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10.1016/j.jenvp.2023.102142

Publication date 2023 Document Version

Final published version
Published in

Journal of Environmental Psychology

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Link to publication

Citation for published version (APA):

Dimitrov-Discher, A., Gu, L., Pandiť, L., Veer, I. M., Walter, H., Adli, M., & Knöll, M. (2023). Stress and streets: How the network structure of streets is associated with stress-related brain activation. *Journal of Environmental Psychology*, *91*, Article 102142. Advance online publication. https://doi.org/10.1016/j.jenvp.2023.102142

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Contents lists available at ScienceDirect

Journal of Environmental Psychology



journal homepage: www.elsevier.com/locate/jep

Stress and streets: How the network structure of streets is associated with stress-related brain activation



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ARTICLE INFO

Handling Editor: L. McCunn

Keywords: Urban stress Social stress Street network Space syntax fMRI Brain activity

ABSTRACT

Previous research has examined the relation between urban design factors and mental health, but the impact of street networks is underrepresented. This exploratory, cross-sectional study examines the association between street network variables based on the Space Syntax theory and whole-brain activation during a social stress paradigm. Forty-two individuals who lived in Berlin participated in an fMRI study during which acute social stress was induced. Saliva cortisol concentrations, subjective stress ratings, and mean heart rate were assessed as proxies for a successful stress induction. Space Syntax was used as a tool to objectively measure street network characteristics including global integration ('proximity' of a street to all the other streets in a network), local integration ('proximity' of a street to a certain number of streets within a walkable area), connectivity ('direct street connections' a street has), and normalized angular choice (NACH) ('straightest and shortest' route for a street in a street network). They were analyzed within a 1500 m radius of participants' address (i.e., neighborhood) as well as for the street closest to their address (i.e., point address). Higher mean neighborhood global and local integration, which equate to better integrated streets in the network, were associated with less activation during stress provocation in several brain regions, including dorsal anterior cingulate cortex, insula, and thalamus, which play a role in the detection of salient stimuli and threats. No association was found between brain activity and global and local integration for the point address. There was also no association between brain activity and connectivity or NACH for any conditions. The study indicates that Space Syntax is a useful tool for measuring macro-scale urban space (e.g., street networks) in neuro-urbanistic studies. The results underline the need to explore the potential of optimizing street networks to better understand pathways to urban mental health.

1. Introduction

Research on healthy city planning has recognized the importance of connected street networks to support active transport (i.e., walking and cycling) and healthy lifestyles, but it has also highlighted the lack of measurable planning and policy targets for cities to facilitate more sustainable and compact development (Lowe et al., 2022). In addition, Giles-Corti et al. (2022) identified 11 integrated urban system policies to develop more compact cities that support sustainable mobility (this

includes design of pedestrian- and cycle-friendly movement networks). It focuses on how integrated city planning is crucial for creating healthy and sustainable cities and reflects how destination 'proximity' is important for walkable cities.

Less attention has been paid to how 'active' city planning can promote social and mental well-being for better exercise, increased opportunities for social activities, community building, and psychological restoration. Street aesthetics and network qualities have been largely neglected in previous research (Roe & McCay, 2021). Streets are an

https://doi.org/10.1016/j.jenvp.2023.102142

Received 13 March 2023; Received in revised form 13 September 2023; Accepted 15 September 2023 Available online 16 September 2023

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important platform for urban life, as people are exposed to them daily; they act as multi-functional urban public places providing opportunities for traffic movement, social and economic exchange, and mental health improvement (Carmona, 2010; Roe & Mondschein, 2023; Van Nes & Ye, 2014). As the development of a street network is a slow-growing process (Mohajeri & Gudmundsson, 2014), it largely remains stable in a developed urban area over a long period (Marshall, 2004), in comparison to buildings and land use (Hajrasouliha & Yin, 2015). However, with the onset of COVID-19 pandemic, frequent temporary on-street changes were witnessed via 'pop-up' lanes fostering active mobility (Pandit et al., 2021), with some resulting in permanent changes. Considering the physical form of cities, streets act as a major constituent of urban form, with street networks contributing to urban resilience (Sharifi, 2019). A method to quantify streets and their network is provided by Space Syntax theory, which emerged in the late 1970s to explore the interactions between spatial structure and social activity (B. Hillier & Hanson, 1984). Space Syntax theory provides multiple measures, such as integration, connectivity, and normalized angular choice (NACH), which have been used by several studies to examine the associations between street networks and general physical activity, walking and cycling activity, and social activities (Table 1).

Few studies have explored the association between street network characteristics and stress. A study in Darmstadt, a city with a population of 160,000 in Germany, suggested that highly integrated street segments were related to the perception of an adjacent open space as stressful (Knöll et al., 2015, 2018) (Table 1). Thus, evidence suggests that urban living and stress exposure are interconnected. Current urban living, defined as living in cities with populations exceeding 100,000, has been linked to heightened amygdala activity, whereas urban upbringing is associated with stronger activity in the perigenual anterior cingulate cortex in a neuroimaging social stress paradigm using functional magnetic resonance imaging (fMRI) (Lederbogen et al., 2011). Whereas the amygdala is a key region responsible for emotional processing and threat detection, the perigenual anterior cingulate cortex takes part in the regulation of the amygdala, stress, and negative affect (Etkin, Büchel, & Gross, 2015). The findings from Lederbogen et al. (2011) imply that living in a larger city compared to rural areas is linked to stronger amygdala activation during social stress. However, this does not answer whether certain factors within a large city, such as street networks, could affect amygdala activity differently. Another recent fMRI study explored potential differences in brain activity after a walk in natural or urban environments, reporting reduced activity in the amygdala after a nature walk (Sudimac, Sale, & Kühn, 2022). However, there was no difference in amygdala activity after an urban walk, contrary to the expected increase. This indicates that an urban walk alone does not necessarily involve negative emotion processing. In the same sample, the authors provided evidence that amygdala activity decreased only in women, not men (Sudimac, Sale, & Kühn, 2022). No study has yet applied fMRI in the context of stress responsivity and further investigated more specific factors of the built environment, such as street networks, which vary considerably within large cities and between neighborhoods. Thus, our study combines street network characteristics based on Space Syntax and fMRI data to examine the effects of urban street network configuration on urban residents.

