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Associations between urban upbringing and cortical thickness and gyrification

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ABSTRACT

Urbanicity has been linked to several psychiatric disorders, especially schizophrenia. Recent studies suggest effects of urban upbringing and stress on brain structure and function. Here, we used surface-based and voxel-based morphometry to study the effects of urban upbringing in different environments on variation in brain structure in a non-clinical sample. We recruited 85 young and healthy individuals from the community and recorded urban vs. rural background in their first 15 years of live. All participants underwent T1-weighted 3T MRI, which were then processed via CAT12 toolbox (in SPM12) to analyse cortical volume, thickness and gyrification. These parameters were correlated with an established measure of cumulative childhood and adolescence exposure to urban environments. We found significant ($p < 0.05$, FWE-corrected) negative correlations of cortical thickness with higher index of urban upbringing in the left dorsolateral prefrontal cortex, bilateral medial prefrontal cortices, as well as temporal cortices including the left superior temporal and left parahippocampal cortex. In contrast, results for volume and gyrification (incl. left posterior cingulate cortex) did not survive correction for multiple comparisons. We show a strong association of early-life urbanicity with cortical thickness in several areas, which are also impaired in schizophrenia patients. Along with other findings, these results converge on the dorsolateral prefrontal cortex as an area mediating this environmental risk.

1. Introduction

Psychiatric disorders are commonly conceptualised as arising from interplay between genetic and environmental factors. Both genetic liability and exposure to environmental stressors (specific and non-specific) might result in the expression of a disease spectrum phenotype, as shown for psychotic disorders like schizophrenia (Gottesman and Gould, 2003; van Os et al., 2008). While genetic factors are of significant importance in many conditions, the assessment of environmental factors is of increasing interest, as for some of these factors targeted interventions are becoming available (Davis et al., 2016).

One of the strongest and longest known environmental factors associated with higher risk of schizophrenia is urbanicity (Faris and Dunham, 1939). In addition to the considerable evidence of increased risk for multiple psychiatric disorders associated with urbanization (Peen and Dekker, 2004; Peen et al., 2010), there is particular evidence for psychotic disorders. Adults and adolescents with urban background show an up to two-fold increase in adult psychosis-risk compared to villagers (Lewis et al., 1992, Newbury et al., 2016). Urban birth and residence have also been shown to positively correlate with the prevalence of schizophrenia (Padhy et al., 2014, van Os et al., 2001). More specifically, urban upbringing, i.e. where an individual was brought up in his/her first 15 years of life, rather than urbanicity at birth might be a determining factor for schizophrenia risk, and operate in a dose-response relationship (Pedersen and Mortensen, 2001).

In contrast to studies illuminating the genetic risk for schizophrenia, there is very limited data to understand the impact of urbanicity on neural systems (Lambert et al., 2015). A landmark study using functional magnetic resonance imaging (fMRI) has demonstrated that urbanicity and urban upbringing are associated with variation in brain function during a stress test: while current urbanicity was associated with amygdala activation, urban upbringing (i.e. where participants had grown up during their first

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15 yrs of life) was correlated with anterior cingulate cortex activation (Lederbogen et al., 2011). These findings have brought forward a strong case for differential modulation of current versus lifetime exposure to urban environments on brain function. A subsequent genetic imaging study has furthermore suggested an interaction with genetic variation in the neuropeptide S receptor gene (Streit et al., 2014).

A more recent study using voxel-based morphometry (VBM) in healthy participants has then shown that early life urbanicity is correlated with right dorsolateral prefrontal cortex volume (Haddad et al., 2015); a similar effect in the anterior cingulate cortex was only seen in men. Altogether these findings show that early environmental factors like urbanicity appear to result in long-lasting effects on brain structure and function, which might elucidate the mechanisms of increased risk for psychiatric disorders, especially schizophrenia.

