Cardiometabolic health, cortical thickness, and neurotransmitter systems: a large-scale multivariate study

Eliana Nicolaisen-Sobesky[1,2*], Somayeh Maleki Balajoo[1,2], Mostafa Mahdipour[1], Agoston Mihalik[3,4,5], Felix Hoffstaedter[1,2], Janaina Mourao-Miranda[3,4], Masoud Tahmasian[1,2,6], Simon B. Eickhoff[1,2], Sarah Genon[1,2*]

[1]Institute of Neuroscience and Medicine (INM-7: Brain and Behaviour), Research Centre Jülich, Jülich, Germany.
[2]Institute of Systems Neuroscience, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
[3]Centre for Medical Image Computing, Department of Computer Science, University College London, London, United Kingdom.
[4]Max Planck University College London Centre for Computational Psychiatry and Ageing Research, University College London, London, United Kingdom.
[5]Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom
[6]Department of Nuclear Medicine, University Hospital and Medical Faculty, University of Cologne, Cologne, Germany.

*Corresponding authors:

Eliana Nicolaisen-Sobesky
Institute of Neuroscience and Medicine (INM-7: Brain and Behaviour), Research Centre Jülich, Jülich, 52428, Germany
elinicolaisen@gmail.com

Sarah Genon
Institute of Neuroscience and Medicine (INM-7: Brain and Behaviour), Research Centre Jülich, Jülich, 52428, Germany
s.genon@fz-juelich.de

Summary

There is a recognized link between risk factors for non-communicable diseases and brain health. However, the specific effects that they have on brain health are still poorly understood, preventing its implementation in clinical practice. For instance, the association between such risk factors and cortical thickness (CT) has been primarily explored using univariate/bivariate methods and global/lobar measures of CT and has yielded inconsistent results. In this work, we aim to study the relationship between risk factors for non-communicable diseases and CT. In addition, we adopt a systems-level perspective to understand such relationship, by integrating several brain features including brain structure and function as well as neurotransmitter systems.

Here, we analyzed latent dimensions linking a broad set of risk factors for non-communicable diseases to parcel-wise CT across the whole cortex (including raw, proportional, and brain size-corrected measures). We used a multivariate approach (regularized canonical correlation analysis (RCCA)) embedded in a machine learning framework that allows to capture inter-individual variability and to assess the generalizability of the model. The brain patterns (captured in association with risk factors) were characterized from a multi-level perspective, by comparing them with patterns of brain structure, function, and neurotransmitter systems. Analyses were performed separately in women (n=3685, 46-81 years) and in age-matched men (n=3685, 46-81 years) to avoid sex-bias on the results.

We found one significant latent dimension (women: r_{range}=0.25-0.30, p=0.005-0.005; men: r_{range}=0.31-0.34, p=0.005-0.005), capturing variability in cardiometabolic health, including physical activity, body morphology/composition, basal metabolic rate, and blood pressure. This cardiometabolic health dimension was linked to a CT axis of inter-individual variability from the insula and cingulate cortex to occipital and parietal areas. Interestingly, this brain

pattern was associated with the binding potentials of several neurotransmitter systems, including serotoninergic, dopaminergic, cholinergic, and GABAergic systems. Of note, this latent dimension was similar across sexes and across CT measures (raw, proportional, and brain-size corrected).

We observed a robust, multi-level and multivariate link between cardiometabolic health, CT, and neurotransmitter systems. These findings support the urgency of further investigation into the interaction between brain health and physical health and contributes to the challenge to the classical conceptualization of neuropsychiatric and physical illnesses as categorical entities. Therefore, regular monitoring of cardiometabolic risk factors may reduce their adverse effects on brain health and prevent the development of brain diseases.

Keywords: Brain structure, cortical thickness, cardiometabolic, risk factors, neurotransmitter systems

Introduction

Non-communicable diseases, including cardiovascular, metabolic, mental, and neurological disorders, represent the predominant global public health challenge nowadays (1,2). Most non-communicable diseases share a common set of risk factors, like tobacco smoking, unhealthy diet, physical inactivity (1,2), excessive alcohol consumption, hypertension (2), sleep problems (3), obesity (increased body mass index (BMI)) and air pollution (2,3). Since non-communicable diseases include mental and neurological disorders, the same set of risk factors also affects brain health (2,4).

One of the biomarkers for brain health is cortical thickness (CT). Several studies have contributed to our understanding of the link between CT and risk factors such as BMI (5–11), waist circumference (10,11), cigarette smoking (10), physical exercise (12), and diet (13). However, even though these studies have advanced our understanding of the link between risk factors and CT, they have some limitations.

One limitation is that the reported findings have been inconsistent. For instance, associations between BMI and both, global or frontal CT, have been reported as negative (5–7,10,11), as positive (8–10), and as not significant (6,7). To improve this point, studies using robust approaches that evaluate the generalizability of results are needed. In this regard, machine learning approaches use cross-validation to test for the generalizability of the implemented models. For that, the available data is divided into splits, allowing to train the model in one split and test its performance in a different split. Second, several of these studies analyzed global or lobar measures of brain structure. This prevents the discovery of extended fine-grained patterns of brain organization that show brain regions with different or even opposite associations with risk factors. To achieve this, region-wise or voxel-wise measures of brain features should be analyzed in association with risk factors. Third, since most of these studies

use univariate/bivariate approaches, they provide a partial view of this association (14) impeding the discovery of distributed brain networks that are associated to several risk factors simultaneously (15). Distributed brain networks and their interactions, as well as their interaction with several risk factors, can be analyzed with multivariate approaches. Multivariate approaches provide a broad and comprehensive view of the phenomena under study, by uncovering relations among variables. Consequently, multivariate approaches take full advantage of the rich phenotyping included in large-scale datasets such as the UK Biobank. In addition, univariate/bivariate approaches cannot account for collinearity of variables, which hinders the interpretation of findings, and which is very common in both, risk factors (16) and neuroimaging (17).

Therefore, despite that there is an established link between risk factors for non-communicable diseases and brain health, there are still several important aspects of this association which are incompletely understood (15,18). The lack of understanding of the relationship between risk factors and brain health prevents their use as biomarkers in the clinical practice, and hence is a major research priority (15). Since structural brain changes may be long-lasting and lead to various neuropsychiatric diseases, it is critical to pinpoint modifiable risk factors that can reduce the risk of those conditions. Understanding how risk factors for non-communicable diseases are related to brain health from a comprehensive and broad perspective requires understanding how multiple risk factors simultaneously interact with brain features across the whole brain. Thus, the main question of this study is which risk factors for non-communicable diseases affect brain health and how is the interplay between several risk factors and the structure of several regions of the brain cortex. This would allow to early detect patients at risk of brain disorders, somatic/physical disorders, or their comorbidities, and potentially prevent such diseases.

