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Large-scale georeferenced neuroimaging and psychometry data link the urban environmental exposome with brain health

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ABSTRACT

In face of cumulating evidence about the impact of human-induced environmental changes on mental health and behavior, our understanding of the main effects and interactions between environmental factors – i.e., the exposome and the brain – is still limited. We seek to fill this knowledge gap by leveraging georeferenced large-scale brain imaging and psychometry data from the adult community-dwelling population (n = 2672; mean age 63 ± 10 years). For monitoring brain anatomy, we extract morphometry features from a nested subset of the cohort (n = 944) with magnetic resonance imaging. Using an iterative analytical strategy testing the moderator role of geospatially encoded exposome factors on the association between brain anatomy and psychometry, we demonstrate that individuals' anxiety state and psychosocial functioning are among the mental health characteristics showing associations with the urban exposome. The clusters of higher anxiety state and lower current psychosocial functioning coincide spatially with a lower vegetation density and higher air pollution. The univariate multiscale geographically weighted regression identifies the spatial scale of associations between individuals' levels of anxiety state, psychosocial functioning, and overall cognition with vegetation density, air pollution and structures of the limbic network. Moreover, the multiscale geographically weighted regression interaction model reveals spatially confined exposome features with moderating effect on the brain-psychometry/cognitive performance relationships. Our original findings testing the role of exposome factors on brain and behavior at the individual level, underscore the role of environmental and spatial context in moderating brain-behavior dynamics across the adult lifespan.

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1. Introduction

Given the global longevity increase, the current focus on extending the healthy lifespan motivates research beyond the assessment of endogenous and lifetime factors towards understanding their interactions with social and environmental determinants – i.e. the exposome. Despite a mounting body of empirical evidence about the impact of exposome factors on aging-related cognitive and mental health decline, we still lack a detailed knowledge about the related brain-behavior outcomes (Xu et al., 2023a; Liu et al., 2023a). In this study, the emphasis is on the urban exposome, driven by the worldwide trend of growing populations living in towns and cities (Rydin et al., 2012).

In the context of brain health, the association between air pollution and depression is among the most replicated exposome risk factors, whilst the role of traffic noise, seasonal allergens, electro-magnetic fields, or pesticides remains controversial (Hao et al., 2022; Qin et al., 2011; Bagheri Hosseinabadi et al., 2019; Zanchi et al., 2023). The beneficial effects of city living on cognitive performance and psychosocial functioning, mainly related to higher social mobility and better access to healthcare, are opposed to the impact of chronic stress, sedentary lifestyle and easy access to high-fat, high-energy food (Dye, 2008; Engemann et al., 2018, 2019; Vassos et al., 2012). The proximity to green spaces, the levels of air pollution, traffic noise, and natural light exposure share a big proportion of variance and strongly depend on individuals' socio-economic status. These intersections render the interpretation of the unique and combined impact of urban and social exposome characteristics on brain health highly debatable (Generaal et al., 2019a, 2019b; Gonzales-Inca et al., 2022).

Although traditionally associated with low mood and high levels of anxiety (Costa e Silva and Steffen, 2019), the urban exposome may have beneficial mental health effects by promoting increased physical activity in the greener city areas (Schipperijn et al., 2017). Conversely, the built environment and lack of green spaces are linked to a higher risk of depression (Sokale et al., 2022). Meta-analyses confirm the initial observations of associations between air pollution and low mood, putting forward the augmented risk of depression due to short- and long-term effects of exposure to particulate matter (PM_{10}) and nitrogen dioxide (NO_2) (Zundel et al., 2022). The proposed underlying mechanisms are pollution-induced neuroinflammation, oxidative stress and cerebrovascular damage (Babadjouni et al., 2017) further linked to dysregulation of the hypothalamus-pituitary-adrenal axis (Blier, 2016; Li et al., 2017). Additional evidence comes from studies showing elevated cytokines plasma levels, similar to those observed in depression, after short- and long-term particulate matter exposure (Pope et al., 2016; Tsai et al., 2019). Complementing the research on the mental health effects, studies show associations between air pollution and resilience to cognitive decline mediated by decreased beta-amyloid burden (Ma et al., 2023). Along these lines, higher levels of residential greenness and attractive public spaces promoting social interaction are associated with slower aging-related cognitive decline (Clarke et al., 2015; de Keijzer et al., 2018), albeit not overcoming the impact of genetic risk for Alzheimer's disease (Zhu et al., 2020). These relationships remain controversial considering country-specific health and social welfare systems and the strong dependence on differential lifespan trajectories (Wang et al., 2023).

The well-established relationship between cognition, behavior and brain imaging-derived anatomy characteristics provides a foundational framework for interpretation of the neurobiological processes underlying the environmental impact on psychometry/cognitive performance outcomes (Polemiti et al., 2024). The cumulating evidence from imaging neuroscience studies offers unique insights into the links between exposome, lifetime factors, brain, and behavior (Liu et al., 2023b; van den Bosch and Meyer-Lindenberg, 2019; Wang et al., 2021; Yang et al., 2023; Olsen et al., 2017; Yeung et al., 2021). Air pollution and traffic noise are associated with brain atrophy in older adults (Nuβbaum et al., 2020), whilst multiple environmental exposome characteristics explain the specific neural activation patterns in stress processing networks (Lederbogen et al., 2011). Correspondingly, urban living influences cognition and behavior via its impact on brain volume and connectivity (Xu et al., 2023a; Glaubitz et al., 2022). These findings resonate previous reports about the moderating effect of family, school environment and social engagement on neighborhood deprivation linked to hippocampal volume and functional connectivity measures (Ku et al., 2022; Rakesh et al., 2021).

Despite major advances in the field, the imaging neuroscience studies using georeferenced data to investigate brain-environment associations reduce the rich geospatial information to descriptive and composite indices of "urbanicity" (Haddad et al., 2015), environmental categories (Kühn et al., 2017) or average values of a single environmental factor within a spatial buffer - e.g. tree cover density or sky view factor (Kühn et al., 2023a, 2023b), air pollution, traffic noise (Nuβbaum et al., 2020; Lucht et al., 2022). While the spatial correspondence between environmental factors and individuals' home address is implicitly included, the statistical analysis rarely incorporates subject-specific geocoded information that accounts for the geospatial heterogeneity of the data. As evident from studies on cardiovascular risk, infectious diseases (Oshan et al., 2020; Gaisie et al., 2022; Xu et al., 2023b; Asori et al., 2023) and affective disorders (Song et al., 2024; Stulz et al., 2018; Giordano et al., 2023; Moore et al., 2022; Rivera and Mollalo, 2022; Chen et al., 2023; Taylor et al., 2018), the impact of social and environmental exposome factors shows a significant geospatial heterogeneity that can be statistically formalized using spatial regression models (Giordano et al., 2023; Brown et al., 2018; Houlden et al., 2019).

Aiming to fill this knowledge gap, we systematically address the question whether anxiety levels, psychosocial functioning and overall cognitive performance will show a spatial dependence associated with environmental exposome factors and brain anatomy characteristics. We use georeferenced data in a spatial statistics' analytical framework to: i. identify spatial clusters of individuals with similar psychometry/cognitive performance, ii. analyze environmental exposome factors and gray matter volume differences across these spatial clusters, and iii. calculate the associations and interaction between the exposome, gray matter volume, and individuals' psychometry/cognitive performance in the geographical space.

2. Methods

2.1. Study design and population

We used data from the CoLaus|PsyCoLaus cohort, a longitudinal study in the community-dwelling population of Lausanne, Switzerland, initiated in 2003 with already three completed follow-ups. At baseline, the cohort involved 6734 individuals aged 35–75 years old (Firmann et al., 2008; Preisig et al., 2009). Given that the brain magnetic resonance imaging (MRI) acquisition started at the second follow-up (FU2) in 2014, we analyzed data collected between 2014 and 2018 from this follow-up. Our sample included only individuals from the urban center and less dense adjacent areas (see Fig. S1; Tables S1 and S2). The brain imaging nested cohort consisted of study participants that consented for an MRI (n = 1341; nmax = 944 after geographical selection and matching with corresponding psychometry/cognitive performance data; see Fig. S2).

2.2. Ethics

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of the Canton of Vaud (www.cer-vd.ch) approved the baseline CoLaus|PsyColaus study (reference 16/03; 134-03,134-05bis, 134-05-2to5 addendum 1 to 4). The approval was renewed for the first (reference 33/09; 239/09), the second (reference 26/14; 239/09 addendum 2), the third (PB_2018-00040; 239/09 addendum 3 to 4) and the fourth (PB_2018_0038 (239/

09)) follow-ups. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants signed a written informed consent.

