1 Satellite Imaging of Global Urbanicity relate to Adolescent Brain Development and 2 Behavior

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151 **Abstract**

152 Urbanicity, the impact of living in urban areas, is among the greatest environmental challenges
 153 for mental health. While urbanicity might be distinct in different sociocultural conditions and
 154 geographic locations, there are likely to exist common features shared in different areas of the
 155 globe. Understanding these common and specific relations of urbanicity with human brain and
 156 behavior will enable to assess the impact of urbanicity on mental disorders, especially in
 157 childhood and adolescence, where prevention and early interventions are likely to be most
 158 effective.

159 We constructed from satellite-based remote sensing data a factor for urbanicity that was
 160 highly correlated with population density ground data. This factor, 'UrbanSat' was utilized in
 161 the Chinese CHIMGEN sample (N=831) and the longitudinal European IMAGEN cohort
 162 (N=810) to investigate if exposure to urbanicity during childhood and adolescence is associated
 163 with differences in brain structure and function in young adults, and if these changes are linked
 164 to behavior.

165 Urbanicity was found negatively correlated with medial prefrontal cortex volume and
 166 positively correlated with cerebellar vermis volume in young adults from both China and
 167 Europe. We found an increased correlation of urbanicity with functional network connectivity
 168 within- and between- brain networks in Chinese compared to European participants. Urbanicity
 169 was highly correlated with a measure of perceiving a situation from the perspective of others, as
 170 well as symptoms of depression in both datasets. These correlations were mediated by the
 171 structural and functional brain changes observed. Susceptibility to urbanicity was greatest in
 172 two developmental windows during mid-childhood and adolescence.

173 Using innovative technology, we were able to probe the relationship between urban
 174 upbringing with brain change and behavior in different sociocultural conditions and geographic
 175 locations. Our findings help to identify shared and distinct determinants of adolescent brain
 176 development and mental health in different regions of the world, thus contributing to targeted
 177 prevention and early-intervention programs for young people in their unique environment. Our
 178 approach may be relevant for public health, policy and urban planning globally.

179 **Introduction**

180 Mental disorders account for 28% of disease burden among non-communicable diseases¹.
 181 Environmental factors account for up to 50% of the attributable risk for mental disorders². The
 182 environmental measures investigated in mental health research are generally limited to
 183 individual life events³, such as trauma, abuse, neglect, or psychosocial stress. While the impact
 184 of these individual life events on brain development and behavior is actively investigated⁴, the
 185 influence of the physical environment, and its social consequences, such as urbanization and
 186 urbanicity, on mental health is less well studied.

187 Urbanicity can be defined as the impact of living in urban areas at a given time, and
 188 refers to the presence of conditions that are particular to urban areas or present to a much
 189 greater extent than in nonurban areas⁵. Urbanicity and urbanization are among the greatest
 190 environmental challenges globally. Whereas in 1950, less than 30% of the world's population
 191 lived in urban areas, this number has increased to presently 55% and is expected to rise to 68%
 192 in 2050⁶. Moreover, environmental impacts of urbanicity are thought to be the most rapidly
 193 growing cause for mental illness⁷. While Europe is among the most stable urbanized regions,
 194 Asia is home to 54% of the world's urban population and subject to massive demographic
 195 changes: for example, by 2050 China will have added 255 million urban dwellers⁸. While there
 196 are likely to exist common environmental factors related to urbanicity that are shared, there
 197 may also be distinct influences in China and Europe that affect people differently and at
 198 different times during the lifespan⁹.

199 As 75% of the lifetime burden from mental disorders emerges by age 20 years¹⁰, the
200 adverse impact of urbanicity can be best addressed and managed in childhood and adolescence.
201 However, data relating urbanicity to mental health have been mainly ascertained in adults, thus
202 our knowledge on how it affects young people is very limited. For example, urbanization may
203 affect brain function in adults¹¹, but there are no such data available for children and
204 adolescents whose continuing brain development renders them particularly susceptible to
205 modifying environmental influences.

206 To facilitate comparative analyses of urbanicity globally, we require common
207 quantitative and longitudinal environmental measures that are ascertained frequently and are
208 identical across different geographic locations and sociocultural conditions. Remote sensing
209 satellite data, having been continuously recorded since the early 1970's, provide globally
210 applicable, standardized quantitative environmental measures that enable the continuous
211 tracing of environmental influences going back more than 50 years¹². Therefore, we were
212 interested in developing satellite data features that are suitable measures for urbanicity in
213 Europe and China. Using these data we then aimed to investigate the relation of urbanicity with
214 structural and functional brain measures in two behavioral neuroimaging datasets of young
215 people: the Chinese CHIMGEN study (www.chimgen.tmu.edu.cn) and the European
216 longitudinal IMAGEN cohort (www.imagen-europe.com)¹³. We tested whether structural and
217 functional brain differences related to urbanicity are similar or distinct in Chinese and
218 European participants, and investigated possible susceptibility windows for the effects of
219 urbanicity during child and adolescent development.

