LETTER

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City living and urban upbringing affect neural social stress processing in humans

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More than half of the world's population now lives in cities, making the creation of a healthy urban environment a major policy priority[1]. Cities have both health risks and benefits[1], but mental health is negatively affected: mood and anxiety disorders are more prevalent in city dwellers[2] and the incidence of schizophrenia is strongly increased in people born and raised in cities[3–6]. Although these findings have been widely attributed to the urban social environment[2,3,7,8], the neural processes that could mediate such associations are unknown. Here we show, using functional magnetic resonance imaging in three independent experiments, that urban upbringing and city living have dissociable impacts on social evaluative stress processing in humans. Current city living was associated with increased amygdala activity, whereas urban upbringing affected the perigenual anterior cingulate cortex, a key region for regulation of amygdala activity, negative affect[9] and stress[10]. These findings were regionally and behaviourally specific, as no other brain structures were affected and no urbanicity effect was seen during control experiments invoking cognitive processing without stress. Our results identify distinct neural mechanisms for an established environmental risk factor, link the urban environment for the first time to social stress processing, suggest that brain regions differ in vulnerability to this risk factor across the lifespan, and indicate that experimental interrogation of epidemiological associations is a promising strategy in social neuroscience.

Urbanization, a process that started in North America and Western Europe but is now mainly occurring in developing nations, is a major socio-ecological change confronting mankind. By 2050, 69% of humans will live in urban areas[1]. Although city dwellers, on average, are wealthier and receive improved sanitation, nutrition, contraception and health care[1], urban living is also associated with increased risk for chronic disorders, a more demanding and stressful social environment and greater social disparities. The biological components of this complex landscape of risk and protective factors remain largely uncharacterized.

Some of the best-established effects of urbanization concern mental health. Meta-analyses show that current city dwellers have a substantially increased risk for anxiety disorders (by 21%) and mood disorders (by 39%)[2]. For the major brain disorder, schizophrenia, incidence is about doubled in subjects born and brought up in cities[3], with evidence of a dose–response relationship[5] that probably reflects causation[3]. Genetically vulnerable individuals are more at risk[6], in agreement with the assumption that schizophrenia represents a neurodevelopmental disorder[11]. Importantly, urbanicity effects on schizophrenia later in life are minor[2,5], providing an epidemiological dissociation between current and early life urbanicity effects, which are associated with mood and anxiety disorders and schizophrenia, respectively.

Because longitudinal studies indicate that urbanicity effects on mental illness are causal and not mediated by other epidemiological variables[3,7], attempts to explain these associations must consider the specifics of the urban situation affecting the brain[12]. Increased social evaluative threat[13], including social defeat and chronic social stress, might constitute such a factor[8]. Consequently, many authors have proposed that social stress processing in the urban environment underlies the greater risk for mental illness[2,3,7,8], and contributes to the manifestation of these disorders in adults. To test experimentally the hypothesis that urban living and upbringing modulate neural processing of acute social evaluative stress, we studied the neural responses of healthy German volunteers undergoing such stress during functional magnetic resonance imaging (fMRI). We confirmed our findings in a second study using a different social stress paradigm and then tested for cognitive specificity by ascertaining the effect of urbanicity on brain activation during cognitive processing without stress. Importantly, our subjects did not have a mental disorder nor were they at high risk for one; the link to these illnesses from the environmental risk factor that we studied is established by the epidemiological evidence discussed earlier.

In our first (discovery) study, we used the Montreal Imaging Stress Task (MIST)[14], a social stress paradigm where participants solve arithmetic tasks under time pressure. Difficulty was varied adaptively to keep success rates—visually presented on a 'performance scale'—at between 25–40%. Study investigators provided further negative feedback after each test segment through headphones. Subjective stress levels were measured before and after the session using a visual analogue scale, and effects of the MIST on salivary cortisol, heart rate and blood pressure were recorded repeatedly. Urbanicity was quantified as follows[4]: city with more than 100,000 inhabitants (3); town with more than 10,000 inhabitants (2); and rural area (1). For urban upbringing, these numbers were multiplied by the number of years living in the area up to age fifteen and added. Thirty-two participants with rural as well as urban upbringing and habitation entered the final analysis (Supplementary Table 1a). City dwellers did not differ in subjective health, depressed mood, social support, or personality dimensions. Baseline circadian cortisol measures were normal[15]. The MIST increased cardiovascular and hormonal measures (Supplementary Fig. 1a and Supplementary Table 2), indicating that stress was successfully induced. Stress-related brain activations (compared to a control condition without social evaluative threat) were most prominent in the right temporoparietal junction ($t = 9.53$, $P = 0.001$, all significance values are family-wise error (FWE) corrected for multiple comparisons), anterior cingulate cortex (ACC) and posterior cingulate cortex (anterior: $t = 7.91$, $P < 0.001$; posterior: $t = 8.09$, $P < 0.001$), insular cortex (right: $t = 8.18$, $P < 0.001$; left: $t = 6.69$, $P = 0.003$) and hypothalamus (right: $t = 7.12$, $P < 0.001$; left: $t = 6.86$, $P = 0.002$, see Supplementary Fig. 1b and Supplementary Table 3 for complete list). Differential brain activation correlated significantly with the test-induced rise in cortisol for hippocampus (right: $r = -0.59$, $P = 0.041$; left: $r = -0.59$, $P = 0.040$) and amygdala (right: $r = -0.61$, $P = 0.016$; left: $r = -0.55$, $P = 0.048$), confirming previous reports[16].