2.3. Magnetic resonance imaging (MRI) data acquisition, processing, and quality control

We acquired magnetization transfer- (MTw), proton density- (PDw), and T1-weighted (T1w) images on a 3T whole-body MRI system (Magnetom Prisma, Siemens Medical Systems, Germany) (Trofimova et al., 2021) (for details on the MRI data acquisition protocol see Methods S1). The MT saturation and effective PD maps calculated with default settings (Taubert et al., 2020) were used to estimate probabilistic maps of gray matter (GM), white matter (WM) and cerebro-spinal fluid (CSF) in the framework of SPM12s (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK, www.fil.ion.ucl.ac.uk/spm) multi-channel "unified segmentation", running under Matlab 2019 (Mathworks, Sherborn, MA, USA). For optimal delineation of subcortical structures we used enhanced tissue priors (Helms et al., 2009). This was followed by an atlas-based parcellation of gray matter structures using factorization-based labeling (Yan et al., 2022) and calculation of regional averages of tissue volume. The atlas-based parcellation is based on the dataset from the MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labelling (Landman and Warfield, 2012; http://www.neuromorphometrics.com) and provides 72 cortical and subcortical labeled anatomical regions per hemisphere. The ROI selection in the study stems from the assumption of their specific involvement in mood disorders (Smagula and Aizenstein, 2016; Ancelin et al., 2019; Wang et al., 2016) and cognitive function (Helie et al., 2013; Tabatabaei-Jafari et al., 2015; Herrmann et al., 2019). The ROIs include both the left and right hemispheres of the accumbens area, caudate, pallidum, putamen, anterior cingulate gyrus, middle frontal gyrus, parahippocampal gyrus, substantia nigra, thalamus, amygdala, hippocampus, entorhinal cortex, and subcallosal area (see Table S3).

For image quality control, we used the established motion degradation index with a threshold $= 4.5 \times 10^{-3}$ ms^{-1} for the PD and T1w contrasts (Castella et al., 2018). All data surpassing the threshold were visually inspected by two experienced imaging neuroscientists reaching 94% agreement, which resulted in excluding 17 participants from the final analysis. Aiming at automated detection of macroscopic brain abnormalities – silent ischemic lesions, benign tumors etc., we created individual tissue class specific binary mask and compared the number of voxels to a canonical group-average tissue map. Among the individuals with less voxels in each tissue class, we identified those surpassing the mean number of voxels +2 SD, excluding 46 additional individuals from the final analysis.

2.4. Psychometry and cognitive assessment

For assessment of anxiety levels, we used the State and Train Anxity Inventory (STAI) (Spielberger et al., 1983), which includes two scales: STAI state [STAI_s] and STAI trait [STAI_t] sub-scores. For each of the two scales, the sum of the item scores was computed to obtain a final score ranging between 20 and 80, with higher values corresponding to higher levels of anxiety. As an indicator for psychosocial functioning we used the Global Assessment of Functioning (GAF) assessing the lifetime [GAF_l], worst [GAF_w] and current [GAF_c] states (Bell, 1994). Higher GAF scores translate into a better overall functioning. We tested individuals' global overall cognitive performance with the Mini Mental State Examination – MMSE (Folstein et al., 1975). The test administration was restricted to individuals aged 60 years and older (see Tables S4 and S5).

2.5. Adjustment for confounding factors

For all analyses, we adjusted the psychometry and cognitive data for the confounding effects of age, sex, educational level, last occupational position recorded and income category at the time of the FU2 assessment. Educational levels were categorized into primary (1), secondary (2), and tertiary (3). Last occupational position was classified as low (1), middle (2), high (3). Finally, income categories were defined as $\leq$ 4999 CHF (1), 5000–9499 CHF (2), >9500 CHF (3).

We used imputation to compensate for missing income values. We observed 991 missing values - out of 4115 total individuals geocoded in the geographic area of interest - in our study sample for the income categorical variable. To handle missing data, we used predictive categorical imputation, leveraging neighborhood income, education level, last job occupation, age, and sex as predictors (Lee et al., 2012). The OneVsRestClassifier with a LinearSVC model, implemented through the scikit-learn package (version 1.5.2), was used to impute values for 977 cases (Pedregosa et al., 2011; Vapnik et al., 1996). For the remaining 14 instances, where fewer than three predictors were available, we imputed the income category based on the strongest single predictor (in order of last occupational position, education, or neighborhood income), given the strong Spearman's rank correlation observed between these variables and income (Lee et al., 2012; Schafer and Graham, 2002). For individuals in the area of interest with available psychometry/cognitive performance outcomes, the imputation resulted in the following extra number of individuals retained in the dataset compared to the case where no imputation was performed: STAI_s: N = 252 (14.55% increase); STAI_t: N = 178 (12.59%); MMSE: N = 225 (19.74%); GAF_l: N = 371 (16.12%); GAF_w: N = 371 (16.13%) (see Fig. S2). The missing SES values in Fig. S2 correspond to individuals for whom a complete SES profile could not be obtained, even after income imputation.

We performed the adjustments before conducting any spatial analysis. All results presented in this study use the psychometry and cognitive health outcomes that have already been adjusted for the confounding factors introduced in this section.

2.6. Georeferencing and exposome data

We georeferenced participants at their current home address using the geospatial information of the Swiss Confederation via its API REST services. Using the QGIS software (version 3.10.11) we extracted the following variables: i. night-time traffic noise (road and rail); ii. Vegetation density as quantified by the Normalized Difference Vegetation Index (NDVI) and by the Atmospherically Resistant Vegetation Index (ARVI); iii. Incoming solar radiation using the Total Solar Insolation (TSI) and Daily Duration of Insolation (DDI); and iv. Atmospheric pollution using Nitrogen Dioxide (NO_2) and Particulate Matter (PM_{10}) averaged considering circular buffers of 25 m, 50 m, 100 m, 200 m, 400 m, 500 m, 600 m, 800 m, 1000 m, 1250 m and 1500 m around the participants' addresses. We also calculated the minimum walking time to reach the closest public transport stops from each individual address using OpenStreetMap data and the OSMnx Python package (Boeing, 2017) (see Methods S2-S6 for details). We imputed missing data using the median of the particular variable.

2.7. Spatial statistics

2.7.1. Clustering and variance analysis

We used the PySAL (v.4.6.0) Python library suite (Rey and Anselin, 2007) to calculate the Getis-Ord G_i^* (Getis) (Getis and Ord, 1992) and the Univariate Local Moran's I (Moran) clustering statistics (Anselin, 1995). The Getis statistic measures spatial dependence by identifying local clusters in the spatial arrangement of a variable (here, psychometry/cognitive performance). Getis compares the sum of the individuals' psychometry/cognitive performance values within a spatial lag proportionally to the sum of values across the entire study area (Getis

and Ord, 1992). The null hypothesis assumes a random spatial distribution of the values analyzed. The Getis statistic is a Z score. Statistically significant positive and negative Z scores are representative of hot spots (HS) – clusters of high values, and cold spots (CS) – clusters of low values, respectively. Neutral sampling sites are labeled non-significant (NS).

The Moran statistic also assesses spatial dependence by evaluating clustering in geographic space. It is based on the statistical index I developed by Moran (1950), which measures the global spatial autocorrelation of the data in the area under investigation. Moran's I ranges from −1 (negative spatial autocorrelation – or dispersion) to 1 (complete spatial dependence – or clustering), with a value of 0 indicating the absence of spatial dependence. The Moran method introduces two additional classes, compared to Getis, to identify dissimilar values within the local high and low spots (high–low and low–high). This refinement prevents the misclassification of individuals in areas with relatively high numbers of dissimilar neighbors. Classification in both Getis and Moran statistics is based on significance testing, using random Monte-Carlo permutations, which shift the values between sample locations. These permuted values are then compared to the observed Getis or Moran statistics (see details in (Anselin, 1995)). In this study, statistical significance testing was based on a conditional randomization procedure using a sample of 999 permutations (Anselin, 1995). All maps shown in this paper correspond to a significance level of 0.05. For sensitivity analysis, we calculated both cluster statistics using spatial lags of 400 m, 500 m, 600 m and 800 m following values used in prior health related investigations (Joost et al., 2018) and aligning with self-assessed or perceived neighborhood boundaries (Perchoux et al., 2016).

We applied the clustering analysis to each psychometry/cognitive performance outcome separately, rather than to a combined psychometric profile. This approach allowed us to map clusters of high and low values in space for each specific outcome variable. For each cluster obtained from the Getis and Moran statistics, we calculated the average of the environmental exposome factors and brain anatomy volumes. To assess the homogeneity of variance across clusters we applied the Levene's test (Levene, 1960). When the assumption of homogeneity was respected, we proceeded with one-way ANOVA and the subsequent Tukey post-hoc test for multiple pairwise comparisons. Conversely, for data exhibiting heterogeneity, we implemented a one-way Kruskal--Wallis test, followed by a post-hoc Conover test. To account for multiple testing, we applied the Holm method for p-value adjustment.

To optimize the identification of clusters' spatial lags and environmental exposome factors measuring buffers showing stronger effect, we classified the significant results from the ANOVA and Kruskal-Wallis tests by their effect size. We set thresholds of 0.06 and 0.14 to highlight medium to large effect sizes (Cohen, 1988; Miles and mark, 2001).

2.7.2. Spatial regression analysis

We used the multiscale geographically weighted regression (MGWR) method with the mgwr Python library (version 2.1.2) to test for associations between the exposome, brain anatomy, and psychometry/cognitive performance outcomes. The MGWR builds upon the geographically weighted regression (GWR). GWR differs from a conventional OLS regression by accounting for the underlying spatial processes in the analysis, allowing them to vary with geographic context and therefore not assuming constant relationships across the study area (Fotheringham et al., 2003). GWR integrates the spatial component by calculating parameter estimates at each location of interest (here, the participants' home addresses), through location-specific regressions, where a weighting scheme is used to give more influence to nearby data points.

MGWR extends GWR by allowing distinct bandwidths to be associated with each covariate in the model, rather than applying the same for each relationship. This means that the influence of each covariate can vary at different spatial scales, better capturing the spatial heterogeneity within and across processes. Advantages of MGWR include minimizing overfitting, mitigating concurvity (correlated predictors), and producing more accurate spatial relationships (Oshan et al., 2019, 2020; Fotheringham et al., 2017; Yu et al., 2020; Wolf et al., 2018).