In the present study, we sought to extend these studies in order to assess the association of urban upbringing with cortical structure in a healthy non-clinical sample. We tested for the hypothesis that this risk factor for psychiatric disorders might correlate with surface-based morphometry measures of brain structure. We further assumed that early-life urban upbringing is associated with brain structure and that this effect is expressed in general markers of regional brain volume rather than early indicators of aberrant cortical folding. Applying surface-based morphometry (SBM) in our sample characterised for urban upbringing (as used in the above previous studies), we used two complementary indicators of brain structure (cortical thickness vs. gyrification) to map differential effects. These parameters provide complementary information, since the former is amenable to (adaptive) changes, while the latter is assumed to reflect rather stable inherent morphological characteristics. In particular, we hypothesised that the risk introduced through early-life urban upbringing would manifest in variation of cortical thickness in dorsolateral prefrontal and anterior cingulate cortices, but not in gyrification, which is assumed to rather reflect very early development, i.a. intra-uterine and during the first years of life (Nenadic et al., 2015a, Zilles et al., 2013).

2. Methods

2.1. Participants

We included 85 healthy young adults from the community (57 female, 28 male; for demographic and psychometric details, see Table 1). All gave written informed consent to a study protocol approved by the local Ethics Committee of Jena University Medical School.

All participants were screened for exclusion criteria including major neurological, current or former psychiatric conditions and unmedicated general medical conditions, as well as history of psychosis in first-degree relatives. To exclude major cognitive impairment, IQ was estimated using the MWT-B (Antretter et al., 2013), a German language inventory similar to the NART. Most participants were students and had therefore completed German secondary school with a university-entrance diploma (n = 74). The others had either completed structured apprenticeship-based vocational training schemes (n = 9) or already gained a first graduate degree (n = 2). Participants also completed the Edinburgh Handedness Inventory (Oldfield, 1971).

All participants completed the urbanicity inventory, assessing urban upbringing (Lederbogen et al., 2011). This questionnaire registers the rural or urban environment the participant lived in during their first 15 years of life. Distinct categories were formed for rural area (<10.000 inhabitants), small cities (10.000–100.000 inhabitants), and large cities/metropolitan centres (>100.000 inhabitants) and assigned values 1, 2, and 3, respectively, which were rated for each year of life (1–15), and added for these first 15 years of life to give a total score. Hence, scale values could range from 15 to 45. In our sample mean urbanicity score was 27.38 ± 12.18 (range 15–45), indicating a very suitable distribution for correlation analyses. Also, in our population, this early-life urbanicity score had no significant correlations with age, gender, IQ and education. We also assessed current urbanicity using the same scheme as above. At the time of measures most of the participants lived in Jena (>100.00 inhabitants and therefore coded with “3”), and mean current urbanicity of our sample was 2.69 ± 0.72.

To assess subclinical occurrence of psychotic symptoms, we analysed the paranoid ideation and psychoticism subscales of the SCL90-R questionnaire, which subjects completed at the time of study participation. The SCL-90-R is a well established self-rating instrument to assess a broad range of psychopathological symptoms and is a commonly used tool for the assessment of psychological distress across multiple symptom domains (Derogatis et al., 1976). It is among the most widely used self-rating instruments with more than 1000 published studies in various clinical and non-clinical settings (Tarescavage and Ben-Porath, 2014). The SCL-90-R consists of 90 items, each to be rated on a 0–4 Likert-type scale, which can then be analysed syndrome-wise with nine different scales. The participants are asked to rate the symptoms according to their occurrence during the last seven days. We selected scales 8 (paranoid ideation) and 9 (psychoticism) for psychosis-related subclinical symptoms. Dividing the cumulative value of the scale by the number of items we calculated the scale value, which could therefore rank from 0 to 4 and resulted in none to very low distress through psychotic symptoms in our sample (mean 0.2 ± 0.29 for paranoid ideation and mean 0.13 ± 0.25 for psychoticism).