220

221

222 **Results**

223 **Development of a remote sensing satellite measure of urbanicity (UrbanSat)**

224 To develop a satellite-based measure of urbanicity, we carried out a confirmatory factor
 225 analysis (CFA) in CHIMGEN (n=3336) and IMAGEN (n=1205), identifying a latent factor
 226 derived from measures relevant for urbanicity, including nighttime lights¹⁵, NDVI¹⁶, NDBI¹⁷,
 227 NDWI¹⁸ and global land cover mapping¹⁹. We then validated this factor, which we termed
 228 UrbanSat, by calculating correlations with ground-level population density data from
 229 GHSL-POP¹⁴, which were available for both China and Europe for the years 1990, 2000 and
 230 2015. UrbanSat showed very high correlations with ground-level population grid data in rural,
 231 town, city and overall livings, indicating its robustness across time during rapid changes of
 232 urbanicity and across countries in Asia and Europe (CHIMGEN: $r=0.697$, $P=1.76 \times 10^{-143}$ in
 233 1990; CHIMGEN: $r=0.712$, $P=4.90 \times 10^{-196}$ in 2000; $r=0.722$, $P=5.64 \times 10^{-197}$ in 2015;
 234 IMAGEN: $r=0.715$, $P=5.27 \times 10^{-189}$ in 2000-2015; Figure 1).

235

236 **Figure 1. Spatial distribution of subjects in the (A) CHIMGEN (N=3336) and (B) IMAGEN**
 237 **(N=1025) studies.** A. The maps showed the numbers of subjects' distribution from each
 238 recruitment center in CHIMGEN and IMAGEN. CHIMGEN Tianjin main center is marked; B.
 239 The bars plots show correlations between each satellite feature (UrbanSat, percentage of
 240 urban build-up, percentage of cropland, nighttime light and NDVI) and ground-level GHSL
 241 population density grid in rural, town, city and overall livings for the years 1990, 2000 and
 242 2015 in CHIMGEN (Top 3). In IMAGEN, we selected only participants who remained at the
 243 same address (geoposition) between 2009 and 2015. We therefore used the average population
 244 grid between the years 2000 and 2015 (the last one); GHSL_POP, Population density grid of
 245 Global Human Settlement Layers; NL, nighttime light. * $P < 0.05$; ** $P < 0.001$.

The relation of UrbanSat with brain gray matter volume and white-matter microstructure.

We first tested the correlation of UrbanSat with brain gray matter volume (GMV) in 831 participants from the CHIMGEN (23.81±0.82 years) (Supplementary Table S1) for whom geopositioned data were available since birth. We found a negative correlation of UrbanSat with left medial prefrontal cortex (mPFC) volume (MNI-coordinate: x=-3, y=45, z=27; 4180 voxels; F value peak=-6.53; Figure 2A) and a positive correlation with cerebellar vermis volume (MNI-coordinate: x=-4.5, y=-58.5, z=-10.5; 678 voxels; F value peak=5.71; Figure 2A) (FWE-correction, voxel $P<0.05$, cluster-size>100 voxels).

Figure 2. Voxel wise correlation between UrbanSat and GMV across the whole brain. A. In the CHIMGEN sample (N=831), there was a significant negative correlation of the average exposure to urbanicity (measured by UrbanSat before age 18 years) with left mPFC volume (left) and a significant positive correlation with cerebellar vermis volume (right) (FWE-correction, voxel $P<0.05$); B. In the IMAGEN sample at 19 years(N=791), there was

261 also a significant negative correlation of UrbanSat at 19 years with left mPFC volume (left)
 262 and a significant positive correlation with cerebellar vermis volume (right) (FWE-correction,
 263 voxel $P < 0.05$); C. The correlations of UrbanSat on brain GMV changes in the left mPFC
 264 volume (left) and the cerebellar vermis volume (right) were also present in the IMAGEN
 265 baseline sample at 14 years (FWE-correction, voxel $P < 0.05$); D. The correlation of
 266 longitudinal UrbanSat with the left mPFC volume was highest during adolescence (ages 11 to
 267 14 years). The difference to the adjacent age bands was significant compared to age 10 years
 268 ($P = 0.012$) and to age 15 years ($P = 2.36 \times 10^{-5}$); The correlation of longitudinal UrbanSat with
 269 cerebellar vermis volume was highest during childhood (ages 4 to 7 years). The difference to
 270 the adjacent age bands was significant at $P = 0.016$ compared to age 8 years; BL, baseline
 271 datasets at 14 years old; FU2, follow up 2 datasets at 19 years old; L, left; mPFC, medial
 272 prefrontal cortex; R, right; * $P < 0.05$; ** $P < 0.001$.

273

274 We observed similar results in the ground-level Chinese population grid data¹⁴, thus
 275 validating the effect of urbanicity obtained by satellite measures on brain volume
 276 (Supplementary Figure S1). To replicate our findings in a European sample, we carried out a
 277 similar voxel-wise multiple regression analysis in 791 adolescents from the IMAGEN at age 19
 278 (19.00 ± 0.71 years) (Supplementary Table S1). UrbanSat also showed a negative correlation of
 279 UrbanSat with left mPFC volume (MNI-coordinate: $x = -7.5$, $y = 67.5$, $z = -13.5$; 460 voxels;
 280 F -value peak = 5.71) and a positive correlation with cerebellar vermis volume
 281 (MNI-coordinate: $x = -5.5$, $y = -59.5$, $z = -9.5$; 876 voxels; F value peak = 5.65; Figure 2C)
 282 (FWE-correction, voxel $P < 0.05$, cluster-size > 100 voxels), thus replicating the findings from
 283 CHIMGEN. Our findings indicate that the observed correlation between UrbanSat and GMV
 284 was independent of geographical locations and socio-cultural conditions.