To account for multiple hypothesis testing due to the various sets of parameter estimates produced using overlapping subsets of data, the alpha threshold is adjusted within MGWR, making it more conservative than a standard 0.05 threshold (Oshan et al., 2020). Additionally, since the bandwidths used are covariate-specific, MGWR allows for the calculation of adjusted alpha and t-values for each modeled relationship (Oshan et al., 2019). Finally, response and explanatory variables are standardized before implementing MGWR so that the bandwidths are not influenced by the scale of the variables, facilitating the comparison between them (Fotheringham et al., 2017).

This analysis is independent from the cluster analysis but complementary to it, in line with the need for both exploratory (Getis and Moran) and confirmatory (MGWR) statistics in spatial analysis (Tukey, 1980). The spatial clustering identified areas with significantly high and low values of psychometry/cognitive performance, confirming the presence of spatial dependence and enabling to assess mean differences in exposures and brain anatomy across these clusters. The existence of spatial dependence justifies the usage of a spatial regression method, which makes it possible to quantify the associations between exposures, brain anatomy and psychometry/cognitive performance outcomes, allowing for a more detailed understanding of how these relationships vary spatially. By integrating regression coefficients into spatial contexts, MGWR provides a nuanced perspective on the associations.

We conducted the MGWR analyzes using a bi-square kernel function to allocate weights around each calibration point. We selected an adaptive bandwidth (see Methods S7 on the difference between spatial lag and bandwidth), guaranteeing an equal number of sampled observations when estimating the local regression (Fotheringham et al., 2003).

We implemented three types of models to calculate the diverse associations between the environmental exposome factors (EEF), adjusted psychometric and cognitive outcomes, and brain ROIs:

$$y_{STAI\_s|STAI\_t|GAF\_c|GAF\_l|GAF\_w|MMSE\ adjusted}(i) = \widehat{\beta}_{bw_0(i)} + \widehat{\beta}_{bw_1(i)} X_{EEF,1}(i) + \varepsilon(i), i \in \{1, 2, \ldots, n\} \quad (1)$$

$$y_{STAI\_s|STAI\_t|GAF\_c|GAF\_l|GAF\_w|MMSE\ adjusted}(i) = \widehat{\beta}_{bw_0(i)} + \widehat{\beta}_{bw_1(i)} X_{ROI,1}(i) + \varepsilon(i), i \in \{1, 2, \ldots, n\} \quad (2)$$

$$y_{STAI\_s|STAI\_t|GAF\_c|GAF\_l|GAF\_w|MMSE\ adjusted}(i) = \widehat{\beta}_{bw_0(i)} + \widehat{\beta}_{bw_1(i)} X_{EEF,1}(i) + \widehat{\beta}_{bw_2(i)} X_{ROI,2}(i) + \widehat{\beta}_{bw_3(i)} \left[Z(X_{EEF,1}(i)) * Z(X_{ROI,2}(i)) \right] + \varepsilon(i), i \in \{1, 2, \ldots, n\} \quad (3)$$

Equations (1)–(3) delineate three distinct models wherein the psychometric and cognitive variables are the dependent variables (see Methods S8 for details). In equations (1) and (2), we used the environmental exposome factors and brain ROIs as predictors, respectively. Specifically, in equations (1) and (3), we determined the single optimal

buffer radius for calculating the average value of each environmental exposome factor around a subject's home address. This selection was based on the models that yielded the lowest Akaike Information Criterion corrected (AICc), indicating the most efficient model fit.

In the multivariate interaction model presented in equation (3), we used the average values of the environmental exposome factors calculated within the single optimal buffer radius, in conjunction with each brain ROI. The interaction term was obtained by multiplying the standardized values of environmental exposome factors with those of the brain ROIs.

Subsequently, we derived parameter estimates for the interaction term for each subject and focused our analysis on those with significant regression coefficients. We analyzed each of these subjects individually, considering their unique set of covariate coefficients as determined by the MGWR. We plotted the conditional association of brain ROIs with psychometric and cognitive variables across various environmental exposome factors. For this, we incorporated into equation (3) the variable values from the selected nearest neighbors and the uniquely calculated covariate coefficients. Applying the Johnson-Neyman technique (Johnson and Fay, 1950), we identified specific value ranges of the moderating environmental exposome factors where the brain ROIs were significantly associated with psychometry and cognition. Lastly, for each relationship, we averaged these significance ranges, the corresponding thresholds of the exposome's moderating effect, and the conditional slopes of the brain-behavior associations for all subjects with significant interaction terms.

2.8. Exposures additive effects analysis

We complemented our analyses with a Weighted Quantile Sum (WQS) regression with two indices to assess multiple additive effects of the exposures on the adjusted psychometry/cognitive outcomes, while accounting for correlation between exposures (Renzetti et al., 2023).

3. Results

3.1. Clustering and variance analysis

The classification by effect size of the ANOVA and Kruskal-Wallis significant tests, involving environmental exposome factors across

Table 1
Results of ANOVA and Kruskal-Wallis tests for environmental exposome factors' (EEF) variance across Getis and Moran clusters of adjusted anxiety state [STAI_s] and current psychosocial functioning [GAF_c]. Highest effect size (η^2) results from Fig. 1 are reported.

Variance test	cluster analysis	PCV (Spatial lag)	EEF (buffer radius)	Test statistics	p-value	η^2
ANOVA	GETIS	STAI_s (400 m)	ARVI [-] (500 m)	F(2,1970), 133.24	<0.001	0.12
ANOVA	GETIS	GAF_c (500 m)	ARVI [-] (500 m)	F(2,2664), 95.77	<0.001	0.07
ANOVA	MORAN	STAI_s (400 m)	ARVI [-] (500 m)	F(4, 1968), 64.34	<0.001	0.12
ANOVA	MORAN	GAF_c (500 m)	ARVI [-] (500 m)	F(4, 2662), 50.21	<0.001	0.07
K-W	GETIS	STAI_s (800 m)	PM_{10} [µg/m³] (1500 m)	χ^2(2, N = 1984), 222.13	<0.001	0.11
K-W	MORAN	STAI_s (800 m)	PM_{10} [µg/m³] (1500 m)	χ^2(2, N = 1984), 239.13	<0.001	0.12
K-W	MORAN	GAF_c (800 m)	NDVI [-] (400 m)	χ^2(4, N = 2672), 193.05	<0.001	0.07

Key: ANOVA, analysis of variance; K-W, Kruskal–Wallis test; PCV, psychometric and cognitive variables; EEF, environmental exposome factor; ARVI, Atmospherically Resistant Vegetation Index; NDVI, Normalized Difference Vegetation Index; PM_{10}, particulate matter under 10-µm; STAI_s, anxiety state; GAF_c, current psychosocial functioning; F, F-statistic for ANOVA test; χ^2, chi-square statistic for K-W test; η^2, effect size.

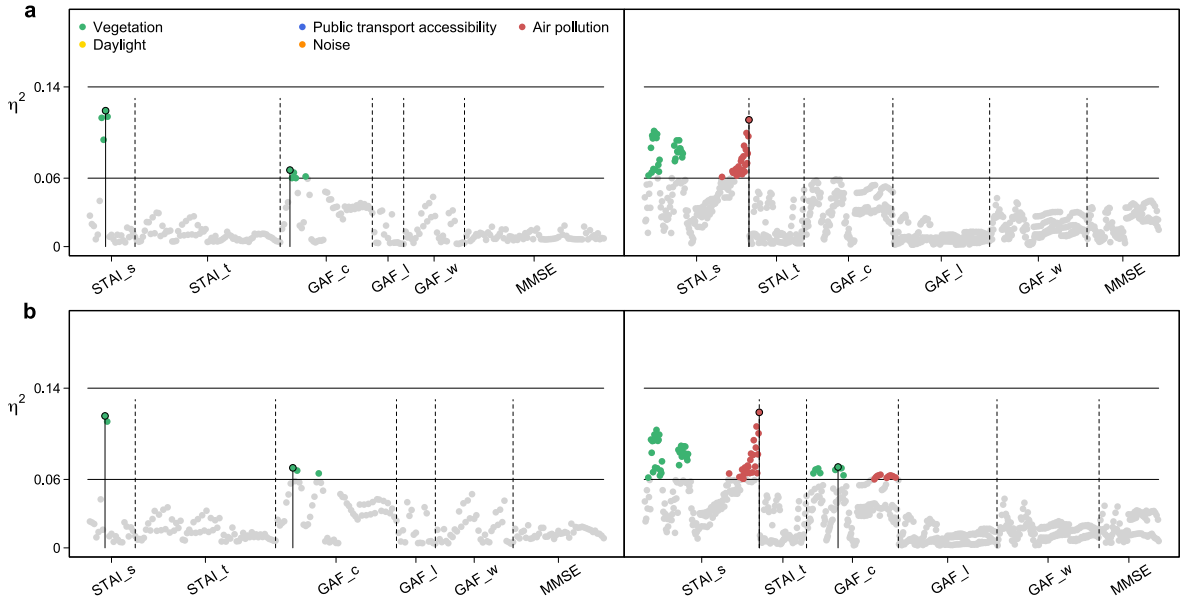

Fig. 1. Manhattan plot of the effect sizes. Effect sizes of the Analysis of variance (ANOVA) (**a** and **b** left-hand panel) and Kruskal-Wallis (K–W) tests (**a** and **b** right-hand panel) for the environmental exposome factors variance analyses across Getis (**a**) and Moran (**b**) clusters of adjusted anxiety state [STAI_s], anxiety trait [STAI_t], current psychosocial functioning [GAF_c], lifetime psychosocial functioning [GAF_l], worse ever psychosocial functioning [GAF_w] and overall cognitive performance (MMSE). Horizontal lines represent medium ($\eta^2 = 0.06$) and high ($\eta^2 = 0.14$) effect size thresholds. Significant results with medium to high effect size ($\geq$0.06) are highlighted: Normalized Difference Vegetation Index (NDVI) and Atmospherically Resistant Vegetation Index (ARVI) (green), particulate matter under 10-µm (PM_{10}) and nitrogen dioxide (NO_2) (red). Significant tests with effect size <0.06 are in gray: public transport accessibility, Total Solar Insolation (TSI) and Daily Duration of Insolation (DDI), night-time road and rail noise.

clusters of psychometric and overall cognitive performance, is presented in Fig. 1. The brain ROIs' variance tests effect size estimates, all falling below the fixated 0.06 medium threshold, are detailed in Fig. S3.