2.2. Magnetic resonance imaging (MRI) data acquisition

All participants underwent high–resolution T1-weighted MRI on a 3 T S Prisma fit + system (an original Tim Trio scanner system upgraded for hardware and software) (Siemens, Erlangen,

Table 1
Demographic characteristics of the sample.

	Study sample (n = 85)
Gender	57 female, 28 male
Age (mean, SD)	24.06 ± 2.98 yrs (range 19–38 yrs)
Estimated IQ (mean, SD)	116.07 (±13.53)
Handedness score (mean, SD)	0.72 ± 0.47
Urbanicity score for urban upbringing in the first 15 years of life (mean, SD)	27.38 ± 12.18 (range 15–45)
Current urbanicity	2.69 ± 0.72
SCL-90-R- paranoid ideation (mean, SD)	0.2 ± 0.29 (range 0–1.17)
SCL-90-R- psychoticism (mean, SD)	0.13 ± 0.25 (range 0–1.5)

Germany) using a standard quadrature head coil and a T1-weighted MPRAGE sequence (TR 2300 ms, TE 3.03 ms, α 9°, 192 contiguous sagittal slices, in-plane field of view 256 mm, voxel resolution 1 × 1 × 1 mm; acquisition time 5:21 min). All images were visually inspected for artefacts and passed this quality control as well as the homogeneity control implemented in the CAT12 toolbox.

2.3. Surface-based morphometry analysis

The CAT12 toolbox contains a processing pipeline for surface-based morphometry, which includes an established novel algorithm for extracting the cortical surface (Dahnke et al., 2013), which then allows the computation of multiple morphometric parameters, including cortical thickness as well as gyrification based on the absolute mean curvature approach (Luders et al., 2006).

The T1-weighted images underwent tissue segmentation to estimate white matter distance. Local maxima were then projected to other grey matter voxels by using a neighbour relationship described by the WM distance. These values equal cortical thickness. This projection-based method also includes partial volume correction, sulcal blurring and sulcal asymmetries without sulcus reconstruction (Dahnke et al., 2012). Topological correction is performed through an approach based on spherical harmonics. For inter-participant analysis an algorithm for spherical mapping of the cortical surface is included (Yotter et al., 2011). An adapted volume-based diffeomorphic DARTEL algorithm was then applied to the surface for spherical registration.

In addition to cortical thickness analysis, the local gyrification index was extracted based on absolute mean curvature (Luders et al., 2006). Central cortical surfaces were created for both hemispheres separately.

Finally, all scans were re-sampled and smoothed with a Gaussian kernel of 20 mm (FWHM).

2.4. Voxel-based morphometry (VBM)

In order to provide a more direct comparison to the study by Haddad et al., we also computed supplementary VBM analyses, again using the CAT 12 toolbox (Structural Brain Mapping group, Jena University Hospital, Jena, Germany) implemented in SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK). All T1-weighted images were corrected for bias − field inhomogeneities, then segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) (Ashburner and Friston, 2005) and spatially normalised using the DARTEL algorithm (Ashburner, 2007). The segmentation process was further extended by accounting for partial volume effects (Tohka et al., 2004), applying adaptive maximum a posteriori estimations (Rajapakse et al., 1997). After pre-processing and in addition to visual checks for artefacts all scans passed an automated quality check protocol. Scans were smoothed with a Gaussian kernel of 8 mm (FWHM). For exclusion of artefacts on the grey/white matter border (i.e. incorrect voxel classification), we applied an internal grey matter threshold of 0.2.

2.5. Statistical analysis

Statistical analyses were carried using the general linear model (GLM) approach implemented in SPM12. We performed one GLM each correlating early-life urbanicity scores with cortical thickness and gyrification, respectively, (and GMV vor VBM analyses) using age, gender, education, and current urbanicity as nuisance variables (in order to remove variance related to these potentially confounding variables). Despite the low variance in this sample, current urbanicity was taken into account as a nuisance variable, given that previous functional studies have indicated a dissociable role for current urbanicity vs. urban upbringing (Lederbogen et al., 2011).