285 We then investigated potential susceptibility periods during which exposure to urbanicity
 286 may have the strongest influence on brain GMV. In the CHIMGEN young adults, for whom

geoposition data were available since birth, we created age sliding windows by averaging UrbanSat for each subject over a period of three years and measured correlations between the exposure to urbanicity in the resulting windows and GMV. The periods showing the greatest susceptibility to urbanicity were childhood (age 4 to 7 years) and adolescence (age 11 and 14 years) (Figure 2B). During childhood, we observed significantly higher correlation of urbanicity with cerebellar vermis volume. While the correlation of longitudinal UrbanSat with the left mPFC volume was highest during adolescence (FWE-correction, voxel $P < 0.05$, see Supplementary Results).

While neuroimaging measures in CHIMGEN were acquired once during young adulthood, neuroimaging measures in IMAGEN were acquired twice, during adolescence at 14 years and in a follow-up assessment during early adulthood at 19 years. To further explore susceptibility periods of GMV to the exposure to urbanicity in IMAGEN participants, we analyzed the same individuals at age 14 years (14.05 ± 0.75 years). We confirmed the negative correlation with left mPFC volume (MNI-coordinate: $x = -1.5$, $y = 58.5$, $z = 33$; 981 voxels; F value peak = -5.64) and the positive correlation of UrbanSat with cerebellar vermis volume (MNI-coordinate: $x = 6$, $y = -55.5$, $z = -10.5$; 2327 voxels; F -value peak = 5.04 ; Figure 2D) (FWE-correction, voxel wise $P < 0.05$, cluster-size > 100 voxels).

We next investigated the correlation of UrbanSat with white-matter microstructure using tract-based spatial statistics analysis of diffusion tensor imaging (DTI) neuroimaging data. We did not find any significant correlation of UrbanSat with brain fractional anisotropy in either CHIMGEN or IMAGEN (FWE and TFCE-correction, voxel wise $P < 0.05$).

The relation of UrbanSat with functional network connectivity within- and between-brain networks

To investigate the shared and distinct relations of urbanicity with brain activity of cognitive processes in China and Europe, we tested the association of UrbanSat with functional network

connectivity (FNC) of 17 within-networks and 136 (17*16/2) between-networks (Figure 3A and Supplementary Methods). In CHIMGEN (N=827), a voxel-wise multiple regression analysis controlling for age, gender and sites revealed a negative correlation of UrbanSat with FNC within the left mPFC of the anterior default mode network (aDMN) (MNI-coordinate: x=6, y=33, z=57; 130 voxels; *F*-value peak=-4.96) and a positive correlation with FNC within the left lingual gyrus of the medial visual network (mVN) (MNI-coordinate: x=-6, y=-84, z=-6; 144 voxels; *F*-value peak=5.21; Figure 3B) (FWE-correction, voxel *P*<0.05, cluster-size>100 voxels). In IMAGEN at 19 years (N=614), UrbanSat showed a negative correlation with FNC within the left mPFC of aDMN (MNI-coordinate: x=-3, y=63, z=6; 106 voxels; *F*-value peak=-4.83; Figure 3D), but not in mVN (FWE-correction, voxel *P*<0.05, cluster-size>100 voxels). The FNC-findings in CHIMGEN and IMAGEN were consistent with the brain GMV changes, indicating that UrbanSat affects both structure and function of the mPFC.

Figure 3. Voxel wise correlations between UrbanSat and FNC within brain networks. A. 17 independent resting state functional networks identified by independent component analysis in the CHIMGEN sample; B. In the CHIMGEN sample ($N=827$), there was a significant negative correlation of UrbanSat before age 18 years with FNC within the left mPFC of the aDMN (left) and a significant positive correlation with FNC within the left LG of the mVN (right) (FWE-correction, voxel $P<0.05$); C. In the IMAGEN at age 19 years ($N = 614$), there was also a significant negative correlation of UrbanSat at 19 years with FNC within the aDMN (FWE-correction, voxel $P<0.05$) (but not with FNC within the left LG of the mVN); D. The correlation of UrbanSat on FNC within the aDMN was also present in the IMAGEN at 14 years (FWE-correction, voxel $P<0.05$). E. The correlation of UrbanSat with FNC within the aDMN was highest during adolescence (ages 13 to 15 years). The difference to the adjacent age bands was significant compared to age 12 years ($P=0.010$) and to age 16 years ($P=6.16 \times 10^{-5}$); The

correlation of UrbanSat with FNC within the mVN was only vulnerable in childhood and highest during childhood (ages 5 to 8 years). The difference to the adjacent age bands was significant at $P=0.027$ compared to 4 years and $P=2.68 \times 10^{-4}$ compared to age 9 years; aDMN, anterior default mode network; FNC, functional network connectivity; L, left; LG, lingual gyrus; mPFC, medial prefrontal cortex; mVN, medial visual network; R, right; * $P<0.05$; ** $P<0.001$.