Another important point to consider is the multi-level nature of the interplay between risk factors and brain health. For instance, risk factors for non-communicable diseases have been associated with several brain features, including brain structure (19,20), function (21), genetics, and neurotransmitter systems (22). This needed integration of different neurobiological features (23) can now be done quantitively with neuromaps (24), which provides access to a wide set of brain maps, including for instance genes transcription and positron emission tomography derived features. Linking different data features will allow to gain a systems-level understanding of the association between risk factors and brain health.

Hence, to gain a comprehensive, generalizable, and multi-level understanding of the relationship between risk factors and brain health, it is needed to use robust machine learning approaches with generalizability testing, along with methods that integrate different data modalities (25,26). In this respect, canonical correlation analysis (CCA) is a multivariate, data-driven approach that can be used to discover large-scale distributed brain networks (i.e., axes of brain organization) associated with several risk factors (27,28). Of note, a regularized version of CCA (RCCA) mitigates the effect of collinearity and yields more stable results than CCA (27), improving the interpretability of results. CCA and RCCA have been previously used to search for robust and generalizable multivariate associations between different data modalities, such as brain structure, brain function, hippocampal structure, behavior, environmental variables, and psychiatric features (14,25,29–32). Using these methods, numerous studies have shown that several healthy and illness-related phenotypes are linked to axes of brain structural organization (25,30,32).

Here, we study the relationship between risk factors for non-communicable diseases and CT. In addition, we explore such association from a systems-level perspective, by integrating several neurobiological features of the brain (Fig. 1). For that, we first searched for latent

dimensions linking a wide range of risk factors for non-communicable diseases to region-wise CT across the whole brain cortex using RCCA embedded in a machine learning framework. In other words, we searched for those combinations of risk factors which are most relevant for CT interindividual variability (14). The CT features included raw, proportional, and corrected (brain-size corrected) measures. On a second step we aimed to characterize the captured brain patterns from a neurobiological perspective. For that, we compared the brain patterns captured in the latent dimensions with existing brain maps spanning brain structure, function, genetics, and neurotransmitter systems. We performed sex-specific analyses in this study because previous works have shown sex differences in the association between brain structure and risk factors (33,34), and also in order to avoid sex-bias in the results (35,36). The existence of a sex bias in human neuroscience is recognized, with the consequence that much of our knowledge in the field is based on men, and do not or might not generalize to women (37).

Methods

Participants

We used data from UKB (application 41655) (38,39). Inclusion criteria for this study were having no self-reported illnesses (Data-Field ID 20002-2.*) and having complete data in all variables utilized in this study (excluding responses like “Do not know” or “Prefer not to answer”). We created two gender/sex specific subsamples matching subject-by-subject by age: a subsample of women (n=3685, age: range 46-81 years, mean 62.3, standard deviation 7.6) and a subsample of men (n=3685; age: range 46-81 years, mean 62.3, standard deviation 7.6). The combined subsample was also analyzed (merging women and men, n=7370) in order to assess if results were stable when improving the samples-per-features ratio.

Risk factors data

Variables of risk factors for non-communicable diseases corresponded to 1622 columns in the dataset. After removing duplicated, incomplete, or skewed variables, 68 variables remained, spanning categories of general health, body size measures, diet, physical activity, residential air pollution, sleep health, alcohol consumption, and smoking (Table S1). Note that UKB has two similar categories (Medication and Medications) and variables from both are used here (see Table S1). As done previously, we computed waist-to-hip ratio dividing waist circumference by hip circumference (10). The intercorrelation among risk factors was analyzed with Pearson's correlation.

Neuroimaging data

Neuroimaging data for the sample used in this study were collected by UKB in four sites using identical protocols and 3T Siemens Skyra scanners with standard Siemens 32-channel receive head coils (40). T1-weighted structural imaging (3D-MPRAGE, sagittal) was acquired with the following parameters (38,40): voxel resolution: 1x1x1 mm, FoV: 208x256x256 matrix, TI/TR = 880/2000 ms, in-plane acceleration iPAT=2. T1 images were processed by UKB using a custom pipeline based on FSL (40), including gradient distortion correction, cutting down the field of view, registration (linear and then non-linear) to the MNI152 standard-space T1 template, brain extraction, defacing, and brain segmentation (40). CT was estimated using FreeSurfer a2009s.

We used mean raw CT of 148 parcels on the white surface (Destrieux atlas, a2009s) (41). In addition, we used proportional estimations of CT (computed subject-wise, dividing the mean raw CT of each parcel by the mean raw CT across all parcels) and CT corrected for brain size (regressing out mean CT in a cross-validation consistent manner) (42). These different CT measures represent different biological properties and can show different patterns of associations with risk factors.

Regularized canonical correlation analysis

Canonical Correlation Analysis (CCA) is a multivariate technique that can discover latent dimensions linking interindividual variability in $\boldsymbol{X}$ and $\boldsymbol{Y}$ (27,32,43). Here, $\boldsymbol{X}$ included CT for each parcel, while $\boldsymbol{Y}$ included risk factors. CCA searches linear combinations of variables in $\boldsymbol{X}$ (brain weights $\boldsymbol{u}$) and of variables in $\boldsymbol{Y}$ (risk factor weights $\boldsymbol{v}$), which maximize the canonical correlation between the brain scores and risk factor scores (27,32). The scores correspond to the projection of $\boldsymbol{X}$ and $\boldsymbol{Y}$ onto their respective weights ($\boldsymbol{Xu}$ and $\boldsymbol{Yv}$).

One limitation of CCA is that it can overfit the data or yield unstable results, especially in high-dimensional datasets (44). A regularized version of CCA (RCCA) reduces the overfitting of the model by adding L2-norm constraints to the weights (27,32,45,46).

To search for multivariate associations between risk factors and brain structure, we ran nine RCCA models: three in the subsample of women, three in the age-matched subsample of men, and three in the combined subsample. Within each subsample, each RCCA model linked the same set of risk factors with either a) raw CT, b) proportional CT, or c) brain size-corrected CT. Age and site were regressed out avoiding data leakage in the machine learning framework (regression parameters were estimated in the training set and applied to the training, test, and holdout sets) (47). In the combined subsample, sex was also regressed out. Confounding variables were included in the $\boldsymbol{Y}$ matrix to check if their variance was properly removed.