We observed variance results exceeding the 0.06 medium effect size threshold across cluster classes of both the anxiety state [STAI_s], and the current level of functioning assessed with the GAF_c, for vegetation measurements, as quantified by the Atmospherically Resistant Vegetation Index (ARVI) and Normalized Difference Vegetation Index (NDVI), and air pollution (primarily PM_{10} over NO_2) (see Fig. 1; Table 1; Tables S6-S9). Detailed Getis and Moran cluster maps for all spatial lags are provided in Figs. S4-S7.

Based on the classification of the variance analysis (Fig. 1) we present selected results from the clustering analysis in Fig. 2. We found a significant spatial dependence for both the anxiety state [STAI_s], and the current level of psychosocial functioning [GAF_c]. Among the individuals assessed with STAI_s, 158 (8.0%) belonged to a HS, 127 (6.4%) to a CS, and 1696 (85.6%) presented no spatial dependency (NS). We identified two primary hot spots of anxiety state near the city center, extending towards the east and northwest and two cold spots in the northern and eastern areas (see Fig. 2a). For the GAF_c, 109 individuals (4.1%) were in a HS, 88 (3.3%) in a CS, and 2470 (92.6%) showed no spatial dependency (NS). We found a primary cold spot of reduced current psychosocial functioning with lower GAF_c in the city center, and smaller hot spots in the southwestern, northern, and eastern parts of the city (see Fig. 2f).

Variance analysis of vegetation density and particulate matter under 10-μm (PM_{10}) within buffer radii of 400 m (see Fig. 2b and d) calculated across the anxiety state clusters showed medium effect sizes ($0.06 \leq \eta^2 < 0.14$). Vegetation density exhibited a dose-response effect: average ARVI levels were lower, whilst the air pollution concentrations were

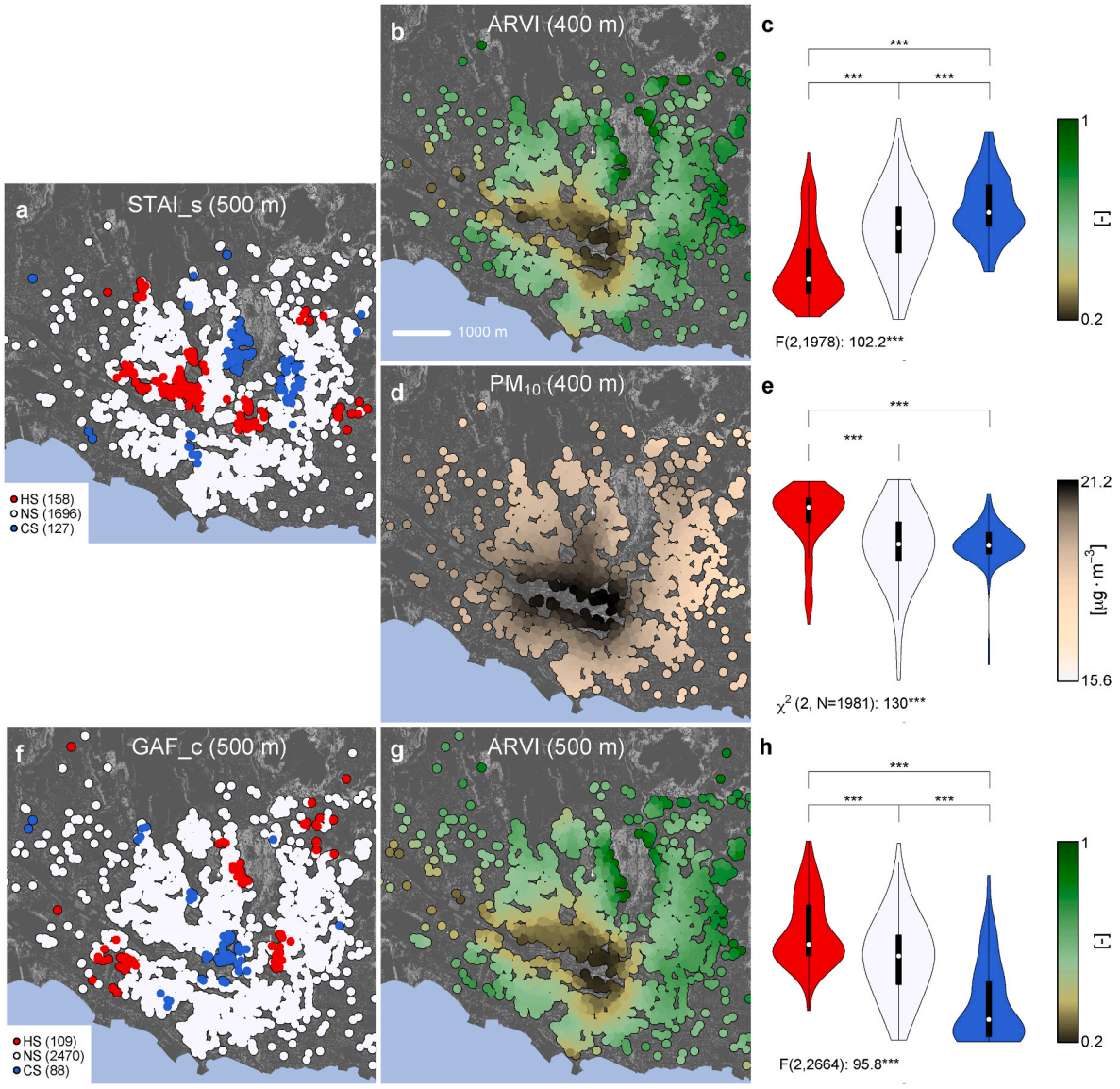

Fig. 2. Spatial clusters of adjusted anxiety state [STAI_s] and current psychosocial functioning [GAF_c] and spatial distribution of environmental exposome factors in Lausanne, Switzerland. **a**, **f** Getis clusters of STAI_s and GAF_c, with hot spots (HS) in red, cold spots (CS) in blue and non-significant (NS) in white, using 500 m spatial lags. **b**, **d**, **g** Average Atmospherically Resistant Vegetation Index (ARVI) levels within buffer radii of 400 m and 500 m and particulate matter under 10-μm (PM_{10}) levels within 400 m around home addresses. **c**, **e**, **h** Violin plots of ARVI and PM_{10} distribution across the Getis clusters with variance analysis significance indicated: $p < 0.001$ (***). The effect sizes for these analyses are $\eta^2 = 0.09$ for ARVI and $\eta^2 = 0.06$ for PM_{10} across STAI_s, and $\eta^2 = 0.07$ for ARVI across GAF_c clusters. F statistic is used for the Analysis of variance (ANOVA) and chi-square (χ^2) for Kruskal-Wallis (K–W). Box plots within the violin plots show the median, as a white dot, and interquartile range. Width of the violin plot shows the density of observation at that value. Upper and lower boundaries of violin plots represent the maximum and minimum values, respectively.

Table 2
Results of group-comparison tests involving the environmental exposome factors (EEF) across the Getis spatial clusters (HS: hot spots; CS: cold spots; NS: non-significant spots) of adjusted anxiety state [STAI_s] and current psychosocial functioning [GAF_c] depicted in the boxplots of Fig. 2. The mean difference of EEF between cluster groups is also reported.

