associations between brain structure and behavior when searched with standard methods in the field. The findings showed that significant univariate/bivariate associations between cortical thickness and behavior were highly unlikely, and that even when significant associations were found they were usually not replicable. Next, in Study 2 we used ML and a multivariate approach (regularized canonical correlation analysis, RCCA) to uncover replicable and generalizable associations between brain structure (cortical thickness, surface area and grey matter volume) and a wide set of behavioral features (alertness, emotion, and cognition). This study found a latent dimension linking brain structure and behavior which, importantly, was replicated in an independent sample. Also, the reported brain structural and behavioral patterns shared genetic mechanisms. Similarly, in Study 3 we used ML and RCCA to uncover replicable and generalizable associations between brain structure (cortical thickness and grey matter volume) and a wide set of risk factors for non-communicable diseases (spanning body morphology and composition, blood pressure, diet, among others). This study found two latent dimensions linking different patterns of brain structure to an axis of cardiometabolic health and to an axis of physical robustness. Overall, these findings highlight the low replicability of brain-behavior associations when analyzed with univariate methods. These results show that the use of ML, big samples sizes and multivariate methods mitigate these limitations, enabling the identification of replicable and generalizable associations between brain structure and both, behavior and physical health.

III List of abbreviations

BMI	Body mass index
CCA	Canonical correlation analysis
CT	Cortical thickness
GMV	Grey matter volume
ML	Machine learning
MRI	Magnetic resonance imaging
PLS	Partial least squares
RCCA	Regularized canonical correlation analysis
sMRI	Structural magnetic resonance imaging
SA	Surface area

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1 Introduction

1.1 The importance of studying brain health

The human brain is affected in numerous illnesses and disorders. This includes neuropsychiatric disorders such as depression and Alzheimer's disease (Mateos-Pérez et al., 2018; McCutcheon et al., 2023), and also physical (somatic) illnesses such as hypertensive diseases and diabetes (Tian et al., 2023). Despite the recognized link between health and the brain, much of the specific associations between the brain and neuropsychiatric and physical illnesses remains unknown. This lack of understanding hinders the development of treatment and preventive strategies, contributing to the huge burden of those disorders and illnesses for the patient and society (Williams and Whitfield Gabrieli, 2025).

The field of systems neuroscience focuses on the examination of brain functional and structural organization in both, health and disease (Rizzolatti et al., 2018; Williams and Whitfield Gabrieli, 2025). A better understanding of brain organization would enable the improvement of preventive strategies and early treatment of several illnesses and disorders, for instance by allowing the detection of subjects at risk even before the symptoms are evident (Gabrieli et al., 2015; Kong et al., 2023; Williams and Whitfield Gabrieli, 2025). In the same line, a better understanding of the brain would contribute to uncover the biological bases underlying the heterogeneity in illnesses and disorders, and hence to potentiate diagnostic strategies (Gabrieli et al., 2015, 2015; Kong et al., 2023; Mateos-Pérez et al., 2018). Likewise, advances in systems neuroscience are crucial for progressing towards personalized medicine (Williams and Whitfield Gabrieli, 2025). Altogether, this highlights the urgency of systems neuroscience research focusing on the health of the brain.

One way to examine brain health is by the use of images of the brain, which is the focus of neuroimaging (Gabrieli et al., 2015; Kong et al., 2023; Laumann et al., 2023; Williams and Whitfield Gabrieli, 2025). This field uses powerful techniques to capture brain images, such as Magnetic Resonance Imaging (MRI), Magnetoencephalography, or Positron Emission Tomography. Among those, MRI has many advantages for healthcare, including non-invasiveness and relatively good spatial resolution (Jenkinson and Chappell, 2018a). By the use of different sequencing protocols, MRI allows to capture

different properties of the brain tissue, including anatomical structures (with structural MRI), microstructure and anatomical connectivity (with diffusion MRI) and brain activity (with functional MRI) (Huettel et al., 2014; Jenkinson and Chappell, 2018a, 2018b). This underscores the power and versatility of MRI as a technique to study the brain in health and disease.

Specifically, structural MRI (sMRI), obtained with T1-weighted sequences, allows to measure the shape and size of anatomical structures of the brain (Jenkinson and Chappell, 2018b; Symms, 2004). sMRI is currently used in the clinical practice for some specific cases (Symms, 2004). For instance, under certain conditions it is used as an aid for diagnoses and prognosis of multiple sclerosis, epilepsy, or stroke (Symms, 2004). However, it is important to note that the use of MRI in medical healthcare is rather scarce and its potential for its implementation in the medical practice is not fully developed (Laumann et al., 2023). In that regard, sMRI is commonly used in neuroimaging and systems neuroscience research for the examination of the brain in health and disease, which could potentiate its development in healthcare (Genon et al., 2022; Kong et al., 2023; Mateos-Pérez et al., 2018; McCutcheon et al., 2023).