To visualize and interpret the latent dimensions, loadings were computed (27). Brain (or CT) loadings correspond to the correlation of the original brain variables ($\boldsymbol{X}$) with brain scores ($\boldsymbol{Xu}$). Similarly, risk factor loadings correspond to the correlation between the risk factor original variables ($\boldsymbol{Y}$) with the respective scores ($\boldsymbol{Yv}$). Loadings indicate which variables are more

strongly associated with the latent dimension. To interpret the latent dimensions, only stable loadings were considered (loadings whose error bar does not cross zero).

Machine learning framework

We utilized a machine learning framework that uses multiple holdouts of the data (32,48). This framework implements two consecutive splits: the outer split divides the whole data into optimization and hold-out sets, and is used for statistical evaluation, and the inner split divides the optimization set into training and test sets and is used for model selection. In this study, we used 5 inner splits and 5 outer splits. Model selection was performed based on the highest test canonical correlation and the highest stability (similarity of weights estimated using Pearson's correlation across the 5 inner splits).

Statistical evaluation of the latent dimensions

Statistical significance of the latent dimensions was tested with permutation tests. In each of the 1000 iterations, the rows of the $\boldsymbol{Y}$ matrix were shuffled in the optimization and hold-out sets. The RCCA model (hyperparameters) that was previously selected with the original data was now fitted on the permuted optimization set, and weights were obtained. Then, the permuted hold-out set was projected onto these weights. A canonical correlation under the null model was hence obtained, and a p-value was computed. The permutation test was repeated for each one of the outer splits, hence yielding 5 p-values which were corrected by multiple comparisons (Bonferroni method over 5 comparisons). The statistical significance of the latent dimensions was evaluated using the omnibus hypothesis (48). Here, the null hypothesis states that there is no effect in any of the splits. Hence, if at least one split yields a p-value below 0.05, the null hypothesis is rejected, and the latent dimension is considered significant. When

a significant latent dimension was found, its variance was removed from the data using deflation (32), and an additional latent dimension was sought.

Stability of the latent dimensions across sexes and cortical thickness measures

The latent dimensions yielded by the 9 models (for either men, women, or the combined subsamples; and in each case when using either raw, proportional, or corrected CT), were compared based on their average risk factor loadings and average brain loadings (average across the outer 5 splits). The risk factor loadings were compared with Pearson's correlation across models. The brain loadings were compared using spin test to account for spatial dependencies of brain data (49) using neuromaps (24) software. The p-values were corrected by multiple comparisons using Bonferroni method over 210 comparisons (number of comparisons when comparing all the 21 significant latent dimensions).

Neurobiological characterization of the pattern of cortical thickness loadings

The brain maps provided in neuromaps (24) (Table S3) (excluding the map 'hill2010' which is provided only in one hemisphere) were compared to the sex-specific maps of CT loadings using spin test (49). This was performed to assess if the latent dimensions captured a CT pattern significantly associated with other patterns of brain biomarkers. Multiple comparisons were corrected using the Bonferroni method over 468 comparisons for the first latent dimensions (6 significant CT maps and 78 brain maps) and 390 comparisons for the second latent dimensions (5 significant CT maps and 78 brain maps).

Ethics

Analyses on the data have been approved by the University Hospital Düsseldorf ethics committee votes 2018-317-RetroDEuA, 2018-317_1-RetroDEuA, and 2018-317_2.

Results

Risk factors

The distribution of risk factors is shown in figures S1-S2. The intercorrelation among risk factors was analyzed with Pearson's correlation. In the correlation matrices for risk factors, two groups of highly intercorrelated variables were evident (Figures S3-S4). One group shows intercorrelation among body composition measures, including BMI, body fat percentage, body fat mass, body fat-free mass, body water mass, basal metabolic rate, impedance of whole body, waist circumference, hip circumference, and waist-to-hip ratio. Another group of highly intercorrelated variables was characterized by air pollution.

Latent dimensions linking risk factors to raw cortical thickness in the sex-specific subsamples

We searched for latent dimensions linking risk factors to raw CT using RCCA and a machine learning framework in the sex-specific subsamples. The first latent dimensions linking risk factors to raw CT were significant in women (r_{range}=0.25-0.30, p=0.005-0.005) and men (r_{range}=0.31-0.34, p=0.005-0.005) (Figures 2-3, S5a-b and S6-S7 and Tables S4-S5). Of note, these first latent dimensions for raw CT showed significant cross-sex correlations at the risk factor loadings (r=0.97, p<0.001) and brain loadings (r=0.87, p<0.001) (Figure S15a-b). The second and third captured latent dimensions are shown in supplementary results 2.1-2.2. Interestingly, the same first latent dimensions were captured when analyzing proportional and corrected CT (supplementary results 2.3-2.5) and in the combined subsample (Figure S15, supplementary results 2.6).

In both sexes the risk factor loadings of the first latent dimensions showed a positive pole associated with higher physical activity, higher body impedance, and better self-perceived health, and a negative pole associated to higher body size measures (BMI, hip and waist

277 circumference, and waist-to-hip ratio), higher body fat (mass and percentage), higher basal
278 metabolic rate, higher body water mass, higher body fat-free mass, higher blood pressure
279 (systolic and diastolic), higher pulse rate, and higher sedentarism (higher time spent watching
280 television). Interestingly, the set of risk factors characterizing this first latent dimension
281 includes some but not all the variables captured in the first group in the inter-correlation matrix.
282 Associations between the latent dimensions and demographics are shown in supplementary
283 results 2.7.

284 In both sexes the CT loadings of the first latent dimensions were higher in the insula, cingulate
285 cortex, temporal lobes, inferior parietal areas, orbitofrontal areas, and primary motor cortex,
286 and lower in the primary somatosensory cortex, medial and superior frontal areas, superior
287 parietal areas, and occipital areas. This axis ranged from the insula and cingulate cortex to the
288 occipital lobes and superior parietal areas.

289 Conceptually, this latent dimension links cardiometabolic health to higher CT in the insula,
290 cingulate cortex, temporal lobe, inferior parietal, orbitofrontal, and primary motor cortex, and
291 lower CT in the primary somatosensory cortex, medial and superior frontal areas, superior
292 parietal areas, and occipital areas.