We performed a whole-brain analysis investigating both positive and negative correlations between scale value and anatomical marker. As a non-parametrical statistic, we applied threshold-free cluster enhancement (TFCE) with 5000 permutations (Smith and Nichols, 2009) and corrected for multiple comparisons via family wise error method (FWE) at $p < 0.05$.

3. Results

3.1. Urban upbringing and cortical thickness

We found significant negative correlations of urbanicity and cortical thickness in the left dorsolateral prefrontal cortex, bilateral medial prefrontal cortices, as well as left superior temporal cortex, left parahippocampal cortex, and bilateral medial parietal cortices/precuneus (Fig. 1). An overview is given in Table 2. There were no positive correlations.

3.2. Urban upbringing and gyrification

At corrected thresholds ($p < 0.05$ FWE-corrected), there were no significant positive or negative correlations between urbanicity and gyrification.

We therefore conducted an exploratory analysis at uncorrected thresholds ($p < 0.001$). This analysis yielded clusters in right and left postcentral gyrus, left superior parietal lobule and left posterior cingulate gyrus with a significant positive correlation of cortical gyrification with urbanicity score values (Fig. 2). We did not find any negative correlations.

3.3. Urban upbringing and grey matter volume

In our complementing VBM analysis, we found some small effects of cortical volume negatively correlated with urbanicity scores in our sample. However, those did not hold against correction for multiple comparisons and did not exceed the threshold of expected voxels per cluster.

4. Discussion

While most of the evidence for urbanicity and mental disorders stems from schizophrenia research, our study explicitly did not target (subclinical) psychotic symptoms, but rather aimed to establish and further assess the link between urban upbringing and brain structure, the latter being a putative biological mediator of effects, which then might result in either psychosis-related or other psychopathology. Under this directive we identified several cortical areas, especially in the left dorsolateral prefrontal cortex, bilateral medial prefrontal cortices, left superior temporal cortex and left parahippocampal cortex, which showed a highly significant (and exclusively negative) correlation with upbringing in urban environments. These regions overlap with areas implicated in schizophrenia (Nenadic et al., 2015b, Sugihara et al., 2016), giving potential clues to how the effect of early-life urbanicity on psychosis risk might be mediated through brain structural effects. The divergence of effects on cortical thickness as opposed to gyrification, where we found solely positive correlations in bilateral postcentral gyri, left superior parietal cortex and posterior cingulate gyrus, gives further potential clues to the timing of effects.

Our results extend two previous studies. There is currently only one morphometry study directly investigating the effect of urban upbringing on cortical volume in healthy participants (Haddad

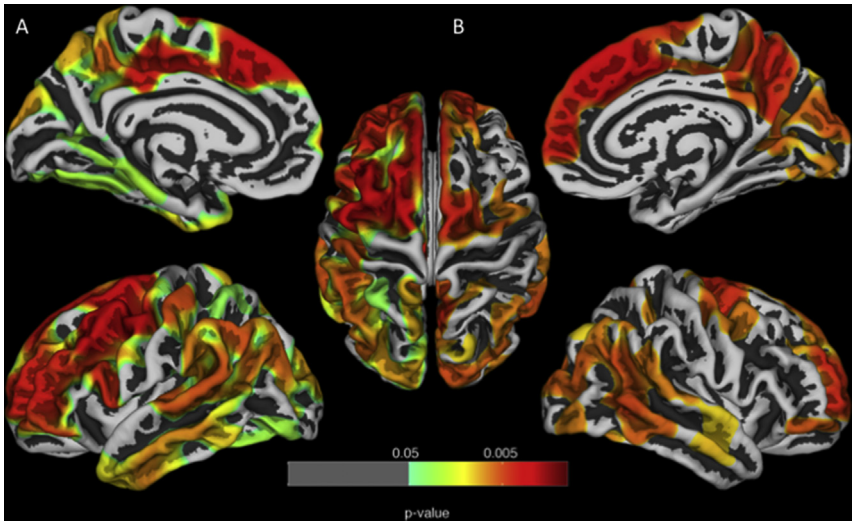

Fig. 1. Projection of significant areas with negative correlation of cortical thickness and urbanicity scores in the 85 healthy individuals ($p < 0.05$, FWE-corrected). **A** – left hemisphere; medial, lateral and cranial view, **B** – right hemisphere; cranial, medial and lateral view.