Although current and early life (birth to age 15) urbanicity shared moderate variance ($r = 0.37$, $P < 0.05$), their neural effects were fully

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distinct. Current urban living was associated with amygdala activity ($t = 3.6$; Fig. 1a), which increased stepwise from subjects living in the country to those living in small towns, and was highest in city dwellers ($r = 0.55$, $P < 0.001$; Fig. 1b). In contrast, urban upbringing was associated with differential activity in the perigenual ACC (pACC, $t = 3.8$; Fig. 2a), increasing linearly with highest activation in participants entirely brought up in cities ($r = 0.56$, $P < 0.001$; Fig. 2b). Results were not explained by demographic or clinical variables (see Supplementary Methods). These effects were regionally specific as no other brain regions showed any urbanicity association at exploratory thresholds ($P < 0.001$, uncorrected).

To test whether our findings were related to specific aspects of the sample or task, we studied a second cohort of 23 participants (characteristics in Supplementary Table 1b) with a modified stress paradigm. Subjects performed two cognitive tasks (arithmetic and mental rotation) while being continuously visually exposed to disapproving investigator feedback through video (see Supplementary Methods). This experiment fully replicated the findings from the previous sample: city living was again specifically associated with activity in the amygdala and was highest in city dwellers ($t = 3.3$, $P < 0.05$, FWE corrected; Fig. 1c, d), whereas a cluster within the pACC ($t = 4.0$, $P < 0.05$, FWE corrected; Fig. 2c) showed a significant linear correlation with urban upbringing ($r = 0.64$, $P < 0.001$; Fig. 2d). Post hoc, to study the effect of current urbanicity in a larger and better distributed sample, we additionally tested 24 predominantly town and rural dwellers. The analysis of the combined sample again confirmed the effect (Supplementary Fig. 2). As before, no other brain regions showed urbanicity associations even at exploratory thresholds. These findings indicated that specifics of the procedure did not confound the urbanicity effects.

Because acute social stress interacts with cognitive processing[13], the question arose as to whether the observed effect of urbanicity in these

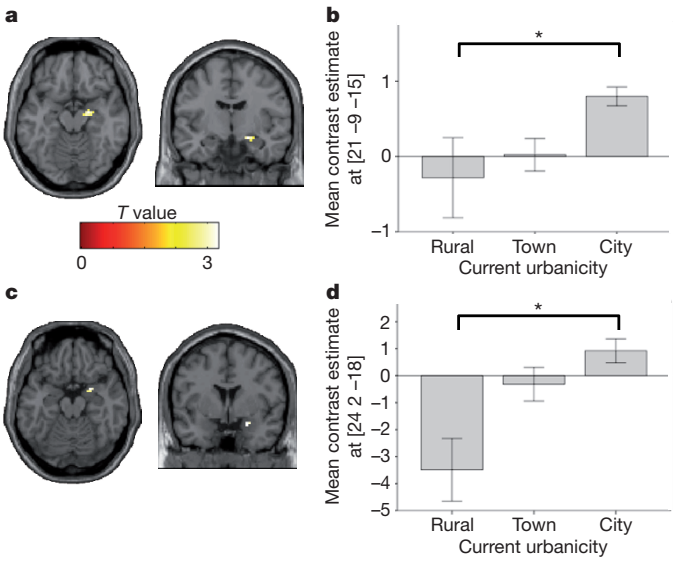

Figure 1 | Relationship between current urbanicity and amygdala activation. **a**, Discovery study ($N = 32$): T map of significant correlations between stress-related activations (in the experimental versus control contrast) and current urbanicity scores shown at a threshold of $P < 0.005$, uncorrected. **b**, Discovery study: contrast estimates at the most significantly correlated voxel in the amygdala (located at $x = 21$, $y = -9$, $z = -15$) for the experimental compared to control contrast for the three current urbanicity groups (*$P < 0.05$; error bars indicate s.e.m.). **c**, Replication study ($N = 23$): T map of significant correlations between activations in the experimental compared to control contrast and current urbanicity scores (shown at $P < 0.05$, FWE corrected for the right amygdala as region of interest (ROI)). **d**, Replication study: contrast estimates at the most significantly correlated voxel in the amygdala (located at $x = 24$, $y = 2$, $z = -18$) for the experimental compared to control contrast for the three current urbanicity groups (*$P < 0.05$, error bars indicate s.e.m.).