293 *Neurobiological characterization of the pattern of cortical thickness loadings*

294 To characterize the latent dimensions from a neurobiological perspective, we compared the CT
295 loadings with brain maps spanning brain function, structure, and neurotransmitter systems. For
296 the first latent dimensions in the sex-specific subsamples, several associations between the CT
297 patterns and brain maps were consistent across CT estimates and sexes (Fig. 4). Namely, the
298 maps of CT loadings of both sexes for proportional, raw, and corrected CT, were positively
299 associated with the cortical distribution of serotonin receptor 5-HT1a (50,51), acetylcholine
300 transporter VAChT (23,52,53), cortical thickness in Human Connectome Project (54), and fifth

gradient of resting-state functional connectivity (55), and negatively associated with oxygen metabolism (56) (Table 1). Also, all the CT loadings maps for men, and the maps for raw and corrected CT in women were positively associated with the cortical distribution of dopamine receptor D2 (23,57–59) and dopamine transporter DAT (60), and negatively associated with GABA receptor GABAa (61) and glucose metabolism (56). Additional associations are shown in supplementary results 2.8.

Discussion

We report a latent dimension characterizing the interplay between a wide range of risk factors for non-communicable diseases with region-wise CT across the whole cortex. This latent dimension highlights the relevance of cardiometabolic health for inter-individual variability of brain structure in a healthy sample. Importantly, this latent dimension was stable across sexes and across CT measures (raw, proportional, and brain-size corrected CT). Accordingly, this latent dimension cannot be explained by a confounding effect of head size/morphology that could be conveyed in CT estimates. Moreover, our results underline the multi-level nature of the association between risk factors and brain structure, linking the brain pattern of the latent dimension with the spatial distribution of several neurotransmitter systems.

Our study has some limitations. The latent dimensions found are restricted by the variables included in the RCCA. Similarly, the neurobiological characterization of the latent dimensions is limited by the brain maps available. The age range of the sample prevents characterization of the latent dimensions on children, adolescents, and young adults. The sample comprised mainly participants of White British ancestry, so it is not possible to generalize these results to other races/ethnicities.

Our results showed an axis of variability in cardiometabolic health which is related to an axis of variability in CT extending from the insula and cingulate cortex to the occipital lobes and

superior parietal regions. Overall, this latent dimension indicates that regions engaged in processing internal information such as emotional and motivational systems (including for instance insula, orbitofrontal cortex, and anterior cingulate cortex) show positive loadings while more dorsal regions typically engaged in dorsal attention and executive systems (such as the lateral superior prefrontal and parietal cortex) show negative loadings. Conceptually, this latent dimension indicates that better cardiometabolic health is associated with increased CT in emotional and motivational systems and reduced CT in dorsal attention and executive systems.

Our results are in line with recent reports pointing to the important role of cardiometabolic health for brain health. For instance, several studies have linked cardiometabolic factors to brain structure, such as reduced total brain volumes (34,62,63), reduced grey matter volumes (20,34,63), or to structural markers of brain aging (64). Interestingly, our findings are in contrast with works that have reported only reductions, but not increases, in brain structural measures in association with risk factors or cardiometabolic health. Differences in the health status of the samples might explain these differential effects. Apart from associations with brain structure, cardiometabolic health has also been associated with brain function, such as to cognition (34), dementia (62), and other neuropsychiatric disorders and symptoms (15,18,34,65,66). Our results are in line with these findings by showing associations between cardiometabolic health and brain structures typically associated with emotion, motivation, attention, or executive functions. In a similar vein, the latent dimension reported here reinforces the relevance of the adipose tissue-brain axis, which links the adipose tissue to brain function (67,68) and structure, and particularly to neurodegeneration (67). Hence, cardiometabolic factors are emerging as promising biomarkers for the interaction between brain and physical health and should be monitored in neurological and psychiatric clinical practice.

Overall, our results shed light on the architecture that supports the interaction between physical health and brain health. Accordingly, our findings contribute to the recognized urgency to characterize brain-body interactions for its implementation in clinical practice (15,18,66). For instance, it is not common to monitor physical illnesses in patients with neuropsychiatric disorders. However, recently it has been pointed out that neuropsychiatric disorders are associated with symptoms of physical illnesses and that actually poor physical health is a more pronounced effect than brain phenotypes in these patients (18). Given that the interplay between brain and body health is not well understood, the clinical practice nowadays has limited tools to exploit this interaction not only for a comprehensive monitoring of health, but also for its use as biomarkers. Hence, research characterizing brain and body interactions is a major priority for global health because it will guide the discovery of new integrated disease manifestations and guide the development of new therapies and clinical interventions (15,18). Of note, the effects of cardiometabolic health on brain structure have been also found in adolescents (34,69) and children (34,70), indicating the importance of understanding these factors throughout the lifespan.

Several studies have pointed out that a causal factor or mediator in the association between risk factors for non-communicable diseases and brain health might be inflammation (34,69,71–73), and in particular low-grade systemic inflammation (15,34,72–75). Risk factors for non-communicable diseases are also risk factors for low-grade systemic chronic inflammation (3,73,75). In turn, low-grade systemic chronic inflammation has been associated with non-communicable diseases (3,74), including neuropsychiatric illnesses (15,34,73–77). For instance, chronic inflammation in the adipose tissue has been associated with the development of neurodegenerative disorders such as Alzheimer's disease (67,73). In addition, behavioral phenotypes related to the risk factors pattern found in this study, such as impaired regulation of energy homeostasis and feeding behavior, have also been associated with inflammation

caused by adipose tissue dysfunction and diet (75). Moreover, inflammatory factors have been reported to mediate the association between BMI and other cardiometabolic factors with cortical structure (71,72). In fact, inflammation has been proposed as the cause of comorbidities between non-communicable diseases (66,76), such as depression and cardiovascular or neurodegenerative illnesses (76).

The precise inflammatory mechanisms underlying the association between cardiometabolic risk factors and brain health is still unclear, but studies suggest the involvement of elevated blood levels of cytokines (34,66) (such as interleukin-6, interleukin-1, interleukin-1β or tumor necrosis factor-alpha (73)), lymphocyte counts (66), C-reactive protein (72), and nuclear factor kappa B (73), as well as microglial activation (34,69,73). These immune factors influence synaptic plasticity (34,69), cell metabolism, cell myelination, neuronal excitotoxicity (69), neuronal apoptosis, oxidative stress, metabolic pathways (for instance those related to insulin and leptin), disrupt cerebrovascular function (34), and impair the brain-blood barrier (34,73). In fact, interleukine-6 has been associated with reduced CT (73). Another potential mechanism underlying the link between risk factors and brain structure is insulin. Insulin modulates synaptic plasticity and the secretion of proinflammatory cytokines and is related to the formation of neurofibrillary tangles and aggregation of β-amyloid, both characteristics of Alzheimer's disease (73). Similarly, glucose and atherosclerosis are associated to the regulation of β-amyloid aggregation (73). However, it is worth noting that the direction of the causality (for instance, if obesity causes low-grade systemic inflammation or vice versa) is still not well understood (34).