EEF (buffer radius)	PCV (spatial lag)	Getis cluster group 1 (Number of subjects; %)	Getis cluster group 2 (Number of subjects; %)	EEF mean value in GCG1 (±SD)	EEF mean value in GCG2 (±SD)	Mean difference (GCG2-GCG1)	[95% CI]	p-value
ARVI [-] (400 m)	STAI_s (500 m)	NS (1696; 85.6%)	HS (158; 8.0%)	0.54 (±0.15)	0.39 (±0.15)	−0.14	[−0.17 to −0.12]	<0.001
ARVI [-] (400 m)	STAI_s (500 m)	NS (1696; 85.6%)	CS (127; 6.4%)	0.54 (±0.15)	0.63 (±0.12)	0.09	[0.06–0.12]	<0.001
ARVI [-] (400 m)	STAI_s (500 m)	HS (158; 8.0%)	CS (127; 6.4%)	0.39 (±0.15)	0.63 (±0.12)	0.23	[0.19–0.27]	<0.001
PM_{10} [μg/m^3] (400 m)	STAI_s (500 m)	NS (1696; 85.6%)	HS (158; 8.0%)	19.35 (±0.99)	20.15 (±0.85)	0.81	[–]	<0.001
PM_{10} [μg/m^3] (400 m)	STAI_s (500 m)	NS (1696; 85.6%)	CS (127; 6.4%)	19.35 (±0.99)	19.37 (±0.58)	0.03	[–]	0.951
PM_{10} [μg/m^3] (400 m)	STAI_s (500 m)	HS (158; 8.0%)	CS (127; 6.4%)	20.15 (±0.85)	19.37 (±0.58)	−0.78	[–]	<0.001
ARVI [-] (500 m)	GAF_c (500 m)	NS (2470; 92.6%)	HS (109; 4.1%)	0.53 (±0.14)	0.64 (±0.14)	0.10	[0.07–0.14]	<0.001
ARVI [-] (500 m)	GAF_c (500 m)	NS (2470; 92.6%)	CS (88; 3.3%)	0.53 (±0.14)	0.36 (±0.15)	−0.18	[−0.21 to −0.14]	<0.001
ARVI [-] (500 m)	GAF_c (500 m)	HS (109; 4.1%)	CS (88; 3.3%)	0.64 (±0.14)	0.36 (±0.15)	−0.28	[−0.33 to −0.23]	<0.001

Key: GCG1, Getis Cluster Group 1; GCG2, Getis Cluster Group 2; PCV, psychometric and cognitive variables; EEF, environmental exposome factor; PM_{10}, particulate matter under 10-μm; ARVI, Atmospherically Resistant Vegetation Index; STAI_s, anxiety state; GAF_c, current psychosocial functioning; HS, hot spot; CS, cold spot; NS; non-significant.

higher in hot spots ($p < 0.001$) (see Fig. 2c and e; Table 2). Variance analysis of vegetation density ARVI at a 500 m buffer radius (see Fig. 2g) across current psychosocial functioning clusters had a medium effect size with a dose-response effect, where average ARVI levels were significantly higher in hot spots ($p < 0.001$) (see Fig. 2h; Table 2).

The lifetime and worse ever psychosocial functioning [GAF_l, GAF_w], anxiety trait [STAI_t] and overall cognitive performance (MMSE) showed specific patterns of spatial dependence (see Figs. S8-S15) but did not meet the effect size criterion set for the significant environmental exposome factors variance analysis. Similarly, there were no significant brain volume differences with effect size ≥0.06 across the psychometry and overall cognitive performance clusters (see Fig. S3).

3.2. Psychometric and cognitive performance associations with the environmental exposome

The vegetation indices NDVI and ARVI showed a positive association with the current levels of psychosocial functioning [GAF_c] and overall cognitive performance (MMSE). The vegetation index ARVI and the quantity and duration of sunlight at home, assessed with Total Solar Insolation (TSI) and Daily Duration of Insolation (DDI), were negatively associated with both anxiety trait and current levels of anxiety [STAI_t and STAI_s]. The vegetation index NDVI was also negatively associated with current levels of anxiety [STAI_s]. The air pollution levels of PM_{10} and NO_2, were negatively associated with current psychosocial functioning [GAF_c] and positively associated with the current anxiety levels [STAI_s]. Night-time traffic noise was associated negatively with overall cognitive performance (MMSE) and positively with the current anxiety levels [STAI_s] (see Table 3). These associations exhibited varying spatial patterns throughout the city, with significant regression coefficients appearing in different locations for each relationship. Additionally, we report that the association between the duration of sunlight at home (DDI) and the anxiety trait [STAI_t] occurred at a global geographical scale, whilst all other significant associations showed local dependence, involving fewer than 10% of individuals (see Fig. 3).

3.3. Psychometric and cognitive performance associations with environmental exposome mixture

Corroborating our previous results, the mixed exposures models showed significant association with the anxiety state (STAI_s). Here, the mixed exposures demonstrated a negative association with the outcome, interpreted as reduction of the anxiety state in the urban context. The models testing for associations with metrics of psychosocial functioning - GAF and overall cognition – MMSE, did not result in significant findings, which we interpret as lack of strong evidence for combined or synergistic effects of the studied environmental exposures. The results are available as Supplementary material (see Fig. S16-S29; Tables S10-S23).

3.4. Psychometric and cognitive performance associations with brain anatomy

The analysis testing for the spatially distributed associations between brain anatomy, and psychometry/cognitive variables across the city showed negative associations between the current level of anxiety [STAI_s] and the left amygdala, bilateral entorhinal cortex, and left thalamus volumes. Additionally, we found negative associations between the overall cognitive performance assessed with the MMSE and the bilateral substantia nigra volumes, and positive – with the left entorhinal cortex and thalamus (see Fig. 4 and Table 4).

3.5. MGWR multivariate interaction analysis

The multivariate interaction analysis confirmed the negative main effect associations between the left amygdala, bilateral entorhinal cortex, left thalamus volumes and the anxiety state [STAI_s], and the main effects of the bilateral substantia nigra, left entorhinal cortex and thalamus volumes on overall cognitive performance (MMSE). Whilst the brain anatomy main effect associations with STAI_s remained significant across all environmental exposome factors, the significance of associations with MMSE varied according to individual factors (see Table S24).

We found night-time traffic noise to interact with the right

Table 3
Results of the univariate multiscale geographically weighted regression (MGWR) predicting adjusted psychometric and overall cognitive performance variables (PCV) with environmental exposome factors (EEF). Results are reported as the mean of the parameter estimates, averaging the values of the regression coefficients of the significant subjects.

PCV	EEF (buffer radius)	adjusted alpha	Mean of regression coefficients (±SD)	Min regression coefficient	Max regression coefficient	Number of significant subjects	Number of non-significant subjects	MGWR bandwidth	Adjusted R^2
STAI_s	L_{totn} [dB] (50 m)	0.012	0.11 (±0.01)	0.09	0.13	253	1731	1243	0.003
STAI_s	NO_2 [μg/m^3] (200 m)	0.009	0.14 (±0.01)	0.11	0.16	140	1844	966	0.004
STAI_s	PM_{10} [μg/m^3] (200 m)	0.004	0.27 (±0.04)	0.22	0.35	43	1941	398	0.010
STAI_s	NDVI [-] (500 m)	0.003	−0.23 (±0.07)	−0.46	−0.18	51	1933	376	0.014
STAI_s	ARVI [-] (400 m)	0.003	−0.21 (±0.03)	−0.33	−0.17	92	1892	376	0.013
STAI_s	TSI [W/M^2] (100 m)	0.023	−0.07 (±0.0)	−0.08	−0.07	45	1939	1946	0.001
STAI_s	DDI [h] (50 m)	0.030	−0.06 (±0.0)	−0.07	−0.05	57	1927	1982	0.001
STAI_t	ARVI [-] (25 m)	0.012	−0.11 (±0.01)	−0.11	−0.09	142	1669	1101	0.002
STAI_t	TSI [W/M^2] (25 m)	0.031	−0.06 (±0.0)	−0.07	−0.06	19	1792	1802	0.002
STAI_t	DDI [h] (25 m)	0.033	−0.06 (±0.0)	−0.08	−0.05	1811	0	1810	0.002
GAF_C	NO_2 [μg/m^3] (1500 m)	0.028	−0.05 (±0.0)	−0.05	−0.05	74	2598	2669	0.001
GAF_C	PM_{10} [μg/m^3] (25 m)	0.011	−0.09 (±0.0)	−0.1	−0.09	100	2572	1689	0.002
GAF_C	NDVI [-] (800 m)	0.034	0.05 (±0.0)	0.04	0.06	89	2583	2669	0.001
GAF_C	ARVI [-] (800 m)	0.031	0.06 (±0.01)	0.05	0.07	92	2580	2662	0.002
MMSE	L_{totn} [dB] (50 m)	0.009	−0.14 (±0.01)	−0.16	−0.13	47	1318	626	0.004
MMSE	NDVI [-] (100 m)	0.004	0.3 (±0.02)	0.24	0.37	59	1306	271	0.016
MMSE	ARVI [-] (100 m)	0.003	0.3 (±0.03)	0.24	0.4	78	1287	271	0.016

Key: PCV, psychometric and cognitive variables; EEF, environmental exposome factor; MGWR, Multiscale Geographically Weighted Regression; MGWR bandwidth, number of nearest neighbors used for calculation of parameter estimates; NO_2, nitrogen dioxide; PM_{10}, particulate matter under 10-μm; NDVI, Normalized Difference Vegetation Index; ARVI, Atmospherically Resistant Vegetation Index; TSI, Total Solar Insolation; DDI, Daily Duration of Insolation; L_{totn}, Night-time road and rail traffic noise; STAI_s, anxiety state; STAI_t, State Trait Anxiety Inventory trait; GAF_c, current psychosocial functioning; GAF_l, lifetime psychosocial functioning; GAF_w, worse ever psychosocial functioning; MMSE, overall cognitive performance.

hippocampus in predicting current psychosocial functioning [GAF_c]. This interaction was characterized by a mean negative regression coefficient across significant subjects, indicating a decreasing right hippocampus-current psychosocial functioning association with rising noise levels. For instance, Fig. 5 illustrates this relationship for a specific subject. Calculating Johnson-Neyman significance region, we show that the conditional association between the right hippocampus and current psychosocial functioning is positive but decreases with raising noise levels and becomes non-significant above 39.83 [dB]. More generally, for all subjects with significant interaction terms, we observed variability in the number of significant ranges for the moderating effects. While some subjects exhibited a single significant range, as in Fig. 5, for the moderating effect of night-time traffic noise on the association between the right hippocampus and current psychosocial functioning, others showed two distinct significant ranges (see Table S25). In that case, the association between right hippocampus volume and current psychosocial functioning becomes negative.