To understand the changes in the brain activity associated with social stress response, it is important to explain three networks of brain regions that have been found to consistently play a role: the Salience Network (SN), the Central Executive Network (CEN), and the Default Mode Network (DMN) (van Oort et al., 2017). The SN becomes active during emotional processing and in the presence of salient stimuli, thus promoting the detection of possible threats. It includes, amongst others, the amygdala, the dorsal anterior cingulate cortex (dACC), and the insular cortex. The CEN, on the other hand, is active during higher-order cognitive tasks and includes regions like the dorsolateral and dorsomedial prefrontal cortex, and posterior parietal cortex. Meanwhile, the DMN shows heightened activation during resting state and is linked to

various functions, including self-referential processing due to negative feedback during a psychosocial stressor. It includes, amongst others, the posterior cingulate cortex/precuneus, medial prefrontal cortex, and hippocampus.

To explore the association between street networks and psychosocial stress, it is essential to consider several mediating factors. This list of mediators includes aspects like physical activity, social support, and air pollution, all of which exhibit an association with street network variables (Baran et al., 2008; Hillier & Vaughan, 2007; Wineman et al., 2012) as well as with stress processing (Dimitrov-Discher et al., 2022; Gröpel et al., 2018; Sarkar et al., 2013; Sladek et al., 2017; Wood et al., 2018). Notably, higher levels of air pollution, which have been linked to higher global integration values and increased motorized traffic, exhibit a negative correlation with activation in several brain regions during provocation of psychosocial stress in the scanner, amongst others, the dACC, insula, ventral striatum (all SN), posterior cingulate cortex/precuneus (DMN), and prefrontal regions (CEN) (Dimitrov-Discher et al., 2022). As air pollution data were available from a previous study from our group (Dimitrov-Discher et al., 2022), we included air pollution as a mediating factor in our analysis.

The current study aims to examine the association between street network characteristics—specifically connectivity, global and local integration, and normalized angular choice—in participants' neighborhoods and their brain activation during a social stress paradigm in the fMRI. Although no previous research has explored the impact of street networks on stress responsivity using fMRI, we assume that an association exists. This assumption is based on the fact that a lively street network promotes several health-protective mediators, e.g., physical activity and social support, both of which have been shown to promote adaptive stress processing. Similarly, health-harming mediators, such as increased motorized traffic and air pollution, should be taken into consideration when interpreting potential results.

2. Methods

2.1. Participants

Fifty healthy male volunteers were recruited via mailing lists, website advertisements, and flyers. Eight were excluded due to incidental findings in their anatomical scans (e.g., enlarged subarachnoid space, cysts; n = 4) or because their addresses were outside the city borders of Berlin (n = 4). Thus, the final study cohort for analyses comprised 42 healthy men (mean age (SD) = 30.12 (5.57) years; range, 20–48 years) with a mean BMI of 23.71 (SD = 2.35; range, 19.70–30.35). All participants had a mean depression score below clinical significance (Beck Depression Inventory: mean (SD) = 4.26 (4.05); range, 0–15). Participants were tested after a working day; therefore, scanning always took place on a Wednesday (n = 22) or Thursday evening (n = 20) between 17:00 and 22:00. Participants refrained from taking caffeine 2 h before scanning and from strenuous physical activity for the entire day (e.g., sporting activities, fast cycling, running upstairs). The study was approved by the Ethics Committee of Charité - Universitätsmedizin Berlin and Technical University of Darmstadt. Written informed consent was obtained from all participants. The fMRI data of the same 42 participants was used in a previous publication examining the association between stress processing, amount of green space, and air pollution surrounding the place of residence (Dimitrov-Discher et al., 2022).

2.2. Space Syntax—Street network characteristics

The analysis of a street network by Space Syntax is based on the topological distance (i.e., step) between axial lines or segments representing the street space as experienced by people. An axial line is the longest straight line that extends as far as possible through a point in space. A segment is the part between adjacent intersections of an axial line (Fig. 1 (a)–(c)).

Table 1

Space Syntax and related outcomes.

Independent Variable	Observational limit	Method	Outcome	Method	Finding	Reference
Integration	Area	 Calculate the value of each segment with considering all segments in a 1 km radius from its center (r = 1 km); Calculate the mean value of all segments in the study area 	Walking activity	Self-reported frequency of walking for transports and car use $(n = 16345)$	Integration ($r = 1$ km) was positively related to odds of home-based walking for transport and negatively related to odds of using car over 60 min	Koohsari et al. (2017)
	Area	Same as above	Walking activity	Self-reported frequency of walking for transport (n = 2544)	Integration (r = 1 km) was positively related to odds of walking for transport	Koohsari et al. (2016)
	Street segment	Calculate the value of each segment with considering all segments (i.e., n) in the study area $(r = n)$ and within a topological depth of 3 $(r = 3)$	Walking activity	Survey (n = 393); household self- reported travel diaries (n = 364)	Integration $(r = n)$ was positively related to walking for leisure and utilitarian purposes; Integration $(r = 3)$ was positive related to utilitarian walking trips and negative related to leisure walking trips	Baran et al. (2008)
	Street segment	Calculate the value of each segment with considering all segments (i.e., n) in the study area $(r = n)$ and in a 100 m radius from its center $(r =$ 100 m)	Walking activity	Path searching task based on visual stimuli (n = 20)	Integration ($r = n$, 100 m) was positively related to frequency of one street being selected for walking	Emo et al. (2012)
	Street segment	Calculate the value of each segment with considering all segments within a topological depth of 3 ($r = 3$)	Walking activity	Pedestrian counts of 302 street segments	Integration ($r = 3$) was positively related to pedestrian volumes	Hajrasouliha and Yin (2015)
	Area	 Calculate the value of each segment with considering all segments (i.e., n) in the study area (r = n); Calculate the mean value of all segments within 1/2 mile and 1/4 mile area of each address. 	Physical activity	Physical activity survey (n = 461)	Integration $(r = n)$ was positively related to physical activity in adults over 25	Wineman et al. (2012)
	Area	1. Calculate the value of each segment with considering all segments (i.e., n) in the study area (r = n); 2. Calculate the mean value of all segments within 1/2 mile area of each address	Cognitive performance	Psychometric test (n = 64)	Integration $(r = n)$ was negatively related to cognitive performance and positively related to 1) declines in attention and verbal memory in healthy older adults and 2) declines in attention in older adults with mild Alzheimer's disease	Watts et al. (2015)
	Street segment	Calculate the value of each segment with considering all segments (i.e., n) in the study area $(r = n)$ and in a defined metric radius from its center (r = 1200 m, 3000 m)	Stress perception	Online survey (n = 134)	Integration ($r = n$, 3000 m) was positively related to stress ratings and negatively related to relaxedness ratings; Integration ($r = 1200$ m) was negatively related to stress ratings	Knöll et al. (2015); Knöll et al. (2018)
Connectivity	Street segment	Calculate the value of each segment in the study area	Walking activity	Survey (n = 393); household self- reported travel diaries (n = 364)	Connectivity was positive related to walking for leisure and utilitarian purposes	Baran et al. (2008)
	Area	 Calculate the value of each segment in the study area; Calculate the mean value of all segments within 1/2 mile and 1/4 mile area of each address 	Physical activity	Physical activity survey (n = 461)	Connectivity was positively related to physical activity	Wineman et al. (2012)
	Street segment	Calculate the value of each segment in the study area	Social interaction	Social interaction survey and behavior	Connectivity was positively related to long-duration activities and social interaction	Can and Heath (2016)
	Area	 Calculate the value of each segment in the study area; Calculate the mean value of all segments within 1/2 mile area of each address 	Cognitive performance	Psychometric test (n = 64)	Connectivity was positively related to cognitive performance in healthy older adults	Watts et al. (2015)
NACH (route directness)	Street segment	Calculate the value of each segment with considering all segments (i.e., n) in the study area $(r = n)$ and in a defined metric radius from its center (r = 400 m, 800 m, 1200 m, 1500 m, 1800 m, 2000 m, 2500 m)	Cycling activity	Cycling activity data from smart phone App	NACH was positively related to cycling activity; The analysis radius (r) was positively related to cycling activity	Orellana & Guerrero (2019)