1.2 Measuring brain structure with T1-weighted MRI

Three widely used brain structural measures that can be estimated using sMRI are grey matter volume (GMV), cortical thickness (CT) and surface area (SA) (Genon et al., 2022; Jenkinson and Chappell, 2018c; McCutcheon et al., 2023). GMV reflects the composition of the brain tissue with regards to the local amount of grey matter (Gaser et al., 2024; Jenkinson and Chappell, 2018c). The measurement of CT is based on surface representations of the boundaries between the grey matter and the white matter (white surface) and between the grey matter and the pia mater (pial surface) (Fischl and Dale, 2000; Jenkinson and Chappell, 2018c). CT is computed as the distance between these two boundaries across multiple points (vertices) of the surface, hence reflecting the thickness of the cortex (Fischl and Dale, 2000). Surface area is also a surface-based measurement, and reflects the area of the local triangles on the surface mesh interpolated to the corresponding vertices (Winkler et al., 2012).

The value of GMV, CT and SA in systems neuroscience is reflected in multiple studies having reported associations between those brain structural measures and neuropsychiatric disorders, such as Parkinson's disease, Alzheimer's disease, mild

cognitive impairment, autism (Mateos-Pérez et al., 2018) and mood-related disorders (Du et al., 2014; McCutcheon et al., 2023). These brain structural markers have also been associated with physical health variables, such as body mass index (BMI) (Caunca et al., 2019; Gurholt et al., 2021; Kim et al., 2015; Medic et al., 2016; Opel et al., 2021; Ronan et al., 2016; Tüngler et al., 2021), hypertension and diabetes (Kim et al., 2019). Multiple additional features of interest in medicine have been associated with GMV, CT and SA, however, as elaborated in the next sections, there are several limitations preventing the implementation of these findings in medical healthcare.

It is worth noting that some authors have argued against the use of GMV in combination with SA, since GMV of a brain region appears to be recovered by SA of the corresponding region (Winkler et al., 2010). However, it is important to note that other studies have promoted the inclusion of the three structural measures in research (Abé et al., 2016; Mills et al., 2014). For instance, some studies showed different findings for SA and GMV (Abé et al., 2016; Hämäläinen et al., 2018; Lemaitre et al., 2012), and some studies even reported opposite effects between GMV and SA (Storsve et al., 2014; Tamnes et al., 2017). So, even though GMV and SA share variability, it seems that the three brain structural measures (GMV, SA and CT) carry specific information and can provide valuable and complementary insights into the brain.

1.3 Challenges in understanding how brain structure relates to behavior and physical health

It is well established in the scientific literature that brain structure is associated with behavior (Gabrieli et al., 2015; Genon et al., 2022; Kanai and Rees, 2011). A myriad of behavioral features have been associated with GMV, CT or SA, including working memory, emotions, political orientation (Genon et al., 2022), perception, attention, intelligence, personality, social cognition and metacognitive abilities (Kanai and Rees, 2011). Similarly, it is well accepted that GMV, CT and SA are related to risk factors that affect physical health, such as BMI (Caunca et al., 2019; Gurholt et al., 2021; Kim et al., 2015; Medic et al., 2016; Opel et al., 2021; Ronan et al., 2016; Tüngler et al., 2021), cigarette smoking (Chen et al., 2006; Gurholt et al., 2021; Kharabian-Masouleh et al., 2018) or physical exercise (Vakhrusheva et al., 2016). However, there are several complex factors preventing a clear understanding of these associations, which are explained in the next sections.

1.3.1 Replicability crisis

One of the most striking challenges for understanding how brain structure relates to behavior and physical health pertains to replicability (Laumann et al., 2023; Monsour et al., 2022; Williams and Whitfield Gabrieli, 2025). Replicability refers to obtaining the same findings than a previous study when using different datasets (Nosek et al., 2022). Recently, concerns have been raised on this regard, with studies claiming that the replication of structural brain-behavior associations is low (Genon et al., 2022; Kharabian Masouleh et al., 2019; Marek et al., 2022). These low replicability rates could not be accounted for methodological differences between the studies (such as different preprocessing pipelines, differences between the studied samples, etc.), since robust replication studies with identical methodological procedures also confirmed these worrying findings (Genon et al., 2022; Kharabian Masouleh et al., 2019). Specifically, it has been reported that significant associations between GMV and a range of psychological variables in healthy samples are not frequent when searched with an exploratory univariate/bivariate approach (Kharabian Masouleh et al., 2019). Moreover, it was reported that when significant univariate/bivariate associations between GMV and psychological variables were found in an exploratory study, they could hardly be replicated (Kharabian Masouleh et al., 2019). These studies raised an alarm in the field, since they indicated that an important portion of the published studies in the scientific literature linking neuroimaging brain features to behavior might not be replicable (Genon et al., 2022).