Interestingly, the brain pattern captured by the latent dimension was not only related to cardiometabolic health, but also to the spatial distribution of several neurotransmitter systems. Specifically, the brain pattern was associated with the spatial distribution of the binding

potentials to serotonin receptor 5-HT1a (50,51), dopamine receptor D2 (23,57–59), dopamine transporter DAT (60), acetylcholine transporter VAChT (23,52,53), and GABA receptor GABAa (61). This indicates that the latent dimension captured a brain axis in which cortical regions that covaried the most with the pattern of risk factors (either positively or negatively) were those that showed either high or low binding potentials with these neurotransmitter receptors and transporters. This suggests that the clinically relevant interaction between brain and body health that has been called to attention recently (15,18) might be mediated by processes associated with neurotransmitter systems. Hence, our results join the body of evidence showing an overlap between physical illnesses and neuropsychiatric disorders, and the need of a holistic approach in clinical practice integrating body and brain factors instead of considering them as categorical entities (18).

Interestingly, these neurotransmitters associated to the latent dimension have in turn been linked to phenotypes related to the risk factors captured in the latent dimension. For instance, the serotoninergic system is associated with energy balance and feeding behavior (78,79), obesity (78), and physical activity (80). Specifically, the 5-HT1a receptor has been associated with food intake (79), anorexia nervosa and bulimia nervosa (81). The dopaminergic system has been associated with physical activity (80), and specifically, the receptor D2 has been associated with disorders related to eating behavior, such as anorexia nervosa, bulimia nervosa, and obesity (81). Overall, the evidence indicates that these neurotransmitter systems are associated with imbalances in energy homeostasis and feeding behavior, which are phenotypes related to the pattern of risk factors captured in our latent dimension.

Interestingly, evidence of the mechanistic cause linking neurotransmitter systems with both, risk factors for non-communicable diseases and brain structure, also points to inflammation. Several studies have shown a cross-talk between the immune system and several

neurotransmitter systems, such as serotoninergic, noradrenergic, dopaminergic (77,82), GABAergic (74), and cholinergic systems. For instance, certain neurotransmitter receptors, including 5-HT1a, D1 and D2, have immunologic functions (74,82), and can lead to the disruption of homeostasis (74) and to inflammation. Accordingly, immune cells express neurotransmitter receptors (82). In turn, immunological factors can regulate normal cellular functions, including neurotransmission and synaptic plasticity (74). In sum, the cross-talk between immunologic factors and neurotransmitter systems is bidirectional (74,82) and is relevant for several non-communicable diseases (82). Moreover, since these neurotransmitter systems are implicated in mental disorders and in somatic non-communicable diseases (74,76), the mechanisms underlying the comorbidity between mental and somatic disorders might be associated with alterations in neurotransmitter systems (66).

Conclusion

Our study shows a latent dimension linking cardiometabolic health to increases of CT in emotional and motivational systems and to reductions of CT in dorsal attention and executive systems. In turn, this brain pattern is associated with the cortical distribution of several neurotransmitter systems. Hence, our study shows that cardiometabolic health, brain structure, and neurotransmitter systems are interrelated, highlighting the multi-level nature of health. Our results underline the role of cardiometabolic health in brain health. Also, our work contributes to questioning the classic consideration of neuropsychiatric and somatic illnesses as separate categories (74) and supports the view of a needed integration of brain and physical health in clinical practice (15,18).

Declarations

Authors' contributions

ENS conceptualized the study, developed software, prepared data, performed analyses, and contributed to discussion and interpretation of results. SMB contributed to study conceptualization, data preparation, software development, and to interpretation and discussion of results. MM contributed to data preparation and software development. AM contributed to software and methodology development. FH contributed to data preparation and preprocessing. JMM contributed to software and methodology development. MT contributed to discussion and interpretation of results. SBE acquired funding and contributed to discussion and interpretation of results. SG acquired funding, conceptualized the study, and contributed to discussion and interpretation of results. The contribution of ENS has been done in partial fulfillment of the requirements for a Ph.D. thesis. All authors contributed to the revision of the manuscript. All authors contributed to writing and reviewing of the manuscript and approved the final version. ENS and SMB have accessed and verified the data.

Declarations of interest

The authors declare no competing interests.

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Data and code sharing statement

Access to UKB data is explained at https://www.ukbiobank.ac.uk/enable-your-research. The code used for the machine learning framework (https://doi.org/10.5281/zenodo.7153571) has been made publicly available at https://github.com/mlnl/cca_pls_toolkit