Note. NACH = normalized angular choice, n = sample size, r = radius, (r = n) = all segments in a radius, km = kilometers, m = meters, min = minutes.



Fig. 1. Explanation of axial and segment lines for Space Syntax analysis where (a) is the aerial view of neighborhood blocks, (b) corresponds to the axial lines (1–5), and (c) corresponds to the subdivided segments (1a–5c).

The chosen characteristics are analyzed using a topological radius via depth, i.e., steps from an axial line to other destination lines (for integration and connectivity) (Hillier & Hanson, 1984) within axial analysis, and metric radius (for NACH) (Nordström & Manum, 2015, pp. 1–14) within segment analysis. For the axial analysis, r = n signifies consideration of all possibilities (for the nth axial line) from the origin within the axial network of streets, while r = 3 corresponds to consideration of all possibilities (i.e., axial lines) within three topological step changes from the origin.

Integration measures how closely the origin space is connected to all other spaces in a predefined system (Hillier & Hanson, 1984). It is related to higher amounts of to-movement, i.e., movement directed towards a specific destination. Global integration (r = n) records the value within the whole system (Fig. 2: all streets A–I). It has been associated with more walking activities of residents (Baran et al., 2008) and car movement (Hillier & Vaughan, 2007). Local integration (r = 3) measures how well a street segment is connected to other segments within a topological depth of 3 (Fig. 2: streets G, E, F, B, C, D). It has been considered a good predictor of pedestrian movement (Hajrasouliha & Yin, 2015; B. Hillier & Iida, 2005; Hillier & Vaughan, 2007; Lerman et al., 2014), as a more integrated area provides users with easy access and a welcoming space (Hajrasouliha & Yin, 2015).

Connectivity reflects the number of segments directly connected to a specific route segment, indicating how well a street segment is accessible from its surrounding neighborhood (Hillier & Hanson, 1984). A street with high connectivity relates to a higher number of streets directly

connected to it (e.g., in Fig. 2, street connectivity of '2' relates to the origin street having two more streets connected to it). This is associated with better walkability (a measure of environmental quality) (Frank et al., 2003) that encourages growth of social capital, including social activities and trust (Leyden, 2003).

NACH indicates the shortest path with least angular deviation; in other words, the straightest route (B. Hillier & Iida, 2005), which has been reported to attract cyclists in a city street network (CROW, 2007; Orellana & Guerrero, 2019). It is related to higher amounts of through-movement, i.e., movement that not necessarily starts or ends in the analyzed area but transits. Streets with high NACH values are likelier to be on the shortest path to different destinations. Moreover, straight routes are preferred by pedestrians as well (Broach & Dill, 2015). Thus, NACH has been utilized to build models for predicting pedestrian movement (Lerman et al., 2014; Sheng et al., 2021).

In summary, global integration pertains to the 'proximity' of a street to all other streets; local integration refers to 'proximity' of a street to a specific number of streets (i.e., streets that are maximum three topological steps away); connectivity relates to 'direct street connections' a street possesses; NACH relates to 'straightest and shortest' route for a street within a street network.

2.3. Space Syntax - construction of maps, masking of address data

To generate the selected characteristics for the network of streets surrounding each participant's address, the maps were manually



Fig. 2. Visualization of global integration (r = n), local integration (r = 3), and connectivity for street G.

constructed and analyzed using DepthmapX software (DepthmapX development team, 2017). The city of Berlin has a high share of active mobility (SenUVK, 2019), where walking dominates the modal split (30% of all the journeys, while cycling accounts for 18%). Walking or cycling is the dominant mode of transport in Berlin for distances up to 1 km (92%) and 1–3 km (56%). Considering the timeline for mapping the network of streets surrounding 42 individual home addresses and the range of distances related to active mobility within Berlin, a radius of 1500 m was selected to represent the physical movement characteristics in Berlin, which in turn are associated with the selected street network characteristics via connectivity, local integration (r = 3), global integration (r = n) and NACH (corresponding to straightest and shortest route). This observational boundary of 1500 m is utilized for the topological analysis of the 42 urban neighborhoods.

Prior to the mapping of the street network based on Space Syntax theory, the original coordinates of the participant's addresses were geographically masked to preserve the privacy of the individuals and their corresponding health data, using the masking tool MaskMy.XYZ. Donut masking was performed (Fig. 4), wherein the randomly masked coordinate is located within a minimum and maximum distance from the original coordinate point. For confidentiality reasons, the mean displacement of the 42 coordinates is not mentioned to avoid any potential data unmasking. The masked points lie within a 100 m radius from the original coordinates. In a city like Berlin, where residential density is high, a sufficient degree of confidentiality was achieved. While the utility of masked data in context with Space Syntax is uncommon, the application of masking tools is relatively new. This is why we aimed to compare data from masked and original addresses.