The same worrying trend could be present in studies linking brain structure with physical health. In this line, some studies have reported inconsistent results on the association of brain structure and physical health variables, such as BMI (Caunca et al., 2019; Gurholt et al., 2021; Kim et al., 2015; Medic et al., 2016; Opel et al., 2021; Ronan et al., 2016; Tüngler et al., 2021) and physical activity (Hvid et al., 2021).

One criticism that some replication studies received is that the use of grey matter volume (GMV) could account for the low replicabilities found (Genon et al., 2022; Kharabian Masouleh et al., 2019). In this sense, it has been argued that since GMV is a crude estimate of brain structure, the associated noise could have driven the low replicability of findings, and that the examination of less noisy structural features, such as cortical thickness (CT) could have a positive effect on the replicabilities (Genon et al., 2022). Hence, to confirm this worrying trend, studies that systematically examine the

replicability of brain-behavior associations are needed, specially focusing on less noisy estimates of brain structure, such as CT.

1.3.2 One-to-one mapping: linking a single brain region with a single feature

One of the shortcomings of typical studies linking brain structure to other features is the underlying one-to-one assumption. In other words, studies typically use univariate/bivariate approaches which allow to link one structural measure of a single brain region with a single feature (Genon et al., 2022). However, a growing body of evidence underscores the assumption of a many-to-many mapping instead (Genon et al., 2022; Kanai and Rees, 2011). Still, given the abundance of studies using univariate/bivariate approaches, this many-to-many picture is not well understood (Genon et al., 2022; Kanai and Rees, 2011). More studies should implement multivariate approaches to link several measurements of several brain regions with many features of interest. This would shed light into brain distributed patterns (for instance expanding through the whole cortex) associated with dimensional variables linking multiple behavioral features or risk factors.

Multivariate studies offer the possibility to gain that many-to-many insight on the associations between the brain and other features such as behavior and risk factors (Genon et al., 2022; Kharabian Masouleh et al., 2019; Mahdipour et al., 2026). With regards to the replicability crisis in neuroimaging, the low replicability of one-to-one associations between brain structure and behavior could be due the limitation of univariate/bivariate approaches to capture spatially diffuse patterns on the brain (Genon et al., 2022; Kharabian Masouleh et al., 2019; Marek et al., 2022). Since the brain works as an integrated organ coordinating multiple different regions over diverse timescales, multivariate approaches could capture more reliable associations between brain and behavior (Genon et al., 2022; Marek et al., 2022).

1.3.3 Sources of variation: heritability and genetic correlations

Another important point for understanding how the brain relates to behavior and physical health is to analyze the causes driving the shared variability. This is a complex topic to address, and a first step that can be taken in that direction is the estimation of the heritability and genetic correlation of those associations (Baselmans et al., 2021; Grasby et al., 2020; Han and Adolphs, 2020; Kraljević et al., 2021; Valk et al., 2020). Heritability refers to analyzing the proportion of the observed variability that can be attributed to

genetics (Glahn et al., 2014, 2007; Tenesa and Haley, 2013; Visscher et al., 2008). One way to analyze it is by the twin design, which consists on comparing the phenotypes of monozygotic twins and dizygotic twins (Han and Adolphs, 2020; Tenesa and Haley, 2013). The genetic correlation refers to an estimation of the amount of genetic influences shared by two phenotypes (Valk et al., 2020). The importance of analyzing heritability and genetic correlations underlying the association between brain structure and both, behavior and physical health, relies on informing and justifying further analyses on them that could pinpoint the causes driving such associations (Tenesa and Haley, 2013; Visscher et al., 2008).

1.4 Methodological considerations when studying how brain structure relates to behavior and physical health

In the previous section, limitations on studies linking brain structure to both, behavior and physical health, were introduced. These limitations highlight the urgency of methodological advances to study the brain (Kong et al., 2023; Williams and Whitfield Gabrieli, 2025). This has led to recommendations to consider when evaluating associations between brain and other features such as behavior and physical health.

1.4.1 Sample sizes

Typically, studies linking brain structure with other features analyze samples sizes of a few hundreds of subjects at best (Du et al., 2014; Mateos-Pérez et al., 2018; McCutcheon et al., 2023). The sample size of a study is linked to the power of the experiment or, in other words, to the probability of finding a true positive effect. In this regard, performing studies with big samples sizes, and hence with higher statistical power, could lead to more replicable findings (Bzdok et al., 2021; Genon et al., 2022; Kharabian Masouleh et al., 2019). Big samples allow for a more accurate representation of the variability in the population, potentiating the discovery of generalizable associations (Bzdok et al., 2021). Moreover, big samples allow for the implementation of machine learning approaches, which by the use of cross validation allow for the estimation of the generalizability of the findings. Hence, the use of big samples is encouraged in the fields of neuroimaging and systems neuroscience.