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Figure legends

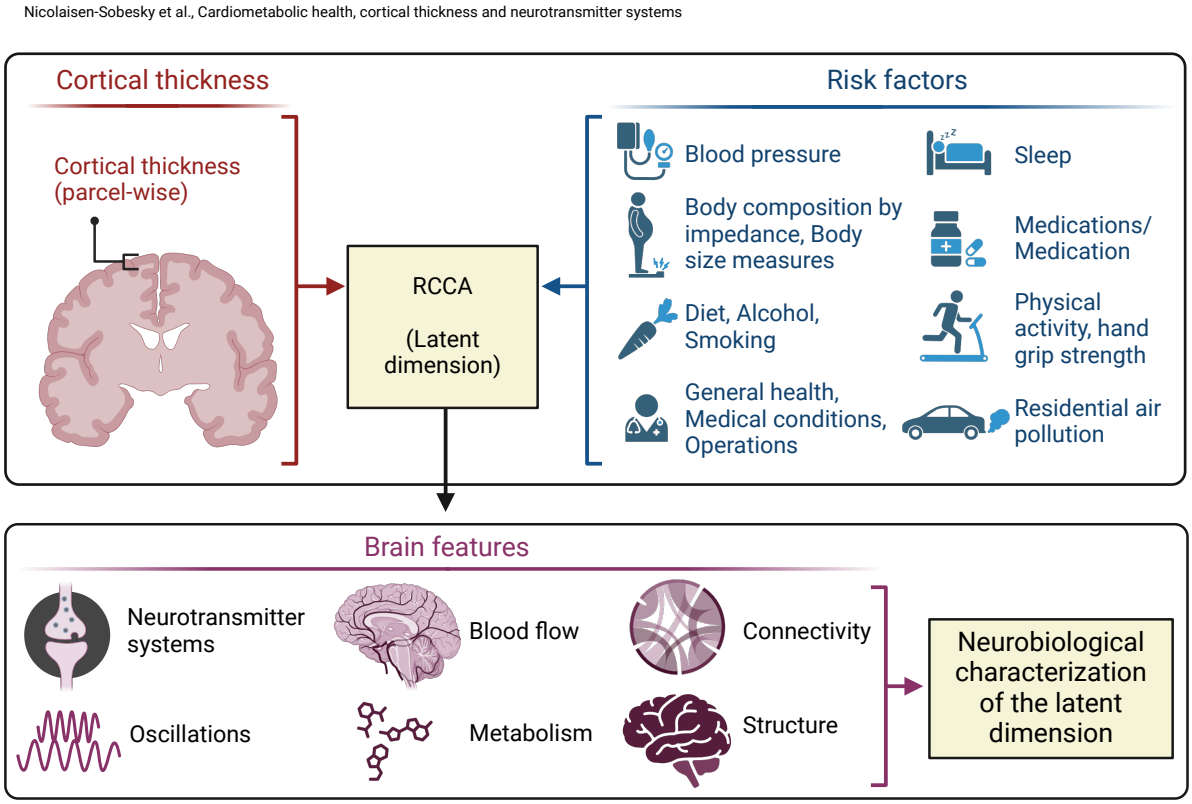
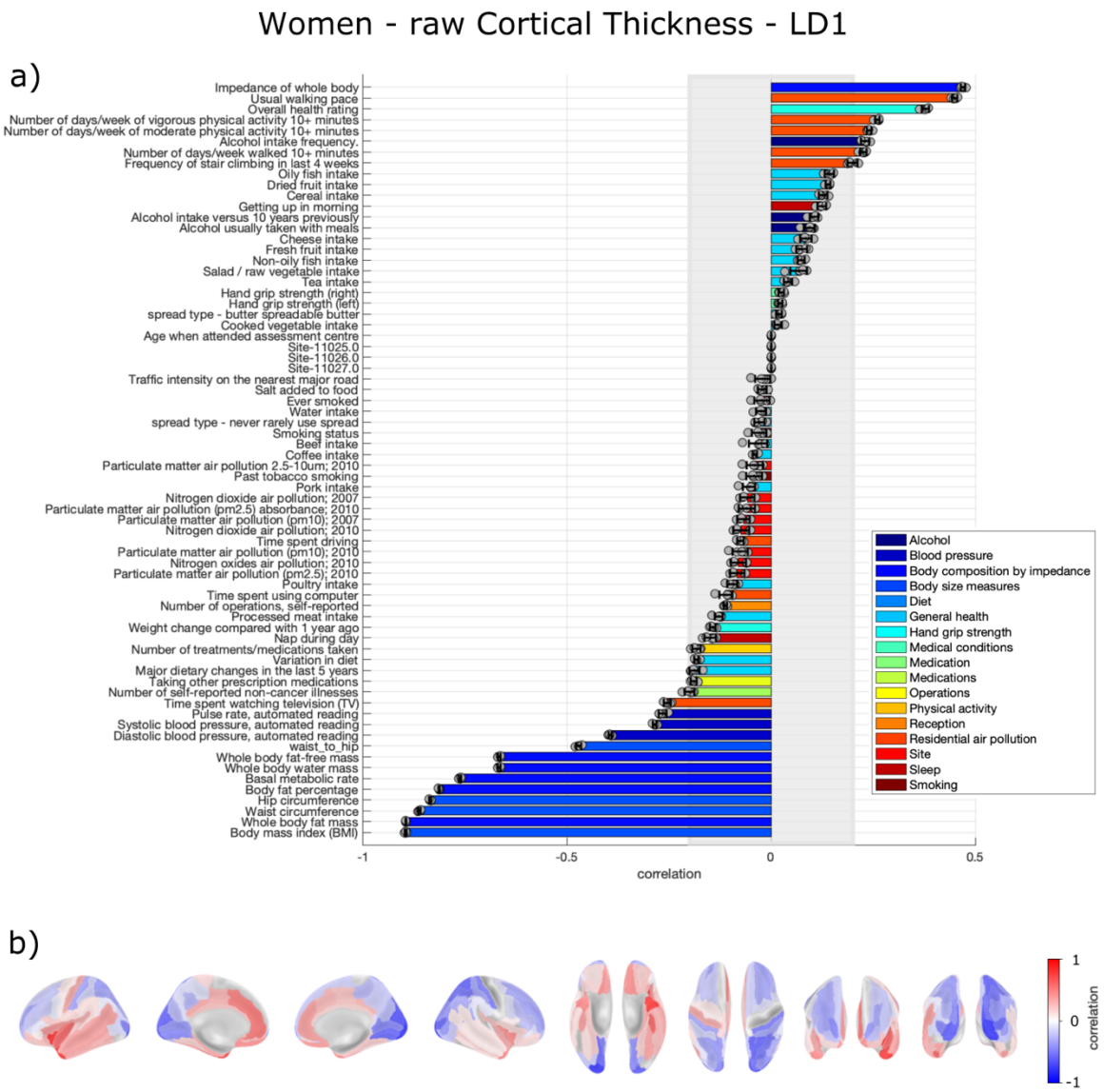
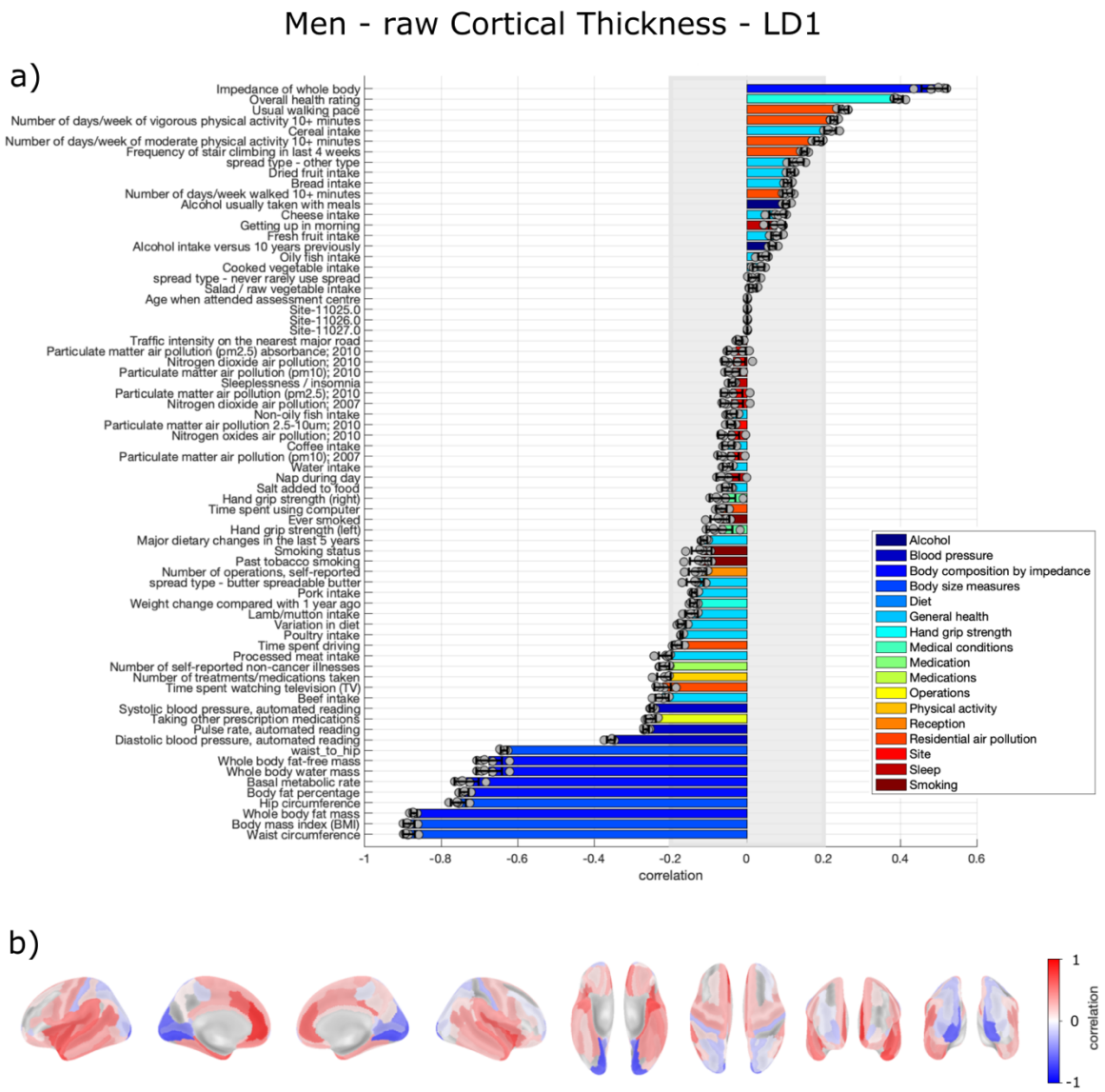