In the MGWR interaction analysis we also report additional findings for main effects of brain ROIs that were not significant in the univariate analysis comprising negative mean regression coefficients for STAI_s and GAF_c and positive for STAI_t and MMSE (see Table S26). The spatial extent of these associations was predominantly local to regional.

We observed a marked difference in the spatial extents within which the environmental exposome factors displayed significant interactions with brain anatomy. Specifically, vegetation indices showed significant interactions when measured within a closer median buffer radius of 100 m, in contrast to the broader median radii of 500 and 550 m for air pollution indicators NO_2 and PM_{10}, respectively (see Table S27). The average proportion of subjects with significant regression coefficients (27.5%) indicated a pronounced localized trend of these interaction associations. Overall, models involving MMSE exhibited the highest MGWR adjusted r-squared values (see Table S27).

4. Discussion

Our large-scale study in the community-dwelling adult population reveals the geospatial heterogeneity of associations between geocoded environmental exposome factors, individuals' psychometry/cognitive performance and brain anatomy. We extend previous studies, which collapse geospatial information to environmental exposome categories, by using spatial statistical models that explicitly test georeferenced exposome-brain-behavior associations at the individual level. Under the assumption of environmental factors' moderating effects on brain structure and resulting behavior, our findings offer an original perspective by mapping brain-psychometry/cognitive performance associations in geographic space, indicating localized associations influenced by the urban context.

Adopting an iterative analytical strategy, we start from a geographic

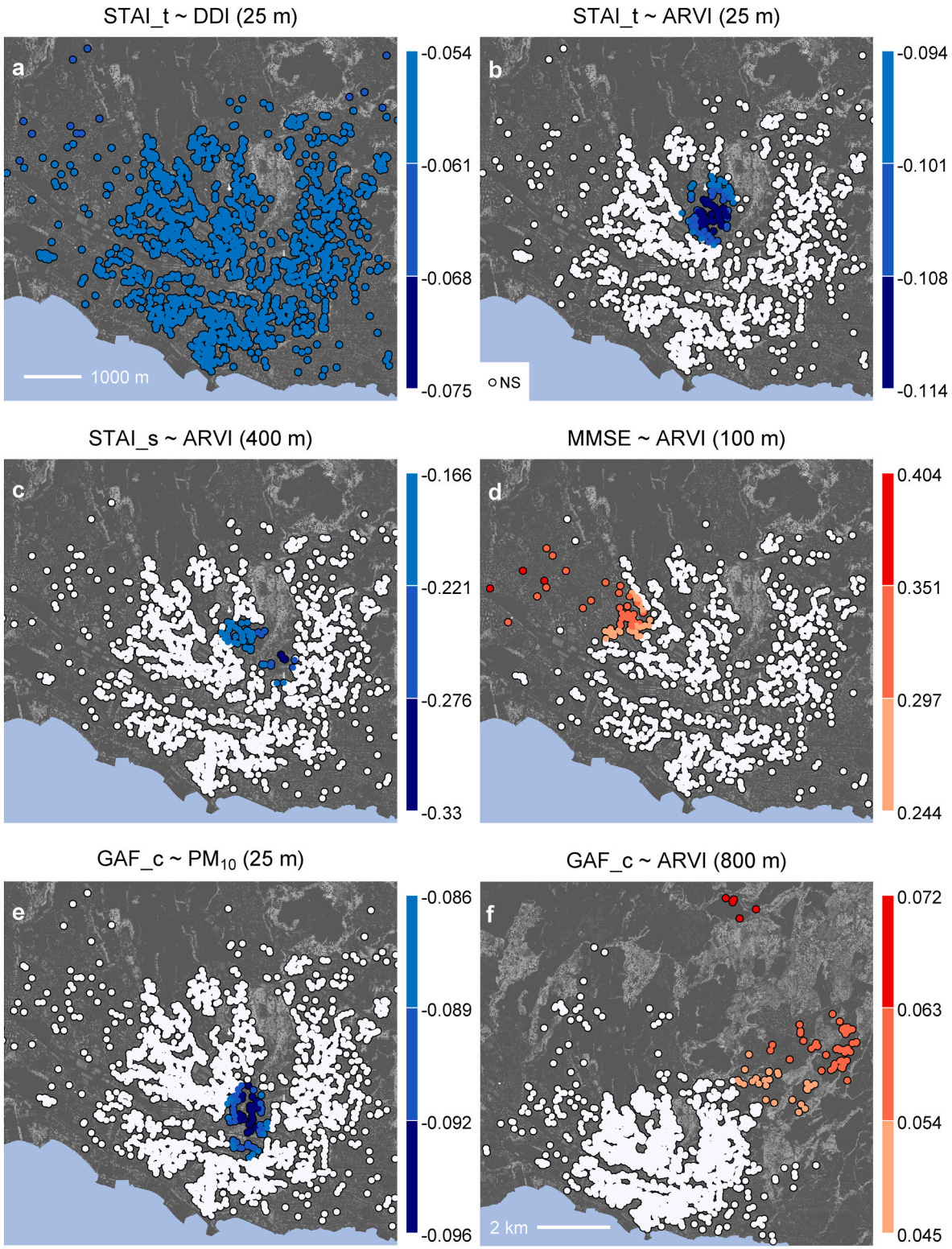

Fig. 3. Spatial distribution of the regression coefficients from the multiscale geographically weighted regression univariate models, showing associations between environmental exposome factors and adjusted psychometric and cognitive variables. Hot colors – positive regression coefficients, cold colors – negative regression coefficients, white – non-significant regression coefficients. Panels of spatial associations between **a** Daily Duration of Insolation (DDI) [h] and anxiety trait [STAI_t]; **b** Atmospherically Resistant Vegetation Index (ARVI) [-] and STAI_t; **c** ARVI [-] and anxiety state [STAI_s]; **d** ARVI [-] and overall cognitive performance (MMSE); **e** particulate matter under 10-μm (PM_{10}) [μg/m^3] and current psychosocial functioning [GAF_c]; **f** ARVI [-] and GAF_c. Brackets: buffer radius to calculate average values of environmental exposome factors around the home address. Color bar: three classes with equal intervals representing the range of significant regression coefficients.