1.4.2 Machine learning: generalizability and stability

Taking into account the low replicability in neuroimaging (Kharabian Masouleh et al., 2019), it is imperative that studies examine the replicability of their findings in unseen data. This can be achieved by the use of machine learning (ML) approaches. ML is a subfield of artificial intelligence whose algorithms capture patterns in the data with the aim that those patterns are generalizable to unseen data (Bzdok et al., 2021; Bzdok and Ioannidis, 2019; Gabrieli et al., 2015; Greener et al., 2022). This is achieved by the use of cross-validation. During cross-validation, the dataset is split into training and test set (k times in the case of k-fold cross-validation) (Greener et al., 2022; James et al., 2023). The patterns in the data are first learned in the training set and then tested in the unseen training dataset, assessing their generalizability (Greener et al., 2022).

In the context of neuroimaging and systems neuroscience, ML has been promoted for extracting novel associations between the brain and other features, which would aid in discovering the neurobiological bases of features of interest in these fields. The unraveled associations could later be assessed for their usefulness as biomarkers for the clinical practice (Bzdok et al., 2021; Mateos-Pérez et al., 2018; Singh et al., 2022), for instance as aids during patient diagnosis (Bzdok et al., 2021; Mateos-Pérez et al., 2018; Singh et al., 2022). One practical example of how ML algorithms could be used in the clinical practice is to perform a prompt preliminary assessment of patients to facilitate prioritization, leading to faster clinical responses (Monsour et al., 2022; Sánchez Fernández and Peters, 2023). Another example is an alert system that could warn clinical practitioners about patterns they might have missed or which are yet not visible as symptoms (Monsour et al., 2022; Sánchez Fernández and Peters, 2023). Still another example is to evaluate an image of the brain to immediately inform clinical practitioners if the quality of an image is low and if a scan repetition is needed, avoiding rescheduling of a new scanning session (Monsour et al., 2022; Singh et al., 2022). Yet another instance is the development of prediction algorithms that could provide a prognosis assessment in order to help determine which patients would benefit from which treatments (Mateos-Pérez et al., 2018; Monsour et al., 2022; Sánchez Fernández and Peters, 2023; Singh et al., 2022). Despite all these advancements, it is important to highlight that the use of ML methods in systems neuroscience is still in its infancy and needs further improvement in order to reach clinical deployment (Monsour et al., 2022; Singh et al., 2022).

Apart from the within-dataset generalizability assessment that traditional ML workflows employ, external (i.e. out-of-cohort) validation has been promoted (Bzdok and Ioannidis, 2019; Mihalik et al., 2019; Xu et al., 2024). This refers to testing the model in a totally independent dataset to assess its out-of-cohort generalizability. The implementation of both, within-dataset and out-of-cohort validation is imperative for discovering associations between brain and other features that could be further testes as biomarkers and used in medical healthcare (Bzdok et al., 2021; Xu et al., 2024).

1.4.3 Leakage in machine learning pipelines

Despite its strengths, ML frameworks also have limitations. One of the most widely spread pitfalls in ML is data leakage (Bernett et al., 2024; Kapoor and Narayanan, 2023; Rosenblatt et al., 2024; Sasse et al., 2025). Data leakage is a common error in ML pipelines that typically leads to overly optimistic results, severely impairing the replicability and generalizability of the findings (Mateos-Pérez et al., 2018; Sasse et al., 2025). The issue of data leakage arises when a ML model access illegitimate information (from the test set) during the training process, invalidating the estimated generalization performance of the model (Sasse et al., 2025). A publication related to the present work introduces and illustrates several ways in which data leakage can appear in a ML pipeline (Sasse et al., 2025). One example of data leakage is when the whole dataset is preprocessed before data splitting (Sasse et al., 2025). Here, preprocessing could refer to dimensionality reduction (for instance with principal component analysis), confound regression, or imputation of missing values. A second example is when preprocessing is performed in training and test sets independently (Sasse et al., 2025). To avoid leakage in these specific cases, the preprocessing parameters should be learned in the training set and applied to the test set (Sasse et al., 2025). Given the importance of replicability and generalizability for research in systems neuroscience, it is imperative to design ML pipelines which avoid data leakage (Sasse et al., 2025).