Upon investigating potential susceptibility periods for FNC within the aDMN, we found the greatest correlation with UrbanSat during adolescence (age 13 to 15 years) (FWE-correction, voxel $P<0.05$, Figure 3C and see Supplementary Results). We confirmed the relation of UrbanSat with the FNC of the left mPFC within the aDMN in the IMAGEN participants at age 14 years (MNI-coordinate: $x=0$, $y=60$, $z=24$; 104 voxels; F value peak=-5.61; Figure 3E) (FWE-correction, voxel $P<0.05$, cluster-size>100 voxels). Together, our data suggest a susceptibility window for the correlation of urbanicity and FNC within aDMN in adolescence. In the case of the mVN, we found the greatest correlation with UrbanSat from age 5 to 8 years, indicating a susceptibility window in childhood (Figure 3C).

In the resulting 136 between-network FNCs we found overall similarity of resting-state activity between CHIMGEN and IMAGEN (Supplementary Figure S2). For the 136 pairs of between-network FNCs, However, UrbanSat was significantly correlated with 42 connections in CHIMGEN, 19 connections in IMAGEN at age 19 and 27 connections in the same IMAGEN participants at age 14 (Figure 4A-C) ($P<0.05$; to account for correlations in between-network connectivity we carried out 10000 permutations), suggesting a greater sensitivity to urbanicity in the Chinese CHIMGEN sample compared to the European IMAGEN sample. Five connections from six brain networks (aDMN, anterior default mode network; CBN, cerebellar network; ECN, executive control network; LN, language network; rFPN/lFPN, right or left frontal parietal network) were shared between CHIMGEN and IMAGEN: aDMN-CBN, aDMN-rFPN, aDMN-ECN, rFPN-LN and rFPN-lFPN (Figure 4D and Supplementary Table S2 and Figure S3). Whereas the susceptibility period for between-network connectivity involving self-referential thoughts²² and executive control²³, such as aDMN-CBN,

365 aDMN-rFPN, aDMN-ECN, and IFPN-rFPN was during adolescence (Figure 4E and
366 Supplementary Results), between-network connectivity involving the language network
367 LN-rFPN was most susceptible to urbanicity during childhood (Figure 4E and Supplementary
368 Results). These results indicate that between-networks FNCs relate to urbanicity in both shared
369 and distinct ways during brain development and in different socio-cultural and geographic
370 locations.

371

372 **Figure 4. Correlations of UrbanSat with between-networks FNCs and behaviors.** A. In the
373 CHIMGEN study, UrbanSat was significantly correlated with 42 brain between-networks
374 FNCs; B. In the IMAGEN FU2 study at age 19 years, UrbanSat was significantly correlated
375 with 19 brain between-networks FNCs; C. In the IMAGEN BL study at age 14 years, UrbanSat
376 was significantly correlated with 27 brain between-networks FNCs; D. Only five pairs of brain
377 between-networks FNCs could be replicated in CHIMGEN and IMAGEN sample; E. The
378 correlation of longitudinal UrbanSat on five overlapping brain between-networks FNCs was
379 significantly increased in the childhood period (age 5 to 9 years in rFPN with LN) and
380 adolescent period (age 11 to 15 years in aDMN with CBN, age 12 to 14 years in aDMN with
381 rFPN, age 12 to 15 years in aDMN with ECN, and age 15 to 17 years in rFPN with IFPN) in the

CHIMGEN sample; *F*. In the CHIMGEN sample, the correlation of longitudinal UrbanSat with perspective taking performance was significantly increased in the adolescent period (age 13 to 16 years in accuracy and age 14 to 18 years in reaction time). The difference to the adjacent age bands was significant in accuracy ($P=0.026$ compared to age 12 years and $P=1.45\times 10^{-4}$ compared to age 17 years) and in reaction time ($P=6.58\times 10^{-5}$ compared to age 13 years and $P=1.16\times 10^{-6}$ compared to age 19 years); The correlation of longitudinal UrbanSat on mental health was significantly increased in the adolescent period (age 12 to 16 years in depressive severity and age 14 to 17 years in state anxiety). The difference to the adjacent age bands was significant in BDI ($P=0.016$ compared to age 11 years and $P=3.62\times 10^{-5}$ compared to age 17 years) and state anxiety ($P=0.036$ compared to age 13 years and $P=0.011$ compared to age 18 years). ACC, accuracy; aDMN, anterior default mode network; BDI, Beck Depression Inventory; CBN, cerebellar network; ECN, executive control network; FNC, functional connectivity; LN, language network; lFPN, left frontal parietal network; rFPN, right frontal parietal network; RSQ, Ruminating Scale Questionnaire; RT, reaction time; * $P<0.05$; ** $P<0.001$.