et al., 2015). Their VBM-findings are comparable to ours, since they used VBM8 and applied the same urbanicity scale covering the urban upbringing during the first 15 years of life. In this healthy sample there was a significant negative correlation of cortical volume in dorsolateral prefrontal cortex (DLPFC) alone, whereas the ROI-analyses of ACC and hippocampus showed no significant effects (Haddad et al., 2015). We could not replicate this finding with VBM, despite similar sample size. Instead, we found robust changes in cortical thickness in the DLPFC (but not anterior cingulate cortex) as a potential neurobiological substrate or mediator of effects of urban upbringing. One explanation for our positive findings for cortical thickness (as opposed to VBM-derived grey matter volume) could be a higher sensitivity of the surface-based measure. Although both measures might be interrelated, cortical thickness measures have been suggested to be more specific in detecting this particular aspect of cortical morphology (Hutton et al., 2009).

A second more recent morphometry study compared schizophrenia patients, their healthy siblings and healthy controls in terms of cortical thickness and its association with urbanicity employing FreeSurfer software and a different urbanicity measure, thus limiting direct comparison to our findings. The authors did not find a differential influence of urbanicity on cortical thickness between the groups and no consistent pattern of reduction or increase in cortical thickness with increasing levels of developmental urbanicity in any group.

They concluded that urban upbringing was not associated with reductions of cortical thickness in individuals at risk for/suffering from psychotic disorder or healthy controls (Frissen et al., 2017). All participants in that study received PANSS-scale to measure psychotic symptoms, which served as criterion for post-hoc-analysis with the most affected patients, but mostly a categorical comparison was performed. Subtle subclinical symptoms in controls were unaccounted for, and PANSS, which was developed for patients (Kay et al., 1989), might be limited in detecting these in healthy persons, which could be related to their urban background after all. Because of that, urbanicity could still mediate risk for psychotic symptoms, even if they were subclinical.

But also there is considerable overlap between our findings and the current knowledge of changes in cortical thickness in schizophrenia patients. Most studies show GMV deficits in widespread prefrontal, temporal and parietal sectors (Bartholomeusz et al., 2016, van Haren et al., 2011), whereas cingulate cortex is more often altered in patients with depression (Schmaal et al., 2017).

In our study, we used current urbanicity as a nuisance variable (although the overall variance in this population was very small, given that most subjects were recruited from the same town). While our sample had the advantage of being rather homogeneous with regards to current urbanicity, our inclusion of current urbanicity as a nuisance variable and additional removal of variance might have made the analysis slightly more prone to false negatives. However, in view of the literature distinguishing between effects of current urbanicity and urban upbringing on brain function (Lederbogen et al., 2011), we deemed this approach preferable. Along these lines, education and other variables were considered as nuisance variables and their variance was removed, which mirrors previous studies (Haddad et al., 2015) as well as reduces likelihood of spurious results. For example, a most recent study found a relation of both urban birth as well as increase in urbanicity during childhood to be associated with schizophrenia, with the former being independent of IQ, while the latter showing an interaction effect (Toulopoulou et al., 2017).

There are no previous findings on the influence of urbanicity on gyrification or similar measures of cortical surface folding. Cortical gyrification is a biological parameter determined during the first months of life with little change afterwards (Zilles et al., 2013). Hence, adverse events occurring during this period leave traces that will be identifiable at later ages. Hypergyrification may be associated with impaired function, as it is associated with schizophrenia (Nenadic et al., 2015a) and also with impairment of executive function (Sasabayashi et al., 2017), which matches the positive correlation in our analysis. Especially superior parietal and posterior cingulate cortex seem to be relevant, since alterations of these areas have been reported in schizophrenia (Shenton et al., 2001), but also depression (Peng et al., 2015).