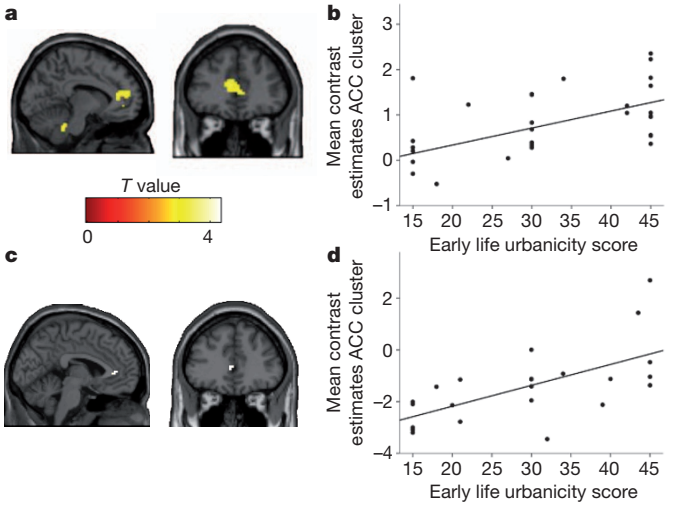

Figure 2 | Relationship between early life urbanicity scores and pACC activation. **a**, Discovery study ($N = 32$): T map of significant correlations between stress-related activations (in the experimental versus control contrast) correlating with urbanicity scores shown at a threshold of $P < 0.005$, uncorrected. **b**, Discovery study: scatterplot of urbanicity scores and mean contrast estimates of the significantly (at $P < 0.005$) correlating voxels within the ACC in the experimental compared to control contrast. Results indicate a linear relationship between these two variables ($r = 0.56$, $P = 0.001$). **c**, Replication study ($N = 23$): T map of significant correlations between activations (in the experimental compared to control contrast) and urbanicity scores (shown at $P < 0.05$, FWE corrected for the rostral ACC as ROI). **d**, Replication study: scatterplot between contrast estimates for the stress compared to control contrast and the urbanicity score shown for the mean of all significantly ($P < 0.005$) correlated voxels ($r = 0.64$, $P < 0.001$).

experiments was related to social evaluative stress per se or to the cognitive tasks used. To investigate this issue, we studied a sample of 37 healthy adults from an ongoing study[17] (Supplementary Table 1b) during a working memory and an emotional face matching task, both without stress. Even at a threshold of $P < 0.01$, uncorrected, there were no voxels within the ACC or amygdala whose activations were correlated to current or early life urbanicity, indicating that our findings were indeed related to social stress with a degree of specificity. In a secondary analysis, we increased the sample size for this experiment to 80 (Supplementary Table 1c), with power to detect an effect of similar size to the discovery study of 0.99. Again, no significant associations with urbanicity were observed.

In this initial examination of the effects of urbanicity, no neural circuit was hypothesized a priori. Nevertheless, the regions identified, controlling for false positives, can plausibly be related to previous epidemiological observations. In the amygdala, activity during social stress was specifically related to city living. The amygdala, which among other functions signals negative affect and environmental threat[18], has been strongly implicated in anxiety disorders, depression, and other behaviours that are increased in cities, such as violence[19]. Conversely, urban upbringing showed a distinct, but equally regionally specific effect on the pACC, a major part of the limbic stress regulation system[18] that exhibits high neuronal glucocorticoid receptor expression[20], modulates hypothalamic–pituitary–adrenal axis activation during stress[10], and is implicated in processing chronic social stressors such as social defeat. In schizophrenia, reduced cingulate grey matter volume[21] has been reported in patients, emerging during adolescence[22]. Connectivity abnormalities of the pACC with the amygdala during processing of affectively negative stimuli were seen in schizophrenic patients, but not in genetically at-risk individuals[23], suggesting a link to environmental factors. Therefore, the epidemiological distinction between current and early life urbanicity maps onto distinct neural regions that are associated with the disease phenotypes implicated by the environmental risk data. A direct link between psychopathology

and these circuits during social evaluative stress must be established in future work, including the study of subjects with mental illness.