Figure 1. Overview of the analyses. Top panel: Latent dimensions were search using RCCA, linking cortical thickness measures (parcel-wise across the whole brain cortex) with a wide set of risk factors for non-communicable diseases. Below panel: In order to interpret the latent dimension, the brain loadings were compared with several brain features.



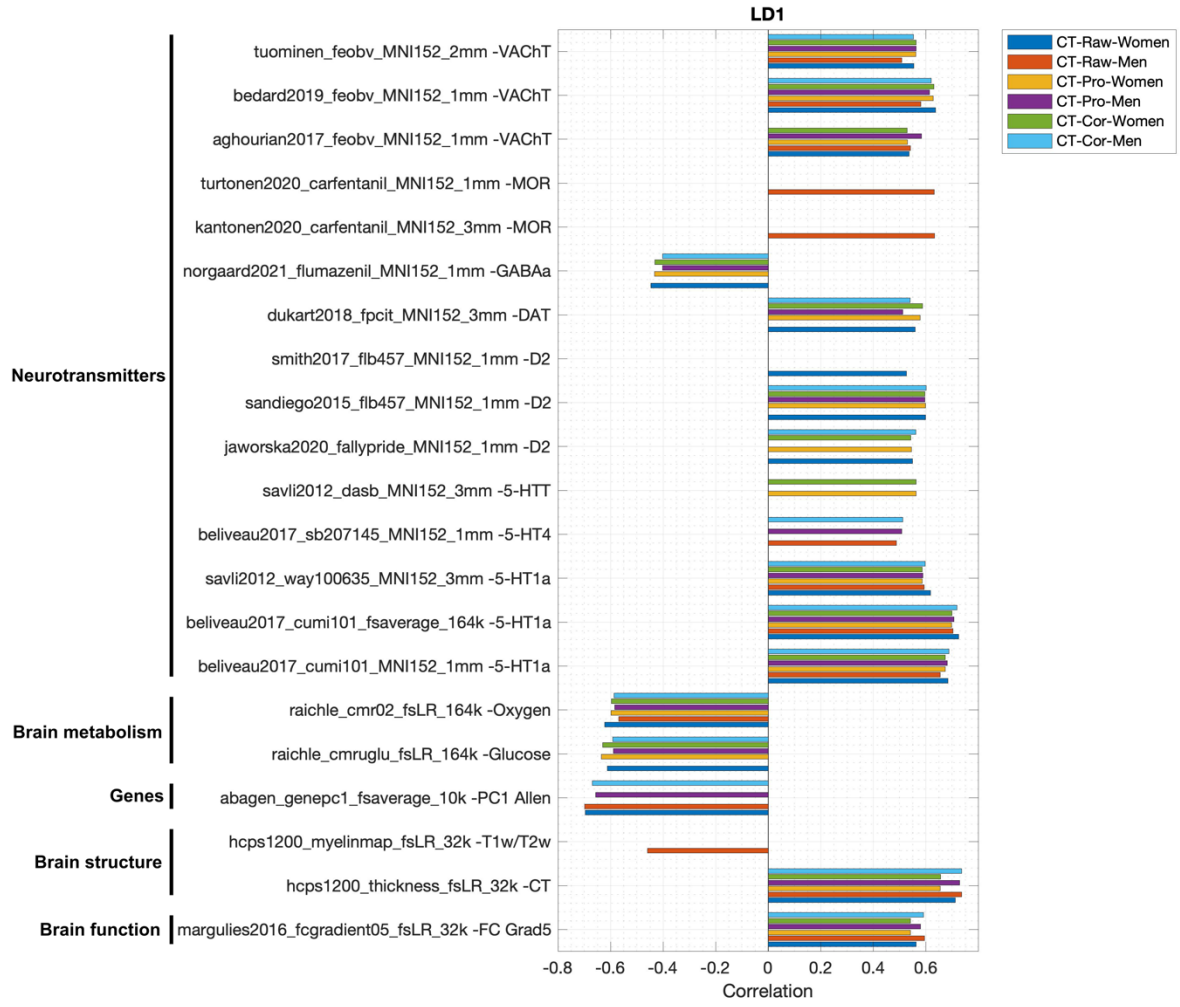
731

732 **Figure 2. Loadings of the first latent dimension from regularized canonical correlation**
733 **analysis between risk factors for non-communicable diseases and raw cortical thickness**
734 **in women.** a) Risk factors loadings. b) brain loadings. Shown loadings represent the average
735 over the five outer splits. Error bars depict one standard deviation. The shadowed zone marks
736 loadings between −0.2 and 0.2.