The relation of UrbanSat with behavior

We investigated whether UrbanSat was correlated with measures of cognition and mental health-relevant behavior, in particular symptoms of depression and anxiety. Of the domains of neuropsychology, only one measure of social cognition, namely perspective taking, a measure of perceiving a situation or understanding a concept from an alternative point of view²⁴, was significantly positively associated with UrbanSat (accuracy: $r=0.124$, $P=0.002$; reaction time, $r=-0.245$, $P=6.10\times 10^{-7}$; Table 1 and Supplementary Figure S4) (Bonferroni-correction $P<0.05$). The correlation between UrbanSat and perspective taking performance was strongest during adolescence (age 13 to 16 years in accuracy and 14 to 18 years in reaction time). We confirmed the positive correlations between UrbanSat and perspective taking in IMAGEN at age 16 years ($r=0.103$, $P=0.009$), the earliest age these data were available (Figure 4F, Table 2 and Supplementary Figure S4). In the IMAGEN at age 19 years, we observed a trend-level significant correlation between UrbanSat and perspective taking ($P=0.056$) (Table 2 and Supplementary Figure S4).

In CHIMGEN, UrbanSat was correlated with number of symptoms in the Beck Depressive Inventory (BDI) ($r = 0.209$, $P = 1.44 \times 10^{-5}$) and state anxiety ($r = 0.132$, $P = 0.001$) (Bonferroni $P < 0.05$) (Table 1 and Supplementary Figure S4). The correlations between UrbanSat with BDI and state anxiety suggested greatest susceptibility during adolescence. (Figure 4F and Supplementary Results). In IMAGEN, we validated the correlation between UrbanSat and depressive symptoms at age 19 ($r = 0.118$, $P = 0.004$) using the Ruminating Scale Questionnaire (RSQ) (No depression questionnaire was available at age 14 or 16). There was no association between UrbanSat and anxiety at any timepoint in IMAGEN (Table 2 and Supplementary Figure S4).

Mediation of the correlation of UrbanSat with behavior by brain measures

We then investigated if left mPFC and cerebellar vermis volume, as well as the significant within- and between-network connectivity mediate the correlation of UrbanSat with perspective taking and symptoms of depression and anxiety.

In CHIMGEN, the correlation of UrbanSat with perspective taking was mediated by the left mPFC volume ($P < 0.001$, $r^2 = 0.20$), cerebellar vermis volume ($P < 0.001$, $r^2 = 0.15$), FNC within aDMN ($P < 0.001$, $r^2 = 0.12$) and VN ($P < 0.001$, $r^2 = 0.13$), as well as by the between network FNCs aDMN-CBN ($P < 0.05$, $r^2 = 0.10$), aDMN-rFPN ($P < 0.001$, $r^2 = 0.13$) (Figure 5A). In IMAGEN at age 16, the association of UrbanSat with perspective taking was also mediated by left mPFC volume ($P < 0.05$, $r^2 = 0.10$), FNC within the aDMN ($P < 0.001$, $r^2 = 0.36$), between network FNC aDMN-CBN ($P < 0.001$, $r^2 = 0.23$), aDMN-rFPN ($P < 0.001$, $r^2 = 0.20$) (Figure 5D). We did not find a mediation effect of the cerebellar vermis volume in the IMAGEN at age 16 ($P = 0.26$).

In CHIMGEN, the correlation between UrbanSat and BDI was mediated by left mPFC volume ($P < 0.001$, $r^2 = 0.40$) and aDMN-ECN ($P < 0.05$, $r^2 = 0.12$) but not by the cerebellar vermis volume ($P = 0.97$) (Figure 5B). Susceptibility to state anxiety was mediated by the left

medial frontal superior cortex volume ($P < 0.001$, $r^2 = 0.38$) as well as by cerebellar vermis volume ($P < 0.001$, $r^2 = 0.30$) (Figure 5C). In IMAGEN the correlation between UrbanSat and depressive symptoms was mediated by FNC within the aDMN ($P < 0.05$, $r^2 = 0.11$) and aDMN-ECN ($P < 0.001$, $r^2 = 0.25$) (Figure 5E), but not by the left mPFC ($P = 0.09$) or by the cerebellar vermis ($P = 0.16$).

Figure 5. Mediation analysis in the UrbanSat-brain-behaviour pathway. A. In the CHIMGEN sample, the left mPFC and cerebellar vermis volume, FNC within the aDMN and the VN, as well as between-networks FNC of the aDMN and CBN and the aDMN and rFPN mediated the effect of UrbanSat on perspective taking performance; B. The left MPFC volume and between-networks FNC of the aDMN with ECN mediated the effect of UrbanSat on BDI; C. The left mPFC and cerebellar vermis volume mediated the effect of UrbanSat on state anxiety; D. In the IMAGEN FU1 assessment at 16 years, but not in the FU2 at 19 years, the effect of UrbanSat on perspective taking was mediated by the left MPFC volume, FNC within the aDMN, between-networks FNC of the aDMN with CBN and the aDMN with rFPN; E. In the IMAGEN FU2 assessment at 19 years, the effect of UrbanSat on RSQ was mediated by FNC within the aDMN, between-networks FNC of the aDMN with ECN. RSQ data were not available at IMAGEN BL sample at 14 years. aDMN, anterior default mode network; CBN, cerebellar network; ECN, executive control network; FNC, functional connectivity; FPN, frontal parietal