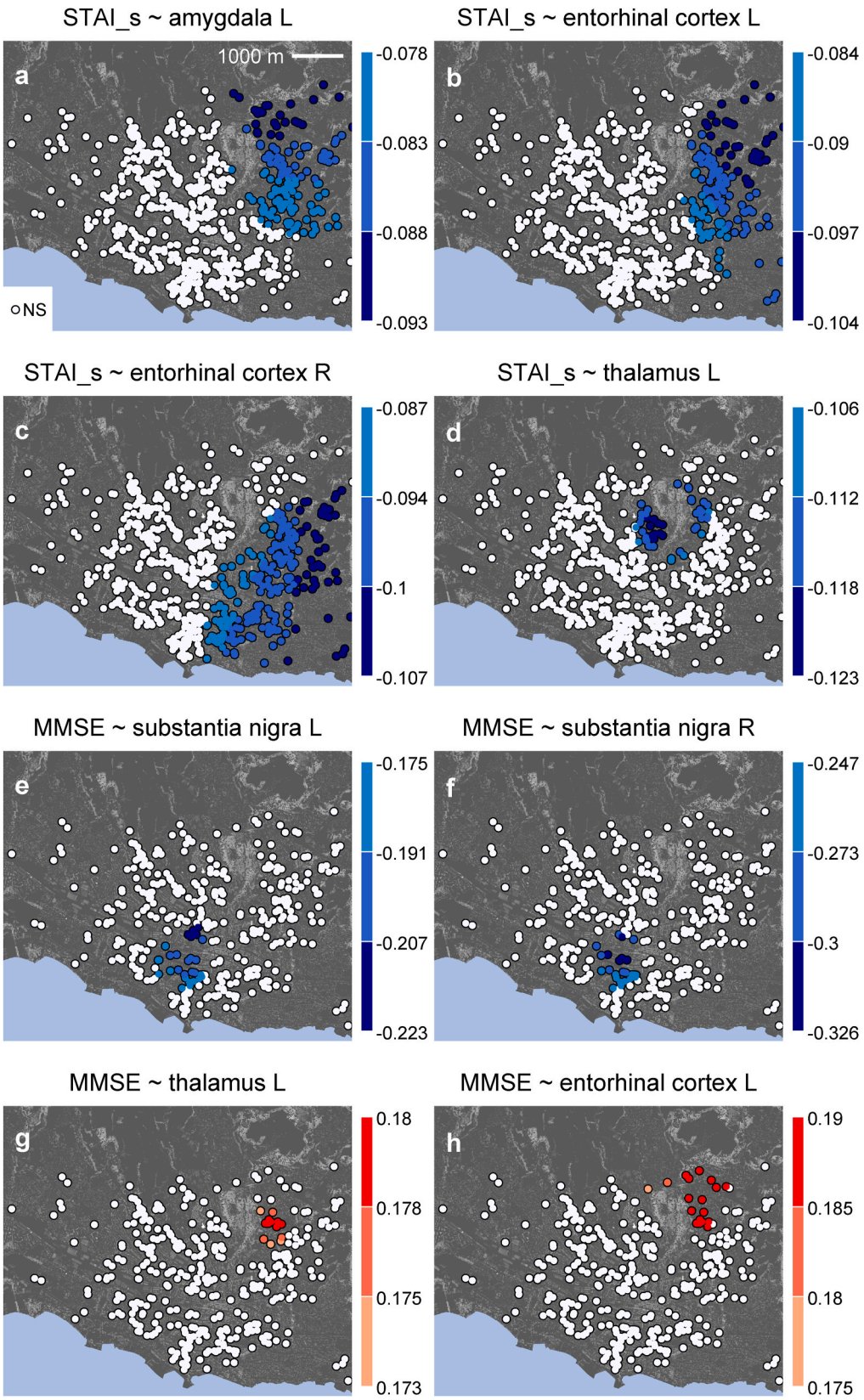

Fig. 4. Spatial distribution of regression coefficients from the multiscale geographically weighted regression univariate models, showing associations between brain anatomy and adjusted psychometric and cognitive variables. Hot colors - positive regression coefficients, cold colors - negative regression coefficients, white - non-significant regression coefficients. Panels of spatial associations between **a** left amygdala volume and anxiety state [STAI_s]; **b** left entorhinal cortex volume and STAI_s; **c** right entorhinal cortex volume and STAI_s; **d** left thalamus volume and STAI_s; **e** left substantia nigra volume and overall cognitive performance (MMSE); **f** right substantia nigra volume and MMSE; **g** left thalamus volume and MMSE; **h** left entorhinal cortex volume and MMSE. Color bar: three classes with equal intervals representing the range of significant regression coefficients.

Table 4
Results of the univariate multiscale geographically weighted regression (MGWR) predicting adjusted psychometric and overall cognitive performance variables (PCVs) with brain anatomic regions (ROIs). Results are reported as the mean of the parameter estimates, averaging the values of the regression coefficients of the significant subjects.

PCV	Brain ROI and hemisphere	Adjusted alpha	Mean of regression coefficients (±SD)	Min regression coefficient	Max regression coefficient	Number of significant subjects	Number of non-significant subjects	MGWR bandwidth	Adjusted R^2
STAI_s	Th L	0.019	−0.12 (±0.0)	−0.12	−0.11	61	713	691	0.002
STAI_s	Agd L	0.037	−0.08 (±0.0)	−0.09	−0.08	158	616	770	0.001
STAI_s	Ent R	0.025	−0.1 (±0.0)	−0.11	−0.09	256	518	732	0.004
STAI_s	Ent L	0.029	−0.09 (±0.0)	−0.1	−0.08	171	603	749	0.002
MMSE	SN R	0.007	−0.28 (±0.02)	−0.33	−0.25	26	384	163	0.022
MMSE	SN L	0.012	−0.2 (±0.01)	−0.22	−0.18	29	381	267	0.017
MMSE	Th L	0.015	0.18 (±0.0)	0.17	0.18	16	394	304	0.009
MMSE	Ent L	0.015	0.19 (±0.0)	0.18	0.19	22	388	313	0.008

Key: PCV, psychometric and cognitive variables; ROI, brain region of interest; MGWR, Multiscale Geographically Weighted Regression; MGWR bandwidth, number of nearest neighbors used for calculation of parameters estimates; STAI_s, anxiety state; MMSE, overall cognitive performance; Agd, amygdala; Ent, entorhinal cortex; SN, substantia nigra; Th, thalamus; L, left; R, right.

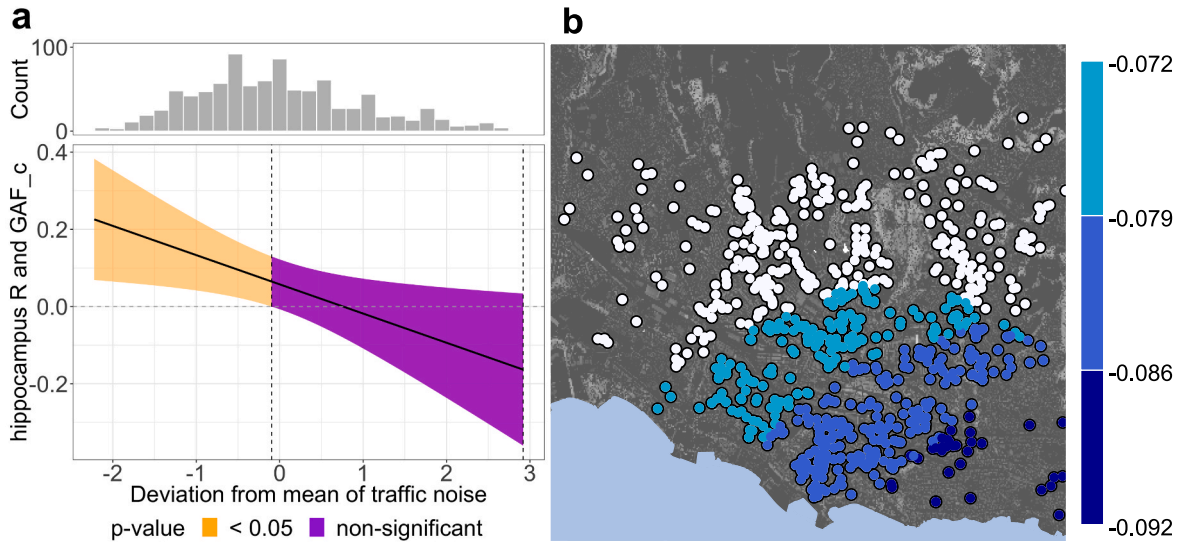

Fig. 5. Conditional association of brain anatomy and adjusted psychometry for one subject. a. Conditional association of right hippocampus volume with current psychosocial functioning [GAF_c] at different night-time traffic noise levels for one random individual with a significant regression coefficient for the interaction term in **b** and histogram of noise levels from bandwidth neighbors. Orange - significant conditional association in black with 95% confidence interval (CI). Purple – non-significant conditional association in black with 95% CI. The conditional slope of significant association ranges from a 0.23 S.D. increase (95% CI: 0.07–0.38) to a 0.07 S.D. increase (95% CI: 0.00–0.13) in GAF_c scores for each one S.D. increase in right hippocampus volume. Dotted lines - limits of significance of the moderator. Conditional significant association between right hippocampus and GAF_c is observed for values of the moderating night-time traffic noise < -0.097 S.D. from centered mean (true mean = 40.55 dB; −0.097 S.D.≙39.83 dB). Night-time traffic noise was measured with a 25 m buffer radius and the range of observed values is [-2.22 S.D., 2.92 S.D.] ≙ [24.21 dB, 62.00 dB]. **b.** Spatial distribution of interaction term regression coefficients. Cold colors - significant regression coefficients for interaction between right hippocampus volume and average night-time traffic noise measured within a buffer radius of 25 m in predicting GAF_c. Significant coefficients observed for 516 subjects. White – 427 subjects show non-significant interaction regression coefficients. Color bar: three classes with equal intervals representing range of significant regression coefficients for the interaction term.

analytical perspective and demonstrate the distribution of spatial clusters of high and low levels of anxiety and psychosocial functioning. These results indicate that psychometry levels are not randomly distributed across the city. The additional assessment of environmental exposures across clusters of anxiety state and current psychosocial functioning corroborates previous research, showing strong associations of psychometric outcomes with air pollution and vegetation density, which exhibited the highest effect sizes. These findings motivate elaborating guidelines to design cities supporting mental health (Vidal Yañez et al., 2023; Collins et al., 2024; Giebel et al., 2022). The fact that the exposome factors show associations with individuals' current state psychometry, suggests short term effects with rapid changes in mood linked to the environment.

Building on these findings, the applied univariate multiscale geographically weighted regressions allow for differentiating exposome-brain-behavior associations at the global, regional, and local spatial scales. Our assessment of exposome-behavior associations extends the observed clustering variance results by also showing their unique spatial distribution. The obtained scale dependent results of the associations between, on the one hand side, overall cognitive performance and vegetation density, and on the other – current psychosocial functioning and PM_{10} air pollution, align well with previous research (Houlden et al., 2021) and increase the confidence in the validity of inferences. The spatial specificity is also evidenced by the observed geographical variation in the associations between air pollution factors and current psychosocial functioning – the associations with PM_{10} are restricted to the city center, whilst the NO_2 ones - to the city periphery. Further support for the existence of scale-dependent effects comes from the demonstrated negative relationship between daylight duration and individuals' anxiety trait at the global scale. These findings contrast with

the localized dependencies between the other investigated environmental exposome factors and current psychometry measures, including the negative association between indoor daylight and anxiety state. Here, the direction of the associations between indoor daylight and both anxiety state and trait remained consistent with previous findings (Morales-Bravo and Navarrete-Hernandez, 2022). The negative associations between night-time traffic noise and measures of overall cognition, additionally to the positive associations with current anxiety levels corroborate with the published literature (Lan et al., 2020; Tzivian et al., 2017). However, we also demonstrate that these relationships are spatially constrained.

In the next step we integrate the neurobiological question about associations between brain anatomy and behavior in the geospatial context. Given our assumption of a moderator role of exposome factors on the association between brain anatomy and psychometry/cognitive performance outcomes, we focus on the behavioral outcomes and abstain from testing for associations between environment and brain structure. The observed geospatial distribution of brain-behavior associations is exemplified by negative associations between current anxiety levels and amygdala volume, additionally to positive associations between overall cognitive performance and entorhinal cortex volume. Beyond the confirmatory findings on the directionality of behavior-brain anatomy associations that align with the literature (Wang et al., 2021; Yang et al., 2023; Olsen et al., 2017; Mah et al., 2015), our study advances this understanding by explicitly mapping the spatial distribution of the tested relationships. The geospatial mapping not only provides insights into how specific environmental contexts shape neurological and psychological outcomes, but it might help explaining additional variance in previous conflicting studies (Wang et al., 2021; Bas-Hoogendam et al., 2018; Brühl et al., 2014).