737

738 **Figure 3. Loadings of the first latent dimension from regularized canonical correlation**
739 **analysis between risk factors for non-communicable diseases and raw cortical thickness**
740 **in men.** a) Risk factors loadings. b) brain loadings. Shown loadings represent the average over
741 the five outer splits. Error bars depict one standard deviation. The shadowed zone marks
742 loadings between −0.2 and 0.2.



743

744 **Figure 4. Association of cortical thickness loadings with neuromaps for the first latent**
745 **dimension.** The association between the brain pattern of the first latent dimension and
746 neuromaps was assessed with spin test. Only data for neuromaps that yielded a significant
747 association with at least one CT loadings map of the first latent dimension are shown. CT:
748 cortical thickness; Pro: proportional; Cor: corrected

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Table 1. Correlation of CT loadings of the first latent dimension with brain maps.

Brain maps			Women						Men					
			Raw CT		Proportional CT		Corrected CT		Raw CT		Proportional CT		Corrected CT	
annotation	Category	Subcategory	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
margulies2016_fcgradient05_fsLR_32k	Brain function	FC Grad5	0.5631	**<0.001**	0.5948	**<0.001**	0.5420	**<0.001**	0.5797	**<0.001**	0.5420	**<0.001**	0.5906	**<0.001**
hcps1200_thickness_fsLR_32k	Brain structure	CT	0.7120	**<0.001**	0.7361	**<0.001**	0.6554	**<0.001**	0.7291	**<0.001**	0.6556	**<0.001**	0.7369	**<0.001**
hcps1200_myelinmap_fsLR_32k	Brain structure	T1w/T2w	-0.4068	>0.999	-0.4590	**<0.001**	-0.3329	>0.999	-0.3719	>0.999	-0.3375	>0.999	-0.3868	>0.999
abagen_genepc1_fsaverage_10k	Genetics	PC1 Allen	-0.6963	**<0.001**	-0.6986	**<0.001**	-0.6359	0.4675	-0.6572	**<0.001**	-0.6403	0.4675	-0.6694	**<0.001**
raichle_cmruglu_fsLR_164k	Metabolism	Glucose	-0.6119	**<0.001**	-0.4808	>0.999	-0.6360	**<0.001**	-0.5894	**<0.001**	-0.6307	**<0.001**	-0.5925	**<0.001**
raichle_cmr02_fsLR_164k	Metabolism	Oxygen	-0.6230	**<0.001**	-0.5696	**<0.001**	-0.5985	**<0.001**	-0.5848	**<0.001**	-0.5967	**<0.001**	-0.5868	**<0.001**
beliveau2017_cumi101_MNI152_1mm	Neurotransmitters	5-HT1a	0.6843	**<0.001**	0.6546	**<0.001**	0.6733	**<0.001**	0.6818	**<0.001**	0.6733	**<0.001**	0.6885	**<0.001**
beliveau2017_cumi101_fsaverage_164k	Neurotransmitters	5-HT1a	0.7249	**<0.001**	0.7033	**<0.001**	0.6983	**<0.001**	0.7068	**<0.001**	0.6995	**<0.001**	0.7188	**<0.001**
savli2012_way100635_MNI152_3mm	Neurotransmitters	5-HT1a	0.6180	**<0.001**	0.5934	**<0.001**	0.5854	**<0.001**	0.5890	**<0.001**	0.5863	**<0.001**	0.5973	**<0.001**
beliveau2017_sb207145_MNI152_1mm	Neurotransmitters	5-HT4	0.4501	>0.999	0.4878	**<0.001**	0.4355	>0.999	0.5083	**<0.001**	0.4370	>0.999	0.5117	**<0.001**
savli2012_dasb_MNI152_3mm	Neurotransmitters	5-HTT	0.5155	>0.999	0.3160	>0.999	0.5625	**<0.001**	0.4385	>0.999	0.5634	**<0.001**	0.4577	>0.999
jaworska2020_fallypride_MNI152_1mm	Neurotransmitters	D2	0.5494	**<0.001**	0.4991	>0.999	0.5451	**<0.001**	0.5493	0.9351	0.5431	**<0.001**	0.5613	**<0.001**
sandiego2015_flb457_MNI152_1mm	Neurotransmitters	D2	0.5987	**<0.001**	0.5536	>0.999	0.5982	**<0.001**	0.5959	**<0.001**	0.5964	**<0.001**	0.6019	**<0.001**
smith2017_flb457_MNI152_1mm	Neurotransmitters	D2	0.5262	**<0.001**	0.4938	>0.999	0.5110	0.4675	0.5168	0.9351	0.5095	0.4675	0.5256	0.9351

dukart2018_fpcit_MNI152_3mm	Neurotransmitters	DAT	0.5593	**<0.001**	0.3989	>0.999	0.5785	**<0.001**	0.5123	**<0.001**	0.5870	**<0.001**	0.5406	**<0.001**
norgaard2021_flumazenil_MNI152_1mm	Neurotransmitters	GABAa	-0.4466	**<0.001**	-0.3979	>0.999	-0.4326	**<0.001**	-0.4023	**<0.001**	-0.4314	**<0.001**	-0.4023	**<0.001**
kantonen2020_carfentanil_MNI152_3mm	Neurotransmitters	MOR	0.5254	>0.999	0.6327	**<0.001**	0.4366	>0.999	0.5148	>0.999	0.4413	>0.999	0.5223	>0.999
turtonen2020_carfentanil_MNI152_1mm	Neurotransmitters	MOR	0.4928	>0.999	0.6320	**<0.001**	0.4008	>0.999	0.4974	>0.999	0.4059	>0.999	0.5034	>0.999
aghourian2017_feobv_MNI152_1mm	Neurotransmitters	VAChT	0.5359	**<0.001**	0.5419	**<0.001**	0.5301	**<0.001**	0.5841	**<0.001**	0.5285	**<0.001**	0.5532	0.9351
bedard2019_feobv_MNI152_1mm	Neurotransmitters	VAChT	0.6376	**<0.001**	0.5811	**<0.001**	0.6284	**<0.001**	0.6144	**<0.001**	0.6309	**<0.001**	0.6208	**<0.001**
tuominen_feobv_MNI152_2mm	Neurotransmitters	VAChT	0.5538	**<0.001**	0.5087	**<0.001**	0.5621	**<0.001**	0.5627	**<0.001**	0.5633	**<0.001**	0.5531	**<0.001**

p-values are corrected using the Bonferroni method
r: Pearson’s correlation coefficient
HCP: Human Connectome Project
Significant results are in bold
Only results for neuromaps that yielded a significant association with at least one latent dimension are shown