456 *network; BDI, Beck Depression Inventory; RSQ, Ruminating Scale Questionnaire; * $P < 0.05$;*
 457 *** $P < 0.001$.*

458 **Discussion**

459 Using innovative remote-sensing satellite data acquisition, we provide a comparative
 460 characterization of the relation of urbanicity, brain structure and function, cognition and
 461 behavior in large datasets of young people in China and Europe. We found shared correlations
 462 of urbanicity with brain structure and function, as well as perspective taking, a measure of
 463 social cognition, and symptoms of depression in Chinese CHIMGEN and European IMAGEN
 464 sample. In contrast, correlations with anxiety were evident only in the Chinese sample. Brain
 465 structure analyses revealed a negative correlation of urbanicity with volume of the mPFC, with
 466 peaks in the dorsal (dmPFC) and ventral part (vmPFC) in Chinese and Europeans, respectively.
 467 This correlation was significantly greater in adolescence, with strongest correlations at age 13
 468 years. The mPFC mediated the effect of UrbanSat on perspective taking in CHIMGEN and
 469 IMAGEN, and the effect on depression and anxiety in CHIMGEN, only. Reduction of mPFC
 470 structure is implicated in responses to chronic stress²⁵ and pollution²⁶, both associated with
 471 urban living. The areas within the mPFC showing the greatest correlation with urbanicity in
 472 CHIMGEN and IMAGEN, the dmPFC and vmPFC, are thought to be involved in social and
 473 affective behavior²⁷.

474 We also found a positive correlation of urbanicity with cerebellar vermis volume in both
 475 Chinese and Europeans, with the strongest correlation during childhood at age 6. Lesions in the
 476 vermis give rise to the ‘Cerebellar-Cognitive-Affective-Syndrome’, characterized by
 477 impairments in executive function and memory, as well as affective behavior²⁸. Animal studies
 478 extend these findings to impairments in social behavior²⁹ and stress-dependent depressive
 479 affect³⁰, involving dopaminergic²⁹ and serotonergic³⁰ mechanisms, thus providing candidate
 480 neurotransmitter systems for urbanicity investigations. Vermis volume mediates the effect of
 481 urbanicity on perspective taking and anxiety in Chinese only, suggesting distinct structural

482 brain characteristics mediating urbanicity in China and Europe. Together, our findings relate
 483 urbanicity to structural brain changes in regions linked to shared and distinct social and
 484 affective behavior among individuals from different sociocultural conditions and geographical
 485 locations. Our results are supported by reports of associations of urbanicity and prefrontal
 486 cortex, in particular mPFC³¹ and DLPFC³², in smaller European studies.

487 We used FNC of 17 resting-state networks related to cognitive and sensory-motor
 488 processes to measure shared and distinct network connectivity in Chinese and Europeans. The
 489 correlation of urbanicity with FNC within the aDMN was shared between CHIMGEN and
 490 IMAGEN. FNC within the aDMN mediated the effect of UrbanSat on perspective taking, both
 491 in CHIMGEN and IMAGEN, and on depressive symptoms in IMAGEN only. Similarly to
 492 mPFC, FNC within the aDMN has been involved in social cognition³³ and depression³⁴, and is
 493 also moderated by urbanicity-related risk factors, including chronic stress³⁵ and air pollution³⁶.
 494 FNC within the mVN, which might be involved in the organization of cognitive function³⁷, was
 495 associated with urbanicity in CHIMGEN only, with a pronounced peak in susceptibility at the
 496 age of 6 years. It also mediated the effect of urbanicity on perspective taking, again in
 497 CHIMGEN only.

498 The resulting 136 between-network FNCs demonstrated overall similarity of resting-state
 499 activity between CHIMGEN and IMAGEN (Supplementary Figure S2). Of note, urbanicity
 500 was specifically correlated with 42 connections in CHIMGEN, 19 connections in IMAGEN at
 501 age 19 and 27 connections in IMAGEN at age 14. Of the 5 between-network FNCs correlated
 502 with urbanicity present in both CHIMGEN and IMAGEN, aDMN-ECN FNC mediated the
 503 effect of UrbanSat on depressive symptoms in both samples. Consistent with the mPFC
 504 structural and within FNC changes in the aDMN, FNC between aDMN and ECN have been
 505 implicated in the emotional dysregulation of depression³⁸. aDMN-rFPN FNC and aDMN-CBN
 506 FNC, shown to be engaged in social cognition^{39,40}, mediated the effect of UrbanSat on
 507 perspective taking in both CHIMGEN and IMAGEN. It is possible that a combination of
 508 structural changes in the mPFC and cerebellum account for this altered functional connectivity.

509 Together, they may mediate the relation of urbanicity with perspective taking. The majority of
 510 between FNC associated with urbanicity was distinct between CHIMGEN and IMAGEN at age
 511 19 and 14, however, indicating a specificity of between-network connectivity across
 512 geographic locations as well as brain developmental stage. Furthermore, between-network
 513 connectivity was increased in the Chinese sample, suggesting a greater sensitivity to urbanicity.
 514 This might reflect the more drastic changes in urbanization in China compared to Europe⁴¹, but
 515 may also relate to ethnically distinct genetic and environmental interactions, involving different
 516 brain pathways⁴².