4.1. Dorsolateral prefrontal cortex and environmental risk of urban upbringing

Considering both the mentioned previous functional imaging studies (Lederbogen et al., 2011; Streit et al., 2014), as well as VBM findings (Haddad et al., 2015) and the findings from the present study, there appears to be a convergence on effects related to dorsolateral prefrontal cortex structure and function.

Several recent imaging studies in healthy participants indicate

Table 2
Overview of bilateral areas of significant negative correlation of cortical thickness and urbanicity scores in the 85 healthy individuals (FWE-corrected). Atlas labelling was performed according to the Desikan-Killiany atlas (Desikan et al., 2006).

p (FWE-corrected)	Cluster size (number of significant vertices)	Overlap of atlas region
Left-hemispheric		
0.0022	31687	23% superiorfrontal
		20% rostralmiddlefrontal
		14% precentral
		11% caudalmiddlefrontal
		7% postcentral
		5% posteriorcingulate
		5% parsopercularis
		5% paracentral
		4% precuneus
		3% parsorbitalis
		2% lateralorbitofrontal
0.0052	17781	32% supramarginal
		28% inferiorparietal
		16% superiortemporal
		7% bankssts
		6% lateraloccipital
		6% superiorparietal
		4% transversetemporal
0.0068	2302	73% middletemporal
		27% inferiortemporal
0.0088	1763	57% superiorparietal
		37% precuneus
		4% postcentral
		2% paracentral
Right-hemispheric		
0.0166	5225	17% superiorfrontal
		12% precuneus
		12% inferiorparietal
		7% precentral
		7% lateraloccipital
		6% middletemporal
		5% superiorparietal
		4% superiortemporal
		4% rostralmiddlefrontal
		3% lingual
		3% paracentral
		3% cuneus
		2% supramarginal
		2% caudalmiddlefrontal
		2% bankssts
		1% fusiform
		1% isthmuscingulate
		1% parsorbitalis
		1% posteriorcingulate
		1% pericalcarine
		1% inferiortemporal

that visual stimulation with urban as opposed to natural environments elicits different patterns of prefrontal activity, as shown with near infrared spectroscopy (Igarashi et al., 2015). This includes general effects of non-urban environmental stimuli in reducing anxiety and tension (Song et al., 2014), and has been linked to autonomic activity (Igarashi et al., 2014). Similarly, EEG studies have identified changes in cortical connectivity patterns related to exposure to natural as opposed to urban environments (Chen et al., 2016), although this has rather been linked to right hemisphere shifts in lateralisation.

In psychotic patients and their siblings, functional studies have mostly focused on gene x environment interactions of urbanicity in investigated with seed-based fMRI methods.

Decreased functional connectivity between nucleus accumbens, OFC, middle cingulate and middle frontal gyrus has been shown in patients and their siblings compared to healthy controls. But these effects were not modulated by the environmental factors of (among others) urbanicity (Peeters et al., 2015a). Another analysis reported increased default mode network – connectivity in psychosis patients and their siblings compared to healthy controls, again not moderated by urbanicity. They also found no effect of subclinical symptoms on the connectivity (Peeters et al., 2015b).

According to the current literature there are indications of a gene x environment interaction of urbanicity, but not enough to distinguish influence of urban birth, urban upbringing or adult urbanicity. The link to causing psychotic symptoms is not as clear but has yet not been discussed considering subclinical symptoms in healthy control groups with appropriate scales to measure them.

Still it is important to further pursue the link of urban upbringing and/or urban life and mental health, because there is not only an association with schizophrenia, but with major depressive disorder and bipolar disorder reported all over the world as well (Daig et al., 2013; Laursen et al., 2007; Wang, 2004).

