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Trust and the city: Linking urban upbringing to neural mechanisms of trust in psychosis

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Abstract

Objective: Elevated prevalence of non-affective psychotic disorders is often found in densely populated areas. This functional magnetic resonance imaging study investigates if reduced trust, a component of impaired social functioning in patients with psychotic disorder, is associated with urban upbringing.

Methods: In total, 39 patients (22 first episode and 17 clinical high risk) and 30 healthy controls, aged 16–29, performed two multi-round trust games, with a cooperative and unfair partner during functional magnetic resonance imaging scanning. Baseline trust was operationalized as the first investment made, and changes of trust as changes in investments made over the 20 trials during the games. Urban exposure during upbringing (0–15 years) was defined as higher urban (≥2500 inhabitants/km^2) or lower urban (<2500 inhabitants/km^2).

Results: Patients displayed lower baseline trust (first investment) than controls, regardless of urbanicity exposure. During cooperative interactions, lower-urban patients showed increasing investments. In addition, during cooperative interactions, group-by-developmental urbanicity interactions were found in the right and left amygdalae, although for the latter only at trend level. Higher urbanicity was associated with decreased activation of the left amygdala in patients and controls during investments and with increased activation of the right and left amygdalae in patients only, during repayments. During unfair interactions, no associations of urbanicity with behavior or brain activation were found.

Conclusion: Urban upbringing was unrelated to baseline trust. Associations with urbanicity were stronger for patients compared to controls, suggesting greater susceptibility to urbanicity effects during the developmental period. Higher-urban patients failed to compensate for the initial distrust specifically during repeated cooperative interactions. This finding highlights potential implications for social functioning. Urban upbringing was linked to differential amygdala activation, suggesting altered mechanisms of feedback learning, but this was not associated with trust game behavior.

Keywords

Psychotic disorder, urbanicity, trust, functional magnetic resonance imaging, amygdala

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Introduction

The association between urbanicity and non-affective psychosis, psychotic symptoms and experiences has been established by many epidemiological studies, showing elevated incidence rates of non-affective psychosis in densely populated urban areas (for a review, see Heinz et al. (2013)). Studies distinguish between urban birth, urban upbringing and current city living. The effects of the population density in the living area seem particularly pronounced during upbringing (Heinz et al., 2013; Pedersen and Mortensen, 2001), suggesting a maximum impact of urban factors during sensitive developmental periods.

It has been proposed that social characteristics of the urban environment, such as decreased social capital and cohesion, social deprivation and social fragmentation, underlie the association with the development of psychotic disorders (Drukker et al., 2006; Kirkbride et al., 2007, 2008; Michail and Birchwood, 2009; O'donoghue et al., 2016; Van Os et al., 2010; Zammit et al., 2010). Individuals at risk for psychosis may be particularly susceptible to these conditions, given that psychosis is associated with deficits in social information processing (Couture et al., 2006; Fett et al., 2011). A key component of low social capital and cohesion is the lack of trust and reciprocity (Magson et al., 2014). Therefore, growing up in urban environments may well affect the development of the capacity to trust others. The aim of this study was to investigate this hypothesis, focusing on the behavioral and neural mechanisms of trust and distrust in patients with psychotic symptoms and in healthy controls with different degrees of urbanicity during upbringing.