1.4.4 Many-to-many mapping with multivariate approaches

Multivariate approaches offer the possibility to uncover broad associations between datasets, and have been promoted to improve the replicability of findings in neuroimaging (Genon et al., 2022; Marek et al., 2022; Mihalik et al., 2019). One group of multivariate methods that have been used to link neuroimaging data with other features is the Canonical Correlation Analysis (CCA) or the closely related Partial Least Squares

(PLS) (Genon et al., 2022; Küppers et al., 2026; Maleki Balajoo et al., 2024; Mihalik et al., 2022, 2020a, 2020b, 2019; Xu et al., 2024). This method has been successfully used in studies related to this work, for instance to examine associations between cortical GMV, hippocampal GMV, and behavior (Maleki Balajoo et al., 2024) as well as to examine associations between motor performance, sleep quality, depressive symptoms and GMV (Küppers et al., 2026).

CCA/PLS are data-driven methods that search for latent variables capturing the maximal association between two sets of data (i.e. data modalities, X and Y) (Helmer et al., 2024; Mihalik et al., 2022, 2020b). Specifically, these methods search for weights (w_x and w_y) such that when the original variables (X and Y) are projected onto their respective weights (i.e. linear combination or weighted sum of the original variables), the two resulting latent variables are maximally correlated (i.e. canonical correlation) (Mihalik et al., 2022, 2020b). The weights w_x and w_y indicate how much each original variable contributes to the canonical correlation or latent dimension (Mihalik et al., 2022). In order to interpret the obtained latent dimension loadings can be observed. Loadings are computed as the correlation between the original variables and the latent variables (Helmer et al., 2024; Mihalik et al., 2022). The loadings indicate which variables have the strongest association with the identified latent dimension. In the context of the current research, RCCA can be used to find latent dimensions describing the association between multivariate brain data (e.g. brain structural measures of several brain regions) and multivariate features (e.g. cognition and emotion for the case of behavior) (Mihalik et al., 2022, 2020b, 2019).

Latent dimensions uncovered with CCA/PLS offer the advantage of reducing the complexity of the observed associations by a lower dimensional representation of the data. Despite capturing the association of multiple variables at once, these latent dimensions offer a good degree of interpretability, which is highly valuable in systems neuroscience research (Mateos-Pérez et al., 2018; Mihalik et al., 2020b, 2019). In this sense, interpretable models should be favored when the aim of the study is to provide knowledge of the neurobiological bases of the features of interest (Mateos-Pérez et al., 2018). Another advantage of interpretable and explainable models is that they improve the ability of clinical practitioners to detect errors and biases that could be harmful for the patients (Monsour et al., 2022). At the same time, data-driven approaches are able to disentangle patterns between brain measurements and other features which are present in

the data but still not incorporated into the current theoretical frameworks addressing brain health (Williams and Whitfield Gabrieli, 2025). Hence, CCA/PLS represent an excellent choice to uncover a many-to-many view in the currently poorly understood association between brain and other features (Küppers et al., 2026; Maleki Balajoo et al., 2024; Mihalik et al., 2020b, 2019; Xu et al., 2024).

Despite the strengths of CCA/PLS, it is important to note that some studies using these methods have shown unstable results (Helmer et al., 2024; Mihalik et al., 2020a; Xu et al., 2024). In fact, CCA/PLS can overfit the data when the number of variables analyzed is bigger than the number of samples (Helmer et al., 2024; Mihalik et al., 2022). Of note, the use of dimensionality reduction (such as Principal Component Analysis) before the implementation of CCA/PLS, and the use of regularization, have been shown to reduce this problem (Hardoon et al., 2004; Mihalik et al., 2022, 2020a, 2019; Vinod, 1976). Here, regularized CCA (RCCA) introduces L2-norm regularization, which forces some weights to be small but not zero (Mihalik et al., 2022).

1.5 Ethics protocols

The ethics protocols for analyses of these data were approved by the Heinrich Heine University Düsseldorf ethics committee (No. 4039, votes 2018-317-- RetroDEuA, 2018-317_1-RetroDEuA, and 2018-317_2).

1.6 Aims of thesis

This work aims to explore replicable and generalizable associations between brain structure and both, behavior and physical health. While previous studies have examined associations between brain structure and both, behavior and physical health, they come with some limitations. These limitations include small sample sizes, contradictory results, and mostly univariate/bivariate methods. Moreover, concerns regarding the replicability of these findings have been raised. Alarmingly, a systematic evaluation between the replicability of associations between GMV and behavior pointed towards low replicability findings (Kharabian Masouleh et al., 2019). However, this report could be biased by the use of only one structural feature, and more comprehensive evaluations are needed.

In this context, in Study 1 we aimed to evaluate the replicability of findings between brain structure and behavior using a less noisy structural measurement (CT) than

previous studies, in order to assess if the replicability crisis is bound to particularly noisy brain structural measurements (Kharabian Masouleh et al., 2022). In particular, a wide range of behavioral variables was examined, spanning emotion, cognition and personality. To achieve this, a mass univariate/bivariate approach was used in both, an exploratory and a confirmatory framework. In the exploratory framework, univariate/bivariate associations between behavior and the whole brain cortex were searched across 100 samples, and the spatial consistency across the samples was examined. In the confirmatory framework, the significant clusters obtained in the previous step were examined for their replicability, by searching the previously found brain-behavior association in another sample.