4.2. Timing of effects and neurobiological mechanisms

Given the cross-sectional nature of all above studies, inference on the timing of effects is limited. However, there are some clues from methodological considerations. The gyrification parameter used in our study is assumed to reflect a very basic inherent

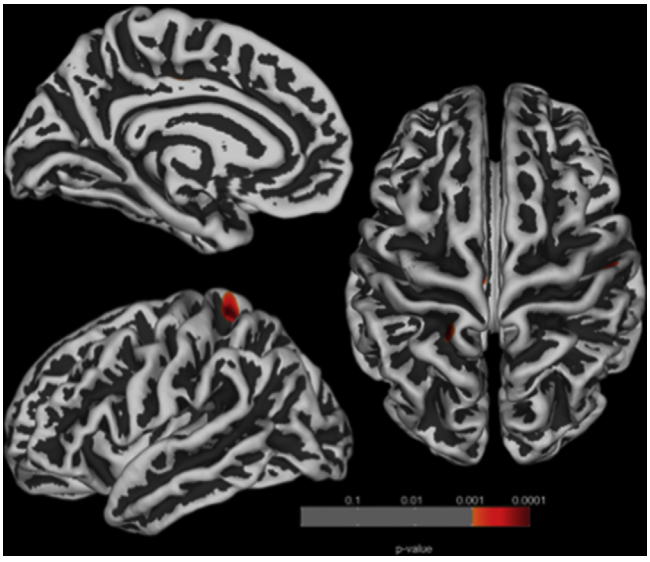

Fig. 2. Projection of left- and right-hemispheric significant areas with positive correlation of cortical gyrification and urbanicity scores in the 85 healthy individuals ($p < 0.001$, uncorrected).

geometrical aspect of brain function, which is established in very early development, i.e. intra-uterine and the first 2–6 years of life (Nenadic et al., 2015a; Zilles et al., 2013). Cortical thickness, in contrast, is more prone to changes during the life span. Hence, the pattern demonstrated in our present study is indicative of changes induced by urban upbringing and a lack of effects of very early childhood neurodevelopmental effects.

It is unclear how these changes in the dorsolateral prefrontal cortex might arise. Animal experiments have well established the role of elevated levels of neurotrophins after prolonged exposure to enriched (vs. isolated) environments (Ickes et al., 2000, van Praag et al., 2000), but it is far from clear how this might translate to human urban upbringing.

Although sample size was a limitation of our study, we found a statistically robust effect for cortical thickness, which sustained correction for multiple comparisons. However, we also need to consider additional limitations of current paradigms studying urbanicity. For example, it is not fully clear whether certain periods in childhood or adolescence might be particularly important for mediating the effects observed. While summing up urban environments across the first 15 years of life allows comparability with previous studies and is grounded in epidemiological studies (as cited above), further studies might elucidate different developmental periods in more detail. Our own study as well as the previous studies considered only a rather coarse delineation of risk and samples did not include participants raised in larger metropolitan areas (>1 million inhabitants), which might be of additional relevance given current urban development. Second, our use of nuisance variables might be conservative and prone to false negatives. Also, future studies extending our approach to both healthy subjects and affected patients, as well as high-risk populations (or those characterised on a phenotype level, e.g. with increased schizotypy) would be useful to add to our understanding of how urbanicity effects interact with disease phenotype expression on the brain structural level. Finally, recently established polyenvironmental scores (Padmanabhan et al., 2017) might be helpful in elucidating the overall vs. specific environmental risks associated with brain structure and function.

In summary, there seems to be a considerable effect of childhood and early adolescent urbanicity on brain development and brain structure in healthy people. Those effects overlap spatially in cortical areas with abnormalities found in patients with schizophrenia, even if there are several genetic and other environmental factors mediating these symptoms. To further elucidate the role of urbanicity for mental health, future studies might need to address these factors, focus on interactions and also include valid measurements of subclinical symptoms to represent the dimensional aspect of psychopathology.

4.3. Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest

None.

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