After geographic masking, the networks of streets within a 1500 m radius from the masked coordinates (or point addresses) were mapped axially, where the lines represented a network of longest visible sight for a human on the street (which is different from the central street lines often used in navigation maps). Prior to calculating any street network characteristics, the maps were revised thoroughly to minimize errors due to different elevation levels of the streets (Fig. S1). Once the axial maps were completed, they underwent analysis for connectivity, local integration, and global integration. For the analysis of NACH, the axial maps were first converted into segment maps (Fig. 5). After the street network characteristics are analyzed for each axial line in an axial map and segment line in a segment map, three urban datasets corresponding to the following observational limits were explored:

- 1. the mean values of street network characteristics for all axial and segment lines within a 1500 m radius (i.e., the neighborhood values) of the masked address coordinates.
- 2. the individual street network characteristic-values of the street closest to the original address coordinates (i.e., the original street values).3. the individual street network characteristic-values of the street closest to the masked address coordinates (i.e., the masked street values).

2.4. fMRI task

To induce acute social stress, the ScanSTRESS task was employed (Streit et al., 2014). During the stress condition, participants had to solve figure rotations and mathematical subtraction tasks while being observed by a two-person expert panel. To incorporate social-evaluative threat, unpredictability, and uncontrollability, which are the main elements of social stress (Dickerson & Kemeny, 2004; Noack et al., 2019), negative verbal feedback was provided by the expert panel after a practice run. Visual feedback was presented on the screen in case of errors ("Incorrect!"), and time pressure was imposed through a visual countdown during task execution, accompanied by the comment "Work faster!" if correct but slow performance occurred. During the control condition, participants merely had to match figures and numbers. The adapted ScanSTRESS paradigm was programmed and presented using

Presentation 18.1, provided by Neurobehavioral Systems (www.neu robs.com/). The stress task was part of a larger study conducted in 2016. Previous results concerning the following aspects are reported elsewhere (Dimitrov-Discher et al., 2022): the main effect of the stress task, a detailed description, as well as a visualization of the timing of the condition blocks and time points for acquisition of saliva samples, subjective stress ratings, and heart rate.

2.5. Acquisition and processing of fMRI data

During the ScanSTRESS task, gradient-echo planar images were acquired on a 3-T scanner (Trio; Siemens, Munich, Germany) with a 32channel head coil using the following parameters: 426 vol; repetition time (TR) = 1560 ms; echo time (TE) = 25 ms; flip angle = 65° . Twentyeight slices of 3-mm isotropic voxels were acquired sequentially in descending order and auto-aligned parallel to the anterior commissure-posterior commissure line. A high-resolution T1-weighted image (magnetization prepared-rapid gradient echo; 1-mm isotropic voxels; TR = 1900 ms; TE = 2.52 ms; flip angle = 9°) and a fieldmap image (3mm isotropic voxels; TR = 434 ms; TE = 5.19 ms; flip angle = 60°) were acquired for registration.

The following preprocessing was conducted using FMRIB Software Library (FSL): motion correction, slice-time correction, brain extraction, and spatial smoothing with a full width at half maximum (FWHM) of 6 mm (Smith et al., 2004). Registration parameters were obtained for the functional-to-structural transformation, using the fieldmap to correct for inhomogeneity artifacts (the epi reg command within FSL employs the Boundary Based Registration [BBR] algorithm). Normalization parameters for the structural to standard space (2 mm, based on Montreal Neurological Institute) transformation were obtained with Advanced Normalization Tools (ANTs) (Avants et al., 2011). Subsequently, the functional data were cleaned further from artifacts using Independent Component-Analysis based Automatic Removal of Motion Artifacts (ICA-AROMA), which regresses out latent signal sources (independent components) classified as 'noise' (Pruim et al., 2015). Finally, a high-pass temporal filter of 420 s, considering the period of task stimulation, was applied to the cleaned four-dimensional images, which were then normalized to standard space using the registration parameters derived previously. The slices stack was positioned to include the entire temporal lobe, resulting in the exclusion of dorsal parts of the brain in some participants due to the restricted number of slices that could be acquired given our TR.

First-level analyses were conducted with the fMRI Expert Analysis Tool within FSL (FEAT v6.00). A general linear model was set up, where stress blocks were compared with control blocks, and tested for each participant, including four regressors: (1) stress figure rotation (stress_fig), (2) stress subtraction (stress_maths), (3) control figure rotation (con_fig), and (4) control subtraction (con_maths). Because it was a block design, we used square as a basic waveform, with the following parameters: skip 6.24 s (4 TRs); duration of on-period = 60 s; duration until on-period returns = 280 s; pause = 25 s. All were convolved with gamma hemodynamic response function and filtered temporally with a high-pass filter of 420 s.

Group-level differences in activity between stress blocks and control blocks were assessed using a one-sample *t*-test, along with the association between these differences and Space Syntax data, each time including age as a covariate. Subsequently, the resulting *t*-statistical maps underwent threshold-free cluster enhancement using default parameter settings (H = 2 (height raised to power H), E = .5 (extent raised to power E), C = 6 (Connectivity)). Significance testing was conducted with permutation testing (4,000 iterations) using TFCE_mediation (https://github.com/trislett/TFCE_mediation) (Lett et al., 2017). In the latter step, a null distribution of random results was generated against which empirical findings were tested. This strategy resulted in statistical images that were Family Wise Error (FWE)-corrected across the whole brain at p < .05 for the main effect of stress.

Considering the mutual correlation between the four street network characteristic measures (average r = .71), the Bonferroni-corrected significance threshold was p = .03 (as calculated with SISA; www. quantitativeskills.com/sisa/). Voxel-wise uncorrected (*t*) and corrected (TFCE *p*) statistical maps of our analyses are available on NeuroVault (http://neurovault.org/collections/12655).

2.6. Descriptive and statistical analyses

To describe the street network characteristics, means, and standard deviations were calculated for the neighborhood, original, and masked street values. Since masked address data provides a higher level of data protection, a Wilcoxon signed-rank test was executed to compare the values between original and masked address data to explore if the application of masked address data is comparable to original values. Additionally, we conducted Pearson correlations for the street network characteristics from the neighborhood to the street scale, enabling us to evaluate the association between the values at each scale.

Successful stress induction was confirmed by performing repeated measures analysis of covariance (RM-ANCOVA), including age and Body Mass Index (BMI) as covariates. This was done for repeated measurements of cortisol concentrations in saliva (4 time points: 2 pre- and 2 post-stress), subjective stress ratings (4 time points: 2 pre- and 2 post-stress), and heart rate (3 time points: mean during stress task, and mean before and after stress task). Greenhouse-Geisser corrections were applied when the assumption of sphericity was not met. Furthermore, we repeated the RM-ANCOVAs and added the four street network characteristics for neighborhood level and masked address as covariates to explore associations between street network characteristics and stress markers. The significance level was Bonferroni-adjusted with SISA to p = .03.