After we confirmed that typical methods used in the field are associated to a replicability crisis in neuroimaging, we adopted robust methods aiming to mitigate the low replicability of associations between brain structure and other features. Following this line, in Study 2 we implemented ML, big sample sizes and a multivariate approach (RCCA) to uncover replicable and generalizable associations between brain structure (GMV, CT and SA) and behavior (alertness, emotion, and cognition) (Nicolaisen-Sobesky et al., 2022). In addition to the within-cohort generalizability assessment implemented in the ML framework, we also tested the replicability of the findings in an independent cohort. Finally, the heritability and genetic correlation of the found association between brain structure and behavior were examined.

Finally, in Study 3 we analyzed robust associations between brain structure and physical health (Nicolaisen-Sobesky et al., 2025). In particular, this study focused on robust associations between brain structure (GMV and CT) and risk factors for non-communicable diseases (spanning body size measures, diet, physical activity, smoking, alcohol consumption, residential air pollution, sleep health and general health). Similar to Study 2, Study 3 used ML, big sample sizes, and a multivariate approach (RCCA). In addition, the brain patterns captured in association with the risk factors were characterized neurobiologically, by correlating them with patterns of brain function, brain structure, and neurotransmitter systems.

2 Study 1: Empirical facts from search for replicable associations between cortical thickness and psychometric variables in healthy adults, Kharabian Masouleh, S., Eickhoff, S. B., Maleki Balajoo, S., Nicolaisen-Sobesky, E., Thirion, B., & Genon, S., Scientific reports, 12(1), 13286, (2022).

DOI: https://doi.org/10.1038/s41598-022-17556-7

3 Study 2: A cross-cohort replicable and heritable latent dimension linking behaviour to multi-featured brain structure, Nicolaisen-Sobesky, E., Mihalik, A., Kharabian-Masouleh, S., Ferreira, F. S., Hoffstaedter, F., Schwender, H., Maleki Balajoo, S., Valk, S.L., Eickhoff, S.B., Yeo, B.T.T., Mourao-Miranda, J., & Genon, S., Communications biology, 5(1), 1297, (2022).

DOI: https://doi.org/10.1038/s42003-022-04244-5

4 Study 3: Cardiometabolic health and physical robustness map onto distinct patterns of brain structure and neurotransmitter systems, Nicolaisen-Sobesky, E., Maleki Balajoo, S., Mahdipour, M., Mihalik, A., Olfati, M., Hoffstaedter, F., Mourão-Miranda, J., Tahmasian, M., Eickhoff, S.B., & Genon, S., PLoS biology, 23(11), e3003498, (2025).

DOI: https://doi.org/10.1371/journal.pbio.3003498

5 Discussion

5.1 Replication crisis in neuroimaging

Our findings in Study 1 strengthened concerns regarding the presence of a replicability crisis in neuroimaging (Kharabian Masouleh et al., 2022, 2019). In particular, we found that CT, as a less noisy structural measure relative to GMV, also was associated with an alarmingly low replicability of brain-behavior associations (Kharabian Masouleh et al., 2022). Altogether, these findings showed that the replicability crisis in neuroimaging is not tied to a specific measurement of brain structure, but reflects a general situation encompassing both, volumetric and surface estimations of brain structure. These findings highlighted the urgent need to use robust methods that capture replicable and generalizable associations, as well as the importance of testing the replicability of findings in neuroimaging studies.

Another striking aspect that has been revealed by Study 1 (Kharabian Masouleh et al., 2022), as well as by other similar studies (Kharabian Masouleh et al., 2019), is the low likelihood of finding significant associations between brain structure and behavior on the first place. Our results showed that 90% of the analyses searching for associations between CT and behavior can be expected to yield non-significant findings. This made evident a huge contrast when compared with the proportion of significant findings reported in the literature. This mismatch, also suggested by other studies (David et al., 2018; Fusar-Poli et al., 2014; Jennings and Van Horn, 2012) indicated a publication bias in the literature, where significant findings, though infrequent, are much more frequently published than null findings (Genon et al., 2022; Kharabian Masouleh et al., 2022, 2019). This publication bias causes severe harm to the development of theories of the association of the brain with other features in systems neuroscience, since the knowledge these theories build on is likely invalid (Kühberger et al., 2014). This highlights the importance of the publication of null findings in the scientific literature and calls for the use of robust methods to improve the replicability of the findings in neuroimaging.