The obtained findings challenge the notion of geographically uniform brain-behavior associations in the community-dwelling population. Here, we emphasize the specificity of exposome-brain-behavioral findings, confirmed by the spatial patterns of associations between the MMSE-based estimates of overall cognition and brain anatomy. The positive spatial associations between MMSE scores, entorhinal cortex and thalamus volume follow the canonical view on episodic memory consisting of two complementary components – a "temporal lobe" stream centered on hippocampus and entorhinal cortex, and a "medial diencephalic" stream centered on anterior thalamic nuclei (Aggleton and O'Mara, 2022). On the other hand, we interpret the negative association between individuals' overall cognition and substantia nigra volumes localized in a different geographical area as evidence for the distinct exposome-brain-behavior relationships for this brain structure spanning limbic, cognitive, and motor domains (Zhang et al., 2017).

Consistent with our intention to fully integrate the multi-domain data in geographical space, we use a multiscale multivariate geographically weighted regression analysis. Our results confirm and expand the findings of the separate univariate analyses by providing proof-of-concept evidence about the differential spatial extent of the interaction between the environmental exposome factors, brain, and behavior. The regression coefficients for specific brain anatomy regions, showing consistent directionality across both univariate and multivariate interaction models that predict current anxiety levels and cognition, underscore the robustness of the identified brain-behavior associations. The assessment of the anxiety trait using interaction models showed that the main effects of brain anatomy were primarily linked to air pollution and public transport accessibility. In contrast, when evaluating current anxiety levels, the main effects of brain anatomy were not tied to any specific environmental exposure. We attribute this difference to the varying impacts of short- and long-term effects on mood states as suggested previously (Li et al., 2021). Here, the reported brain-behavior associations manifesting at local and regional levels, rather than at the global level, underline the importance of geographical context for future studies.

The finding of significant regression coefficients for the interaction term in the multivariate interaction models confirms our hypothesis that brain-behavior associations are contingent upon specific levels or components of the environmental exposome. The predominant local level of these interactions reaffirms the spatially context-dependent nature of the exposome-brain anatomy relationships and their corresponding psychometry/cognitive performance outcomes. This finding aligns with previous reports about the (geo)spatial heterogeneity influencing various health-related outcomes. In a neuroscientific context, it emphasizes the need for spatially explicit models that capture the heterogeneity of brain-behavior dynamics in relation to environmental factors in urban contexts (Pykett, 2018; Pykett et al., 2020; Buttazzoni et al., 2022).

We also identify a scale-dependent effect in the exposome-brain anatomy interactions on behavior outcomes. The small measurement buffer radii for vegetation indices in the interaction terms suggest that the moderating effect of vegetation on the brain-behavior relationship primarily operates within the immediate vicinity or visible surroundings of an individual's home address. This localized effect contrasts with previous findings linking green space with greater activations in emotion-regulating brain regions within large non-walkable buffers (>1500 m) (Dimitrov-Discher et al., 2022). Conversely, we demonstrate larger radii of measurement for air pollution indicators, suggesting indirect exposure and a general impact of air quality over a broader area. The interaction results for cognitive outcomes suggest the environment may act as a moderator in the brain-cognition relationships. The scale-dependent localization of the interaction regression coefficients for vegetation and brain regions supporting cognitive performance aligns with previous research, indicating that social interaction and physical activity, encouraged by specific neighborhood settings (Vallarta-Robledo et al., 2022), can increase cognitive reserve and protect cognitive function (Jammula et al., 2021; Jin et al., 2023). Similarly, the interaction effects for the psychometric outcomes confirm the notion of moderating brain anatomy's association with anxiety and psychosocial functioning.

Besides the novelty aspects of our study, we have to also acknowledge several limitations. These include the focus on the adult population in a Swiss urban setting, potentially limiting generalizability to younger or rural populations in lower-income countries. Further, the cross-sectional design limits our ability to account for long-term health changes and subject relocation within the city. While previous studies have shown that the brain mediates the association between environment and psychometry/cognitive performance outcomes (Glaubitz et al., 2022; Xu et al., 2023c), we examined how varying levels of environmental exposure in an urban setting moderate associations between the brain and these outcomes. In our upcoming work including analysis of longitudinal data, we focus on evaluating different causal models including the question about how these pathways coexist. Similarly, the fact that the environmental exposome factors are calculated at specific time points rather than averaged over longer periods, could have an impact on the obtained results. Additionally, the adoption of a region-of-interest approach as in the UK Biobank (Miller et al., 2016) constitutes another limitation of our study. While we warrant caution in interpretating our findings — particularly as our use of single-environmental exposure models approach may introduce effects from correlated exposures — we aim to provide a comprehensive overview of potential effects and interactions.

Conversely, the strength of this study lies in its use of fine-scale georeferenced measurements and analysis at the individual level, which overcomes the limitations of studies using predefined neighborhood units (Guessous et al., 2014). The analysis of multiple environmental factors, and explicit testing for spatial heterogeneity represents, to our knowledge, a new approach to analyzing exposome-brain-behavior associations. By mapping brain-behavior associations and assessing the moderating effects of the environment, this study fills an important knowledge gap and helps advancing research addressing the etiology and treatment of ubiquitous mental health disorders (Ancora et al.,

2022). In contrast to previous studies in brain-environment exposure research that reduce geospatial information to broader indices or singular exposure measurements, our approaches favorizes a multidimensional set of exposures.

5. Conclusion

Using spatial clustering and multiscale geographically weighted regression methods, we identified significant associations between psychometry/cognitive performance and the environmental exposome, as well as with specific anatomical brain regions, mapped these relationships, and delineated the spatial scales at which they manifest. Our research contributes to the growing body of work examining the interplay between brain, behavior, and environmental factors in urban settings. Our findings align with recent studies that investigated the effects of green spaces, urban street networks, and nature versus urban walks on brain activation in varied scenarios (Dimitrov-Discher et al., 2022, 2023; Sudimac et al., 2022). Additionally, we expand on these findings by demonstrating the spatial scale dependency of these relationships, particularly in the context of brain-behavior associations. We introduce a new perspective, highlighting the pivotal role of environmental contexts in moderating brain-behavior dynamics and argue for contextually tailored environmental research and public health strategies for maintaining brain health. Our results contribute to environmental research demonstrating that urban exposome factors associate with mental health and cognition differently across locations, emphasizing the role of urban spatial organization in shaping cognitive mapping and well-being, and underscoring the importance of health-oriented urban design for accessibility and inclusivity (Mondschein and Moga, 2018).

CRediT authorship contribution statement

Marco Vieira Ruas: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elia Vajana:** Writing – review & editing, Visualization, Methodology, Formal analysis, Conceptualization. **Ferath Kherif:** Writing – review & editing, Methodology, Conceptualization. **Antoine Lutti:** Writing – review & editing, Methodology. **Martin Preisig:** Writing – review & editing, Resources. **Marie-Pierre Strippoli:** Writing – review & editing, Resources, Data curation. **Peter Vollenweider:** Writing – review & editing. **Pedro Marques-Vidal:** Writing – review & editing. **Armin von Gunten:** Writing – review & editing. **Stéphane Joost:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Bogdan Draganski:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Bogdan Draganski and Stephane Joost reports financial support was provided by Swiss National Science Foundation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120632.

Data availability

The data of the CoLaus|PsyCoLaus study and the generated georeferenced environmental exposome measurements used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of the Swiss legislation with respect to privacy protection. However, coded individual level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals requiring baseline data only, will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

We georeferenced participants at their current home address using the publicly available geospatial information provided by the Swiss Confederation via its API REST services: https://api3.geo.admin.ch/services/sdiservices.html.

The modified Copernicus Sentinel data from 2016 processed by Sentinel Hub and used for vegetation indices calculation, were obtained from EO Browser, https://apps.sentinel-hub.com/eo-browser/, Sinergise Solutions d.o.o., a Planet Labs company. The corresponding images and generated Normalized Difference Vegetation Index and Atmospherically Resistant Vegetation Index, as well as the walkable street network from the region of interest that support the findings of this study are publicly available in Zenodo with the DOI: 10.5281/zenodo.12528203.

The institutional road and rail traffic noise data were sourced from the publicly available sonBASE database of the Swiss Federal Office for the Environment at https://www.bafu.admin.ch/bafu/en/home/topics/noise/state/gis-laermdatenbank-sonbase.html. We derived the atmospheric conditions to calculate Total Solar Insolation and Daily Duration of Insolation from publicly available data from the Federal Office of Meteorology and Climatology Meteoswiss at https://www.meteoswiss.admin.ch/climate/climate-change/changes-in-temperature-precipitation-and-sunshine/monthly-and-annual-maps.html.

Data on public transport stops, Digital Terrain model and Digital Surface model were obtained from the Association for the Vaudois Territory Information System (ASIT-VD). Total Solar Insolation and Daily Duration of Insolation were generated using the Digital Surface model. Air pollution data were obtained from the Directorate-General

for the industrial, urban, and rural Environment (DGE-DIREV) of the Vaud canton. However, restrictions apply to the availability of these datasets, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of ASIT-VD and DGE-DIREV.

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