To investigate the potential connection between street network characteristics and air pollution levels, indicative of motorized traffic volume, we utilized data from a previous study, which provided mean values for particulate matter ($PM_{2.5}$ and PM_{10}) and nitric oxide (NO_2 and NO_x) for the year 2015. These values were extracted on a raster of 500 \times 500 m from the Berlin's Senate Department for Urban Development and Housing (for more information on the calculation of air pollution data, refer to Dimitrov-Discher et al., 2022) and Pearson correlations were conducted. Furthermore, to explore PM as a potential mediator variable between street network characteristics and neuronal social stress processing, we performed a simple mediation analysis with the PROCESS macro by Hayes (2018). As dependent variables, we extracted mean activity z-scores from the overlapping significant brain regions for the main effect of PM2.5 and PM10 and street network characteristics (Fig. S3). To compute the confidence intervals and inferential statistics, we employed bootstrapping with 5000 samples together with heteroscedasticity consistent standard errors (Davidson & MacKinnon, 1993). Effects were deemed significant when the confidence interval did not include zero.

All behavioral analyses were performed with IBM SPSS Statistics for Windows, Version 22 (IBM Corp., Armonk, NY).

3. Results

3.1. Descriptive statistics for street network characteristics

Means and standard deviations of the 4 Space Syntax measures for each observational limit are reported in Table 2. A mean neighborhood connectivity of 3.45 corresponds to each street in the neighborhood being connected to 3.45 (approximately 3) streets directly, while a mean masked street connectivity of 8.90 corresponds to the street closest to a masked location, connected to approximately 9 streets directly. Table 2 also showcases how a street closest to the masked (or original) location often falls within the shortest and straightest route with higher mean 1.30 NACH value (which is higher than the average mean NACH value of

Table 2

Descriptive statistics for street network characteristics (following Space Syntax theory).

	Connectivity M (SD)	Local integration <i>M (SD)</i>	Global integration M (SD)	NACH M (SD)
Neighborhood	3.45 (.25)	1.71 (.10)	1.00 (.14)	.62 (.03)
Original street	10.21 (8.81)	2.70 (.67)	1.44 (.32)	1.30
				(.18)
Masked street	8.90 (5.62)	2.67 (.55)	1.43 (.29)	1.30
				(.17)

Note. M = mean, SD = standard deviation, NACH = normalized angular choice.

majority of the cities (Hillier et al., 2012) in comparison to mean NACH value (i.e., 0.62) for all the streets in the neighborhood. The difference between the mean global integration value of the neighborhood and that of the street closest to the masked location was the lowest. Higher integration values, both local and global, indicate greater connectivity, while lower values correspond to more segregation within the street network (e.g., location 1 neighborhood has more segregation locally due to least mean local integration). Fig. 5 shows two neighborhoods and the visualization of street network analysis (with local integration being one of the attributes) based on Space Syntax theory. It shows two distinct neighborhoods based on mean local integration values, where neighborhoods with higher mean local integration are mostly distributed in the main urban area of Berlin (location 42 in Fig. 3 has high mean local integration), whereas those with lower mean local integration are mostly located on the outskirts of the city (location 1 in Fig. 3 has low mean local integration).

Wilcoxon signed-rank test (Table 3) revealed significant differences between both the neighborhood value and the original street value for each of the 4 Space Syntax measures, as well as the neighborhood value and the masked street value (all p < .001). The Wilcoxon signed-rank test showed no significant difference between the original and masked street values for connectivity (p = .616), local integration (p = .442), global integration (p = .486), and NACH (p = .897). Following this, to narrow down the focus on neighborhood and individual coordinate data sets, the 'masked' street data will be used and referred to as 'point address' (after Table 3) in this article.

Within each observational limit, the street network characteristics significantly correlated with each other (Table 4). Connectivity, local and global integration, and NACH showed positive associations with correlation coefficients between 0.496 and 0.936 and a significance value of ≤ 0.001 .

The detailed results of the RM-ANCOVAs with age and BMI as covariates to confirm successful stress induction can be found in our previous publication (Dimitrov-Discher et al., 2022). In summary, stress ratings demonstrated an increase from pre-stress (M(t2) = 2.95) to post-stress (M(t3) = 5.32, t(41) = -9.346, p < .001, d = -1.35, CI [-2.837 -1.829]) and a subsequent decrease to the next time point (M (t4) = 3.61, t(41) = 7.454, p < .001, d = .989, CI [1.198 2.088]). Heart rate demonstrated a significant increase during stress (M(t1) = 65.31, M (t2) = 78.65, t(36) = -8.353, p < .001, d = -1.116, CI[-16.573-10.098]), followed by a decrease during the scan after the stress task (M(t3) = 65.69, t(38) = 10.389, p < .001, d = 1.034, CI [10.313 15.305]). To explore associations between stress markers and street network characteristics, we repeated RM-ANCOVAs and focused on possible interaction effects between time and street network characteristics. No significant interaction effects were found (all p > .03) (Table S1).

3.2. Association with air pollution

All four street network characteristic measures correlated positively with the four measures of air pollution (PM_{2.5}, PM₁₀, NO₂, and NO_x) on neighborhood level (0.328 < r < 0.555, all $p \leq .034$). For the point



Fig. 3. Locations of high local integrated network for 42 neighborhoods in Berlin (Note: Location 1 has the lowest overall mean local integration value amongst the neighborhoods). Map Source: ESRI, DeLorme, HERE, MapmyIndia retrieved from QGIS on 13/07/2021.



Fig. 4. Donut masking criteria for the identified coordinates in Berlin.

addresses, significant correlations were found between both local and global integration and all four air pollution variables (0.410 < r < 0.656, all $p \le .007$) and between connectivity and PM_{2.5} (r = .318, p = .040) as well as PM₁₀ (r = .320, p = .039). In general, correlations were higher for particulate matter (0.346 < r < 0.656, all $p \le .040$) than for nitric oxide (0.328 < r < 0.466, all $p \le .034$) on two observational limits. Highest correlation coefficients with lowest significance level were found for global integration on both observational limits with particulate matter

(0.545 < r < 0.656, all $p \le .001$; see Table 5 for all correlations).