Moreover, our findings indicated that, when searching for associations between brain structure and behavior, samples sizes of at least about 200-300 participants should be used in order to obtain well powered statistical results (Genon et al., 2022; Kharabian Masouleh et al., 2022). In contrast, the use of small samples sizes is still common in the

research literature (David et al., 2018; Du et al., 2014; Fusar-Poli et al., 2014; Hvid et al., 2021; Jennings and Van Horn, 2012; Mateos-Pérez et al., 2018). It is important to recognize that achieving big samples sizes for specific scenarios (such as studies focusing on disorders or illnesses, interventions, multi-modal measurements, etc.) can be challenging and even unfeasible in some cases (such as the case of infrequent diseases). However, when possible, the examination of big sample sizes should be favored.

5.2 A brain structural pattern is associated with an axis of executive-functions/cognitive-control and positive affect

In Study 2, we found a replicable and generalizable latent dimension linking brain structure to behavior (Nicolaisen-Sobesky et al., 2022). We found one latent dimension that captured an axis ranging from higher executive-functions/cognitive-control and positive affect to lower executive-functions/cognitive-control and negative affect. This behavioral axis was linked to variability in GMV, CT and SA trough the brain. Of note, this latent dimension was replicable not only in-sample, but also in an independent cohort. This more stringent test highlighted the value of the use of ML workflows when searching for associations between neuroimaging variables and features of interest for systems neuroscience.

The latent dimension found indicated that higher executive-functions/cognitive-control and positive affect were associated with lower CT in associative cortical regions and with higher CT in sensorimotor cortical regions. The captured behavioral and CT patterns were in line with previous studies in the same sample (Han et al., 2020; Smith et al., 2015) and showed an alignment with the cortical hierarchy of the cortex (Margulies et al., 2016). Also, the brain patterns captured in this latent dimension for cortical GMV and SA were similar. These findings indicated that higher executive-functions/cognitive-control and positive affect were associated with higher SA and GMV in temporal poles and inferior temporal gyri, superior frontal regions and superior parietal areas, and with lower SA and GMV in orbitofrontal cortex and superior frontal gyri. Interestingly, this brain pattern showed similarities with the brain pattern of cortical expansion during ontogeny and evolution (Hill et al., 2010). Furthermore, our results indicated that higher executive-functions/cognitive-control and positive affect were associated with lower GMV in subcortical structures and cerebellum.

Of note, these results indicated that the usually expected result of higher cognitive functions being associated with bigger brain structures is not necessarily the case (Yuan and Raz, 2014). This could point towards the reduction in size of brain regions potentially being associated with maturation or pruning, as typically observed in adolescence (Whitaker et al., 2016), might still take place in adult subjects. Moreover, our results showed that higher-order cognitive functions were associated with brain regions not typically linked with cognition, such as cortical sensorimotor or cerebellar regions. In line with other reports, our results encourage the inclusion of those regions in studies focusing in cognitive or affective processes (Kebets et al., 2019).

The heritability and genetic correlation analyses showed that the behavioral and brain sides of the latent dimension were influenced by overlapping genetic mechanisms. These results supported the biological validity of the results obtained with multivariate analyses and ML approaches. In addition, our results support further analyses to elucidate the genetic bases of the association between brain structure and behavior.

5.3 Brain structural patterns associated with an axis of cardiometabolic health and an axis of physical robustness

Two significant latent dimensions linking brain structure with risk factors were reported in Study 3 (Nicolaisen-Sobesky et al., 2025). One latent dimension linked cardiometabolic health with an axis of variability in CT and an axis of variability in GMV. Specifically, better cardiometabolic health was linked with higher CT in insula, temporal lobe, inferior parietal areas, orbitofrontal areas, cingulate cortex and primary motor cortex, as well as with lower CT in the primary somatosensory cortex, superior frontal areas, superior parietal areas and occipital areas. The GMV pattern indicated that better cardiometabolic health was linked with higher GMV in primary motor cortex and temporal cortex, as well as lower GMV in frontal, parietal, and occipital areas. This latent dimension showed stability across sexes. In the same line, a study related to this work also found that cardiometabolic-related variables (such as blood pressure, diet and diabetes) were linked to brain health (brain age derived from brain structural measures) (Mahdipour et al., 2026).

A second latent dimension showed an association between brain structure and physical robustness. In particular, higher physical robustness was linked with higher CT in superior frontal areas and insula and with higher GMV in anterior cingulate cortex,

medial superior frontal areas, temporal lobe and orbitofrontal cortex. Of note, this latent dimension was significant and stable only in men but not in women. This highlighted the importance of performing sex-specific analyses in order to confirm the replicability of the findings across sexes.