517 Whereas previous studies have investigated urban living before the age of 15 years⁴³, our
 518 characterization of specific age windows of increased susceptibility indicate discrete
 519 neurodevelopmental periods during which brain development is sensitive to the effect of
 520 urbanicity. The susceptibility period for the relation of urbanicity with mPFC-volume during
 521 adolescence coincides with increased synaptic pruning, which depends (in part) on
 522 environmental stimulation of neurons⁴⁴. It is conceivable that adverse social situations that
 523 elevate stress in an urban environment might result in accelerated synaptic pruning⁴⁵, which
 524 might also affect functional network connectivity. Among the shared between-network
 525 connections, those that involve the aDMN and mediate perspective taking and depression show
 526 increased susceptibility for urbanicity during adolescence. The susceptibility period of vermis
 527 around age 6 years is consistent with the high volume increase of midline cerebellar structures
 528 observed in this age group⁴⁶. The fact that behavioral manifestations mediated by cerebellar
 529 vermis are all associated with susceptibility windows during adolescence may indicate an early
 530 neurobehavioral trajectory with delayed behavioral manifestation⁴⁷.

531 In contrast to previous studies reporting an association of urbanicity with social and
 532 cognitive impairments⁴⁸, we find better performance of one social cognition variable,
 533 perspective taking, in an urban environment. These previous findings were mostly derived from
 534 samples at risk for schizophrenia⁴⁸. As our cohorts were recruited from the general population,
 535 it is possible that we detect an adaptive behavior to living in the city, which might be

536 compromised in patients at risk for psychosis, thus exacerbating their social difficulties and
 537 isolation in an urban environment⁴⁹. We are extending previous observations reporting an
 538 increased incidence of depression and anxiety symptoms in urban settings⁵⁰, by demonstrating
 539 the stability of this observation in different geographical and sociocultural regions, and by
 540 discovering possible underlying brain mechanisms.

541 Remote sensing satellites play a critical role in monitoring the Earth's surface and
 542 atmosphere to track environmental conditions that are intimately related to human health⁵¹.
 543 Satellites have been applied to map urbanization, poverty, climate change and pollution⁵², as
 544 well as the spread of infectious disease⁵³. By extending this approach to measuring the relation
 545 of urbanicity with brain development, cognition and mental health, our study provides an
 546 approach that might be useful to characterize and monitor the spatial and temporal patterns of
 547 risk for mental disorders. Advances in resolution of satellite and computing power of
 548 geographic system facilitate integration of remote-sensing environmental parameters with
 549 public health data to develop models for disease surveillance and control. These models might
 550 be useful for sustainable urban planning and policy, and to develop targeted prevention efforts
 551 for young people in their unique environment. Our satellite measure of population density does
 552 not capture with sufficient granularity important social environmental conditions resulting
 553 from increased population density, such as social stress⁵⁴, access to infrastructure and green
 554 space⁵⁵ or crime⁵⁶. Future studies will investigate the integrated effect of urban physical and
 555 social environment, as well as the interaction with genetics and their relation to brain and
 556 behavior. As our approach can be extended and generalized to other geographic locations and is

557 easy to implement even in the absence of detailed or directly comparable ground level data, it
558 may be relevant for public health, policy and urban planning globally.

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586 Competing interests

587 The authors declare no competing interests.

588

589 **Methods**

590 **CHIMGEN and IMAGEN project**

591 In Chinese Imaging Genetics project (CHIMGEN), 7200 healthy Chinese Han participants of
 592 18-30 ages with blood sample, environmental, structural and functional neuroimaging and
 593 cognitive assessment were recruited from 29 centers of Chinese mainland 20 cities. In
 594 IMAGEN study, the first European multisite and longitudinal project¹³, comprehensive
 595 environmental factor, genetics, transcriptome, epigenetics, structural and functional
 596 neuroimaging, neurocognitive measure and mental health outcome were collected from more
 597 than 2000 14-year-old adolescents and 19-year-old follow up young adults.

598 **Remote sensing satellite data**

599 Global Human Settlement Layer (GHSL)¹⁴, Nighttime Lights (NL)¹⁵, Normalized Difference
 600 Vegetation Index (NDVI)¹⁶, Normalized Difference Built-up Index (NDBI)¹⁷, Normalized
 601 Difference Water Index (NDWI)¹⁸ and global land cover mapping¹⁹ were extracted from
 602 Google Earth Engine to measure different urbanicity characteristics based on the acquired
 603 individual geographic position from CHIMGEN (n=3306) and IMAGEN (n=1205)
 604 (Supplementary Methods and Table S3-S5).

605 **Neuroimaging data**

606 In this study, 1104 subjects from CHIMGEN Tianjin main centers, and 1724 and 1423 subjects
 607 from IMAGEN (at 14 years and 19 years, respectively) with available neuroimaging data were
 608 included in the further analysis. In both studies, T1-weighted imaging, DTI and resting-state

functional imaging were acquired using 3.0 Tesla MRI scanners. Brain GMV from the T1-weighted scans, white matter tract based spatial statistics (TBSS) from the DTI and within and between functional network connectivity (FNC) from the resting-state functional imaging were calculated from preprocessed neuroimaging data (Supplementary Methods and Table S1). Only subjects where both quality-controlled neuroimaging data and remote sensing satellite data were available were included in the statistical analysis.