Four simple mediation analyses were performed to analyze whether the direct path between local or global integration and mean brain activity would be mediated by $PM_{2.5}$ or PM_{10} . In the case of local integration and $PM_{2.5}$, local integration predicted the mediator $PM_{2.5}$ significantly (B = 3.31, p = .01), which in turn predicted mean brain activity during the social stress task significantly (B = -.73, p = .05). However, we found that the relationship between local integration and



A1: Satellite map for area surrounding masked location 1



A2: Local integration map for area surrounding masked location 1



A3: NACH segment map for area surrounding masked location 1



B1: Satellite map for area surrounding masked location 42



B2: Local integration map for area surrounding masked location 42



B3: NACH segment map for area surrounding masked location 42

Fig. 5. Cutouts from satellite image showing neighborhood surrounding location 1 (A1) and 42 (B2) (Source: Google Earth 2023), axial maps showing local integration of streets within 1500 m radius of the masked coordinates 1 (A2) and 42 (B2), and segment maps showing straightest and shortest route between any segments via NACH values within 1500 m radius of a masked coordinates 1 (A3) and 42 (B3). Blue street segments in (A3 and B3) represent values lower than 1.2 (which is considered an average value for the majority of cities (Hillier et al., 2012)), while red segments have high values. The red axial lines in (A2 and B2b) represent high local integration values, while blue axial lines represent low local integration. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

mean brain activity is not mediated by $PM_{2.5}$ (B = -7.27, *p* = .003, 95%-CI [-5.34, 0.01]. In the case of global integration and $PM_{2.5}$, global integration predicted the mediator $PM_{2.5}$ significantly (B = 2.88, *p* = .005), which in turn predicted mean brain activity during the social stress task significantly (B = -.77, *p* = .02). We found that the relationship between global integration and mean brain activity is mediated partially by $PM_{2.5}$ (B = -4.80, *p* < .001, 95%-CI [-5.07, -.24], as the direct effect remained significant (B = -6.99, *p* < .001). In the case of

local integration and PM_{10} , local integration predicted the mediator PM_{10} significantly (B = 6.27, p = .002), which in turn did not predict mean brain activity during the social stress task (B = -.40, p = .09). We found that the relationship between local integration and mean brain activity was not mediated by PM_{10} . In the case of global integration and PM₁₀, global integration predicted the mediator PM_{10} significantly (B = 5.33, p = .001), which in turn predicted mean brain activity during the social stress task significantly (B = -.041, p = .04). We found that the

Table 3

Results of Wilcoxon signed-rank test for the comparison of neighborhood values with original and masked street values.

		Neighborhood Z (p)
Original	Connectivity	5.177 (<.001)***
	Local integration	5.402 (<.001)***
	Global integration	5.647 (<.001)***
	NACH	5.646 (<.001)***
Masked	Connectivity	5.520 (<.001)***
	Local integration	5.583 (<.001)***
	Global integration	5.646 (<.001)***
	NACH	5.647 (<.001)***

Note. Z = z-statistic of Wilcoxon signed-rank test, p = significance value, *** p < .001, NACH = normalized angular choice.

Table 4

Pearson Correlation r (p) between street network characteristics for neighborhood and point addresses.

	Local integration <i>r</i> (p)	Global integration <i>r</i> (p)	NACH r (p)
Neighborhood	.888 (<.001) ***	.558 (<.001) ***	.936 (<.001) ***
Point address	.796 (<.001) ***	.609 (<.001) ***	.623 (<.001) ***
Neighborhood		.759 (<.001) ***	.873 (<.001) ***
Point address		.850 (<.001) ***	.644 (<.001) ***
Neighborhood			.644 (<.001) ***
Point address			.496 (<.001) ***
	Neighborhood Point address Neighborhood Point address Neighborhood Point address	Local integration r (p) Neighborhood .888 (<.001) **** Point address .796 (<.001) **** Neighborhood .796 (<.001)	Local integration r (p)Global integration r (p)Neighborhood.888 (<.001) ***.558 (<.001) ***Point address.796 (<.001) ***.609 (<.001) ***Neighborhood.759 (<.001) ***Point address.850 (<.001) ***Neighborhood.850 (<.001) ***

Note. r= correlation coefficient, p= significance value, *** p<.001, NACH = normalized angular choice.

Table 5

Pearson correlation r (p) between street network characteristics on two observational limits with air pollution (modeled annual mean value for the year 2015 on a raster of 500 m \times 500 m).

		PM _{2.5} r (p)	PM ₁₀ r (p)	NO ₂ r (p)	NO _x r (p)
Connectivity	Neighborhood	.435 (.004)**	.472 (.002)**	.395 (.010)*	.386 (.012)*
	Point address	.318 (.040)*	.320 (.039)*	.215 (.171)	.210 (.181)
Local integration	Neighborhood	.455 (.002)**	.474 (.002)**	.365 (.018)*	.360 (.019)*
	Point address	.515 (<.001) ***	.490 (.001)**	.420 (.006) **	.410 (.007) **
Global integration	Neighborhood	.545 (<.001) ***	.555 (<.001) ***	.341 (.027)*	.337 (.029)*
	Point address	.636 (<.001) ***	.656 (<.001) ***	.466 (.002) **	.458 (.002) **
NACH	Neighborhood	.346 (025)*	.395 (010)*	.334 (031)*	.328 (.034)*
	Point address	.149 (.345)	.123 (.437)	.230 (.144)	.232 (.140)

Note. r = correlation coefficient, p = significance value, *** p < .001, ** p < .01, * p < .05, PM = particulate matter, NO = nitric oxide, NACH = normalized angular choice.

relationship between local integration and mean brain activity is partially mediated by $PM_{2.5}$ (B = -5.04, p < .001, 95%-CI [-5.30, -.18], as the direct effect remained significant (B = -7.25, p = .001) (Fig. S2).

3.3. Association between street network characteristics and brain activity

The neighborhood's local and global integration values were negatively associated with task-related activity in the stress paradigm. This means that participants living in street networks of great proximity tended to have lower activation in several brain regions during the stress compared to the control condition (Fig. 6). Local integration showed an association in the right ventrolateral prefrontal cortex (vlPFC), insula, and caudate (p < .03, FWE-corrected for comparison of four street network characteristic measures). At a more lenient FWE-corrected threshold of p < .05, additional associations were found with the right supramarginal gyrus, precentral gyrus, putamen, and thalamus. Negative associations were found bilaterally in the dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC), insular cortex (IC), and caudate. Global integration showed an association in the bilateral insula, right precentral gyrus, and left frontal operculum (p < p.03, FWE-corrected for comparison of four street network characteristic measures). At a more lenient FWE-corrected threshold of p < .05, additional associations were found in the right vlPFC, supramarginal gyrus, putamen, caudate, and lateral occipital cortex. Negative associations were found in the left hemisphere in the dACC, precuneus, and parahippocampal cortex and bilaterally in the frontal operculum and precentral gyrus. Scatter plots illustrating the mean activation in association with mean local and global integration values can be found in Fig. 7. There were no significant results considering the neighborhood values for connectivity, or NACH. When repeating the analysis with concrete values for the point addresses instead of the neighborhood values, no significant associations were found for connectivity, local integration, global integration or NACH. Table 6 provides an overview of the fMRI analyses, results, and corresponding brain networks.