In principle, any of the multiple factors related to urban living[1], such as pollution, toxins, crowding, noise, or demographic factors not captured in our analysis, could be responsible for the observed associations. However, in light of the epidemiological evidence that urbanicity is causal for mental disorders[2,3,7], it is interesting to consider the parsimonious proposal that social stress contributes causally to the impact of urbanicity on the neural circuits identified here. Importantly, although urbanicity effects on the pACC and amygdala were dissociable, these two structures are functionally closely linked: the pACC is a key regulatory region for amygdala[18] activity in the context of negative affect, which is critical for gene–environment interactions[9] and extinction. Further, synaptic and neuronal remodelling of the pACC and amygdala have been described in animals exposed to social stressors[24], and amygdala and cingulate volume relate to social network size in humans[25]. Therefore, we investigated functional connectivity between the pACC and amygdala during the MIST stress paradigm using previously published methods[17]. Urban upbringing was associated with reduced connectivity (Spearman's Rho $= -0.39$, $P = 0.013$; see Supplementary Fig. 3), whereas current urbanicity had no effect, supporting an effect of early urban exposure on this regulatory circuit. Because early life neurochemical alterations in the serotonin system linked to social support have enduring effects on the cingulate in animals[26] and humans[27], these differential effects of early life and current urbanicity may reflect a developmental vulnerability of the cingulate. In line with this, the cortisol stress response has been found to be exaggerated in human adults who were exposed to maternal stress *in utero*[28].

Beyond mental illness, our data are of general interest in showing a link between cities and social stress sensitivity. This indicates that an experimental approach to dissecting epidemiological associations is feasible and that it could be used to characterize further the underlying psychosocial components; for example, the effects of finer-grained quantifiers of individuals' social networks or individual social experience in urban contexts. One such potential component is unstable hierarchical position—a social stressor related to general health that might be relevant in the context of increased socioeconomic disparities in cities—which also affects medial prefrontal cortex and amygdala function[29]. Further, 'prosocial' neuropeptides, molecular mediators of social interactions, modulate the pACC-amygdala circuit[30], indicating that social risk and protective factors might converge on this system.

This first series of studies of the neural effects of urbanicity has several limitations. First, our cross-sectional study does not prove that the observed association is causal. Second, our subjects grew up in relative safety and prosperity in Germany, a developed country, whereas greater urban–rural discrepancies are found elsewhere; however, this would have probably attenuated our findings. Third, the pronounced differences in brain processing did not correlate with cortisol levels, possibly reflecting the greater sensitivity of neural measures compared to downstream peripheral markers; nevertheless, the cortisol stress response should be studied in a larger sample. Fourth, the lack of random population sampling and the fact that our confirmation study largely used college students potentially limits the generalizability of our findings, making replication of these results in different and larger samples important.

Our data reveal neural effects of urban upbringing and habitation on social stress processing in humans. These findings contribute to our understanding of urban environmental risk for mental disorders and health in general. Further, they point to a new empirical approach for integrating social sciences, neurosciences and public policy to respond to the major health challenge of urbanization.

METHODS SUMMARY

The study was approved by the Ethics Committee of Heidelberg University. Three groups of healthy participants were studied after written informed consent. A thorough clinical and psychiatric examination was performed to exclude relevant illness. As in previous work, urbanicity was scored as follows[4]: city with more than 100,000 inhabitants (3); town with more than 10,000 inhabitants (2); and rural area (1). For urban upbringing until age 15, these numbers were multiplied by the years spent in each area and added.

Blood-oxygen-level-dependent (BOLD) fMRI was performed on a 3.0 Tesla Siemens Trio scanner using an echo-planar-imaging (EPI) sequence and analysed using SPM5 (MIST study and non-stress control study) and SPM8 (stress replication study) (http://www.fil.ion.ucl.ac.uk/spm). In the discovery study, participants performed the MIST, in the replication study a variant social stress task (see Supplementary Methods), in the control study a working memory task (the n-back task) and an emotional face matching task.

All imaging results were corrected for multiple comparisons at a significance level of $P < 0.05$ via FWE. For main task effects, correction was performed over the whole brain. For hypothesis-driven analyses, bilateral a priori anatomical regions of interest (ROI) were taken from the Harvard Oxford Atlas (http://www.cma.mgh.harvard.edu). For correlations with cortisol, the amygdala, hypothalamus and ACC were specified based on previous results[16]. For urbanicity analyses, on the basis of the correlations observed with early life and current urbanicity in the discovery study (MIST), we defined a priori anatomical ACC and amygdala ROI for the replication and control studies.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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