Neuropsychological assessment and mental health data

Verbal learning memory, working memory, information processing speed, social cognition and executive control were included in the neuropsychological assessment, and depression and anxiety were included in mental health, in both CHIMGEN and IMAGEN (Supplementary Methods and Figure S5).

Statistical analysis

To test the latent urbanicity variable derived from the satellite features, confirmatory factor analysis (CFA) was applied to the measuring satellite features using R package *lavaan*²⁰. Only the closely correlated satellite features ($r > 0.4$) were included in the CFA model used to construct a factor for urbanicity in China and Europe respectively, which we termed ‘UrbanSat’ (Supplementary Table S6). Population density is the measure currently typically used to map urbanicity processes in sociology²¹, so to consolidate our foundation of using satellite features to measure urbanicity, the UrbanSat was correlated with this “gold standard” ground-level population grid GHSL data from both China and Europe, separately (Supplementary Figure S6). The detailed statistical analysis of the relation between UrbanSat and brain GMV, fractional anisotropy (FA), within- and between- FNC of brain networks are described in the Supplementary Methods.

634 Tables

635 **Table 1. The correlation of UrbanSat with neuropsychological assessments and mental**
636 **health in CHIMGEN sample (N = 622)**

Domain	Scale	Test	Item	Mean (SD)	r value	P value	
Neuropsychological test battery	Verbal learning memory	CVLT	Immediate free memory test 1-5	56.38 (8.36)	0.071	0.079	
			Short-term free memory	12.70 (2.29)	-0.033	0.415	
			Short-term clue memory	12.94 (2.26)	0.028	0.484	
			Long-term free memory	13.12 (2.24)	0.002	0.956	
			Long-term clue memory	13.21 (2.22)	0.001	0.988	
			Long-term recognition ACC	0.99 (0.02)	0.009	0.830	
	Working memory	N-back	ACC in 1-back	0.91 (0.08)	0.024	0.555	
			ACC in 3-back	0.75 (0.14)	0.081	0.053	
	Information processing speed	SDMT	Correct numbers in 90s	70.83 (11.35)	0.035	0.383	
	Social cognition	Ball tossing games	Perspective taking	PT_ACC	0.25 (0.28)	0.124	0.002
				PT_RT (ms)	1030.51 (237.86)	-0.245	6.10x10-7
				AG_ACC	0.02 (0.22)	-0.011	0.778
			Agency	AG_RT (ms)	2.65 (287.37)	-0.029	0.476
Cognitive control	Go-no go	ACC in Go trail	0.96 (0.09)	0.044	0.071		
		ACC in No-go trail	0.56 (0.18)	0.071	0.079		
Mental health	Depressive scale	BDI	-	2.33 (3.32)	0.209	1.44x10-5	
	Anxiety scale	STAI	State anxiety	28.55 (6.20)	0.132	0.001	
			Trait anxiety	32.13 (6.44)	0.039	0.328	

637 ACC, accuracy; AG_ACC, accuracy of agency trails; AG_RT, reaction time of agency trails;
 638 BDI, Beck Depression Inventory; CVLT, California Verbal Learning Test; PT_ACC, accuracy
 639 of perspective taking trails; PT_RT, reaction time of perspective taking trails; RT, reaction
 640 time; SDMT, Symbol Digit Modalities Test; STAI, State and Trait Anxiety Inventory;
 641 *P* values in bold and italic indicate there are significant correlation between UrbanSat and
 642 domains
 643

644 **Table 2. The correlation of UrbanSat with IRI and mental health in IMAGEN sample**

Scale	Item	N	Mean (SD)	<i>r</i> value	<i>P</i> value
IRI FU1	Empathic concern	636	16.17 (3.84)	0.022	0.574
	Fantasy	636	17.08 (4.67)	0.030	0.457
	Perspective taking	636	17.96 (3.78)	0.103	0.009
	Personal distress	636	12.06 (3.81)	-0.036	0.372
IRI FU2	Empathic concern	572	17.12 (4.67)	0.067	0.109
	Fantasy	572	17.12 (3.79)	-0.01	0.819
	Perspective taking	572	18.59 (3.90)	0.08	0.056
	Personal distress	572	11.38 (3.82)	0.049	0.243
Depressive scale FU2	RSQ	575	37.90 (12.03)	0.118	0.004
Anxiety scale FU2	DAWBA-GA	842	1.43 (0.76)	0.059	0.122
	CIDI-AS	813	1.26 (0.63)	0.035	0.320

645 CIDI-AS, Anxiety Screening from the Composite International Diagnostic Interview;
646 DAWBA-GA, Generalized Anxiety Scale from The Development and Well-Being Assessment
647 Interview; FU1, IMAGEN follow up 1 assessment acquired at 16 years; FU2, IMAGEN follow
648 up 2 assessment acquired at 19 years; N, sample size; IRI, Interpersonal Reactivity Index; RSQ,
649 Ruminating Scale Questionnaire; SD, stand deviation.

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