4. Discussion

Exploring what constitutes a healthy city, this exploratory, crosssectional study aimed to examine the association between street network characteristics and brain activation during a social stress paradigm in the MRI scanner.

When analyzing the neighborhood mean values, both local and global integration were negatively associated with brain activity during the social stress paradigm. This indicates that higher proximity between streets was related to less activity during stress compared to the control condition in several brain regions. Interestingly, most of the significant brain regions that showed less signal during stress compared to no stress (dACC, insula, precentral gyrus, caudate, putamen, thalamus) are key regions of the salience network. This network is known to be active during emotional processing and the presence of salient stimuli, promoting the detection of possible threats (van Oort et al., 2017). Firstly, both local and global integration have been reported to increase walking activity (Baran et al., 2008; Hajrasouliha & Yin, 2015; Lerman et al., 2014), which has been associated with deactivations in the caudate and ventral anterior putamen during an emotional face viewing task (Schmitt et al., 2019). Furthermore, motorized traffic intensified in streets with high global integration values (Hillier & Vaughan, 2007; Knöll et al., 2018), augments air pollution. We recently reported deactivations with increased particulate matter (especially PM2.5) in brain regions like the insula, caudate, putamen, thalamus, and dACC (Dimitrov-Discher et al., 2022). Interestingly, we found positive correlations between the street network characteristics and the amount of air pollution. Those correlations were especially pronounced for the neighborhood values (all four street network characteristics showed correlations), probably because air pollution was also acquired for a larger radius (500 \times 500 m) instead of a single street. Global integration showed highest correlation



Fig. 6. Weaker activity related to (a) local integration and (b) global integration for the contrast stress > control overlaid on the 1-mm MNI template. Blue indicates p < .05 (FWE-corrected) and red indicates p < .03 (FWE-corrected for comparison of four street network characteristic measures). R, right; L, left; xyz = MNI-coordinates. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



Fig. 7. Scatter plots to illustrate the association between mean (a) local and (b) global integration neighborhood values and mean activation (z-score, p < .05) during stress processing.

coefficients, which mirrors the hypothesis that it is associated with traffic volume (Hillier & Vaughan, 2007). Mediation analyses supported that the association between global integration and mean brain activity during a social stress task was partially mediated by PM_{2.5} and PM₁₀, whereas for local integration, no mediation effect could be found. Furthermore, the right ventrolateral prefrontal cortex (vlPFC) showed less activation associated with both global and local integration. The vlPFC has been reported to be deactivated in association with PM2.5 (Dimitrov-Discher et al., 2022). High integration has correspondingly been associated with more traffic volume, hence higher air pollution (Hillier & Vaughan, 2007). The results might reflect that highly integrated streets also promote social activities (Sarkar et al., 2013). Social support has been hypothesized to attenuate reactivity to threats and stressful events (Cohen & Wills, 1985), which is mirrored by less activity in, e.g., the insula and dACC (Eisenberger et al., 2007). Meanwhile, high global and citywide integration have been discussed to show exposure to a lot of different stimuli during everyday life, which can be perceived as stressful (e.g., local shops and restaurants, busy streets with people and traffic, noise) (Knöll et al., 2015). Thus, we could hypothesize that the

threshold of perceiving salient stimuli might be higher for someone regularly exposed to a certain amount of input based on high integration levels. Several subcortical regions (rostral ACC, medial prefrontal cortex, hippocampal, and amygdala) demonstrated a habituation of activity when repeatedly exposed to aversive pictures, though it should be mentioned that the study sample only comprised eight participants (Phan et al., 2003). This hypothesis needs to be tested in future studies. Taken together, less activity in the reported regions may point towards a decreased stress responsivity or alertness towards stress.

Furthermore, some regions (precuneus, supramarginal gyrus, parahippocampal cortex) are related to the default mode network (DMN) which has been associated with a variety of functions, amongst others, self-referential processing due to negative feedback during a psychosocial stressor (Buckner et al., 2008; van Oort et al., 2017). Considering that increased feelings of social rejection were associated with increased DMN activity (Muscatell et al., 2015), we hypothesize that highly integrated streets promote social support which buffers the perception of threat-related stimuli correlating with less activations in the DMN. The precuneus by itself is involved in several mental processes, e.g., it has

Table 6

Overview of significant brain regions according to street network characteristic and associated brain network.

	Space Syntax	p (FWE- corrected)	Brain regions	Brain network
Neighborhood	Connectivity	n.s.		
	Local integration	<.03	vlPFC (r)	-
			IC (r) caudate	SN
			nucleus (r)	SN
		<.05	supramarginal	DMN
			gyrus (r)	SN
			precentral gyrus (r)	SN
			putamen (r)	SN
			thalamus (r)	CEN
			dlPFC (b)	SN
			dACC (b)	SN
			IC (b) caudate	SN
			nucleus (b)	
	Global	<.03	precentral gyrus (r)	SN
	integration		frontal operculum	CEN
			(1)	SN
			IC (b)	
		<.05	vlPFC (r)	-
			supramarginal	DMN
			gyrus (r)	SN
			putamen (r)	SN
			caudate (r)	-
			lateral occipital	SN
			cortex (r)	DMN
			dACC (1)	DMN
			precuneus (l)	CEN
			parahippocampal	SN
			cortex (l)	
			frontal operculum	
			(b)	
			precentral gyrus (b)	
	NACH	n.s		
Point address	Connectivity	n.s.		
	Local integration	n.s.		
	Global integration	n.s.		
	NACH	n.s.		

Note. NACH = normalized angular choice, p = significance value, FWE = familywise-error, n.s. = not significant, SN = Salience Network, DMN = Default Mode Network, CEN = Central Executive Network, PFC = prefrontal cortex, IC = insular cortex, ACC = anterior cingulate cortex, vl = ventrolateral, dl = dorsolateral, d = dorsol, r = right, l = left, b = bilateral.

been reported to be deactivated during emotional face viewing in association with physical activity as well as during psychosocial stress in association with $PM_{2.5}$ (Dimitrov-Discher et al., 2022; Schmitt et al., 2019). It should be noted that DMN activity is typically assessed during resting-state scans, where participants will not perform any task but let their minds wander (Buckner et al., 2008). Social stress has been shown to alter DMN activity during resting state after a psychosocial stress task (Veer et al., 2011), which we cannot assess as a resting-state analysis was not included in our study.