The CT and GMV patterns of the two latent dimensions showed different neurobiological profiles. This indicated that the brain regions whose CT or GMV covaried the most with cardiometabolic health were also those which covaried the most with other neurobiological features, including brain function, patterns of genetic expression, and binding potential for different neurotransmitter receptors and transporters. These findings supported the examination of biological systems from a multi-level perspective, integrating information at different levels and modalities, such as biological function, biological structure, genetics, and molecular information.

Our results in Study 2 and Study 3 uncovered latent dimensions that captured associations between multiple brain regions and multiple behavioral and health risk features at once. These findings strengthened the needed shift from a one-to-one to a many-to-many mapping approach in systems neuroscience. This shift has also been supported by studies related to the present work, which examined associations between cortical GMV, hippocampal GMV, and behavior (Maleki Balajoo et al., 2024) as well as associations between motor performance, sleep quality, depressive symptoms and GMV (Küppers et al., 2026). Similarly, the importance of studying multivariate associations in systems neuroscience has also been shown in another study related to this work, which searched for associations between brain health (specifically brain age derived from brain structure) and the exposome (Mahdipour et al., 2026). More studies implementing many-to-many mappings with multivariate approaches will help gain a more comprehensive and valid picture of the biology of the human body. On this line, some authors argue that multivariate methods hinder the interpretability of the results, and hence univariate/bivariate methods should still be preferred. However, even though the interpretability of multivariate approaches could be more challenging in some cases when compared with univariate/bivariate approaches (Kharabian Masouleh et al., 2019), the multivariate patterns captured in our studies offered a good degree of interpretability. Similarly, the generalizability and replicability of the findings presented in Study 1 and Study 2 underscored the importance of using ML frameworks that avoid leakage in systems neuroscience (Sasse et al., 2025). Altogether, this encourages the use of

multivariate methods and leakage-free ML frameworks when appropriate for the scientific questions being evaluated in systems neuroscience.

5.4 Limitations

The studies presented here have some limitations. First, RCCA is able to capture linear associations, so non-linear associations remain unexplored here. Second, the heritability and genetic correlation estimations in Study 2 could be overestimated due to the synthetic variables derived from RCCA. Third, the latent dimensions uncovered by the RCCA in Study 1 and Study 2 are constrained by the data introduced to the models. However, these Studies made use of the biggest available datasets including multivariate data in neuroimaging, behavior and risk factors for non-communicable diseases. Nevertheless, different results could be yielded using different variables such as personality measures, social connections, or genetics. In this regard, this limitation calls for more studies exploring robust and multivariate associations between brain health and diverse features of interest for systems. neuroscience. Similarly, diverse features of the brain should be examined, including not only other structural measures (such as gyrification or sulcal depth), but also brain functional data, microstructure and anatomical connectivity derived from diffusion MRI, molecular binding potentials derived from positron emission tomography, among others. Fourth, the diversity of the analyzed samples is not representative of the world population, hence the results might not generalize to samples with different age ranges or ethnicities. Efforts should be directed for the collection and sharing of diverse and big datasets spanning multiple cultures, age ranges, and other variables. Fifth, our studies analyze healthy samples. Even though studying healthy samples is valuable for advancements in systems neuroscience and medicine, as pointed in the Introduction, it should be noted that the results reported here might not generalize to subjects with illnesses or disorders.

5.5 Conclusion

This study examined replicable associations between brain and both, behavior and physical health. We provided evidence of a replicability crisis in neuroimaging spanning not only volumetric (GMV), but also surface (CT) measures. In line with this, the scientific community should be aware of a publication bias, where significant (but likely not replicable) findings are often published, and which could severely hinder theory development in systems neuroscience. Our findings also strengthened the value of the use

of big sample sizes, ML frameworks and multivariate approaches when searching for replicable and generalizable associations in neuroimaging.

Our results showed a replicable and heritable latent dimension linking several features of brain structure to a behavioral axis of interindividual variability. This axis spanned from good cognitive functioning and positive emotions to negative emotions and sleep problems. This behavioral axis was associated to brain-wide patterns of cortical thickness, surface area, and grey matter volume. Interestingly, the reported axes of behavior and brain structure were heritable and genetically correlated. In addition, we reported two robust latent dimensions linking brain structure and risk factors for non-communicable diseases. The first latent dimension linked brain-wide patterns of cortical thickness and GMV to an axis of cardiometabolic health. The second latent dimension linked axes of CT and GMV to physical robustness. In addition, we found that these brain-wide patterns of CT and GMV were associated to different patterns in the brain distribution of several neurotransmitter systems. Altogether, these findings underscored the value of adopting a many-to-many approach (in contrast to the typical one-to-one mapping) when searching for associations between the brain and other features for systems neuroscience. The role of the reported associations between brain structure and both, behavior and risk factors, in different illnesses and disorders should be examined.

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