Mean connectivity and NACH, as well as all four street network characteristics for point addresses, were not associated with task-related brain activity in contrast to mean global and local integration. On one hand, this questions the comparability of studies that use values derived from radius versus individual segments. It has been discussed that street network characteristics should be aggregated into an area-level measure to properly reflect associations with walking (Koohsari et al., 2019). On the other hand, the specific results for only two of the four street network characteristic measures support the assumption that they relate to different concepts, even though correlations between the four measures indicate that similarity is more dominant than distinctness. NACH is a relatively new Space Syntax attribute compared to integration and connectivity. While a direct route with a higher NACH value has been reported to attract more cyclists, the quality of space—though not assessed in our study—will also influence the mobility behavior of the user group. Connectivity is synonymous with integration, but on the smallest possible scale, specifically with 1 topological depth as radius. This might imply that the selected radius for integration analysis plays an important role, meaning that connectivity covers the street network on a scale that is too small. Furthermore, neighborhoods with similar mean connectivity values might not always represent similar walkable areas, as some of them might have more natural barriers (e.g., rivers) or cul-de-sacs.

When comparing the three observational limits of analysis, we found no significant difference between the street values for original and masked addresses but a significant difference existed between these two limits when compared to the mean values of the 1500 m radius. The advantage of mean values from a radius is that it considers the connections of all streets in the predefined radius, which seems reasonable when examining walkability and physical activity (Koohsari et al., 2019). Moreover, neighborhood-level street network configuration is more connected to residents' daily experience, so it might be more appropriate for examining the long-term effects of daily-life environmental features on residents. However, several studies have used the segment value instead (Baran et al., 2008; Emo et al., 2012; Knöll et al., 2015, 2018; Orellana & Guerrero, 2019), which has the advantage that the analysis would be more context-sensitive as it reflects the characteristics of the most directly exposed environment of a measurement point. Consequently, segment values might be more applicable for examining short-term onsite experiences, such as stress perception in specific public spaces (Knöll et al., 2018) or way-finding decisions at intersections (Emo et al., 2012).

Several limitations need to be addressed for this study. First, the sample was small and only comprised young and middle-aged male participants, restricting generalizability to women and other age groups. The study design was cross-sectional; therefore, we cannot infer causality from our results. Second, interaction effects between the stress markers (saliva cortisol, subjective stress rating, and heart rate) and the individual street network characteristics were not found. We deduct from this that the brain regions we found to be significantly associated with the street network characteristics do not only reflect stress-related processing, but further functions. E.g., the ScanStress task also entails higher cognitive load in the stress compared to the control condition. Regions like the dACC have been reported to be stronger activated with higher cognitive load, whereas PCC showed less activation (Arsalidou et al., 2013). Taken from this, future studies should incorporate additional assessments linking stress processing to street networks, like ambulatory assessments, that allow for a real-time detection of street networks' impact. Third, though both local and global integration have been associated with walking (Baran et al., 2008; Hajrasouliha & Yin, 2015; Lerman et al., 2014), global integration has additionally been considered a good predictor of higher traffic volume (Hillier & Vaughan, 2007). This might lead to the assumption that associations with psychosocial stress could be in opposite directions. Walking or cycling is the dominant mode of transport in Berlin for distances up to 1 km (92%) and 1-3 km (56%) (SenUVK, 2019). However, as the radius for each neighborhood has been chosen at 1500 m, the scale for global integration values might have been too small to comprehensively reflect traffic volume. Also, results might have been different if the whole city of Berlin instead of 42 single radii would have been used as the common system. The fact that both integration values led to fairly high correlation amongst each other might also explain parts of the results. Similarly, correlations with connectivity and NACH appeared, which implies a certain similarity between all four Space Syntax measures, which ideally would not exist. Future studies should also inquire about participants' typical mode of transport and the daily duration spent at the home address. Additionally, urban upbringing might be inquired as to explore differential exposure to urban environments and its effect. Fourth, the list of potential mediators between street networks and stress processing certainly comprises more than the selected ones, e.g., gender,

age, health status, and ethnic background. For future studies, it would be interesting to explore the possibility of directly integrating those mediators into the analysis. An interesting approach to combine Space Syntax variables with information on social activity potential was proposed by Koohsari et al. (2016), who developed a composite measure of population density and integration (Space Syntax walkability). Additional mediators, such as traffic noise and crime rates (Baranyi et al., 2021; Dustmann & Fasani, 2016; Evans et al., 2001; Jensen et al., 2018; Nubani & Wineman, 2005; Summers & Johnson, 2017; Weisburd et al., 2018), should be considered in future studies.

This exploratory study provides the first empirical evidence of the association between neighborhood street network characteristics and brain activity during stress processing. Previous research has focused on the negative characteristics of global integration, as it has been associated with car movement and air pollution. Given the correlation between global integration and air pollution, along with changes in brain activity during stress processing, air pollution seems an important mediator. However, future studies should consider social activities as a potential positive side-effect of high integration, which, in turn, promotes stress processing on a neuronal level. Another potential mediating factor is the distribution of and exposure to green space in the city, which has been associated with mood improvement and stressregulating effects in previous fMRI studies (Dimitrov-Discher et al., 2022; Tost et al., 2019). However, no study has yet reported a correlation between street network characteristics (based on Space Syntax theory) and green space distribution, although studies have stressed the benefits of placing parks in more integrated areas to ensure accessibility (Huang et al., 2020; Tannous et al., 2021).

The findings of this exploratory study indicate that optimizing the structure of neighborhood street networks can be one possible pathway to mitigate the negative effects of urban densification on mental health. From a neuro-urbanistic perspective, Space Syntax provides an efficient approach to objectively quantify urban environment (i.e., street network) characteristics on different urban scales. More evidence demonstrating the effects of neighborhood street network characteristics on mental well-being-related outcomes is needed in future studies.

Funding

This work was supported by Deutsche Forschungsgemeinschaft (DFG) [Project number 437818133 and 438075992] and partly funded by a research grant from Servier Deutschland GmbH and payments by the German Environment Agency.

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Acknowledgements

We would like to thank Prof. Dr. Nadja Kabisch and Jan Hemmerling for the consent to incorporate the processed air pollution data and information, which they provided for a previous study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.jenvp.2023.102142.

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