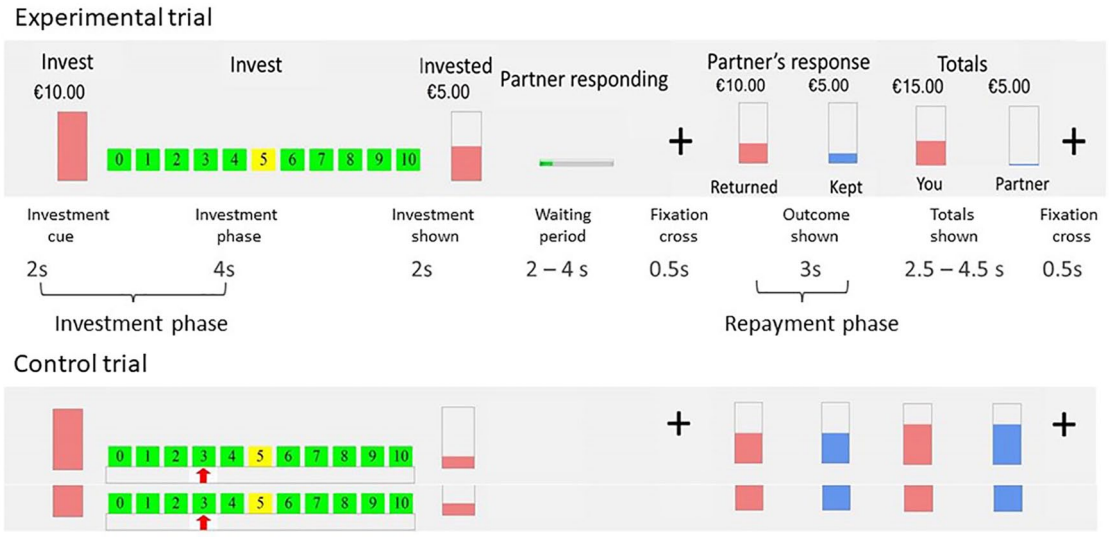
A suitable paradigm to experimentally study mechanisms of trust in real-time social interactions is the trust game (Berg et al., 1995). In this game, one participant invests money, while the amount returned depends on the other participant. An iterative trust game with the same partner allows for the investigation of baseline trust toward unknown others (i.e. first investment) and the development of trust or distrust based on either cooperative or unfair returns from the partner (Fett et al., 2014, 2016; Gromann et al., 2013; Lemmers-Jansen et al., 2017). Previous studies have shown lower baseline trust in patients with non-affective psychosis compared to healthy controls (Fett et al., 2012, 2016). In addition, chronic patients showed no increase in trust in response to repeated cooperative feedback (Fett et al., 2012). In first-episode patients (FEP) and patients at clinical high risk for psychosis (CHR), however, learning from cooperative feedback in the trust game was still intact (Fett et al., 2016). FEP showed less adaptive response to negative social feedback than CHR and healthy controls (Fett et al., 2016; Lemmers-Jansen et al., 2018a).

Two key processes can be distinguished in the trust game: reward learning (Fehr and Camerer, 2007; King-Casas et al., 2005) and mentalizing (Fett et al., 2014; Sripada et al., 2009). At the neural level, development of trust is associated with activation in the reward-related caudate, possibly reflecting the rewarding aspect of positive interactions (King-Casas et al., 2005). The caudate is active in signaling if a repayment is different than expected, and in an iterative trust game participants learned to predict the counterpart's response, with the signal shifting from the repayment to the investment phase (King-Casas et al., 2005). Patients with chronic schizophrenia showed reduced caudate activation in response to cooperative interactions (Gromann et al., 2013). Mentalizing is essential for learning about the trustworthiness of others. During both giving and receiving trust, healthy participants showed activation of mentalizing areas, the medial prefrontal cortex (mPFC) and the temporo-parietal junction (TPJ). Reduced TPJ activation was found in patients with chronic schizophrenia during cooperative and unfair interactions (Gromann et al., 2013), but not in FEP compared to controls (Lemmers-Jansen et al., 2018a). CHR showed increased TPJ activation during investments in the unfair condition (Lemmers-Jansen et al., 2018a).

There is preliminary evidence that the effect of city living and urban upbringing can be observed in the brain. One study in healthy individuals found that, during a social stress processing task, current city living was associated with increased activation of the amygdala, whereas urban upbringing affected the perigenual anterior cingulate cortex (pACC; Lederbogen et al., 2011). These regions are implicated in the regulation of negative affect, suggesting that the urban environment affects the neural mechanisms for social stress processing. Increased sensitivity to social stress is a key characteristic of psychosis and may further contribute to the problems patients encounter during social interactions (Myin-Germeys et al., 2005). Studies investigating the associations of brain structure and urbanicity in patients found that urban upbringing was associated with gray matter volume reduction in patients compared to siblings and controls (Frissen et al., 2018), but not with reduced cortical thickness, nor with resting-state connectivity in the posterior cingulate cortex and the nucleus accumbens (Peeters et al., 2015a, 2015b).

To our knowledge, this is the first neuroimaging study investigating the association between urbanicity and trust in patients with psychotic symptoms. Based on previous trust game findings and given an increased sensitivity to stress in psychosis, we hypothesized that higher urbanicity during upbringing in patients compared to controls would be associated with reduced baseline trust toward unknown others and with decreased sensitivity to cooperative, and possibly also to negative, social feedback. Furthermore, we hypothesized that urbanicity would be associated with altered activation in the reward-related caudate and in mentalizing areas such as the mPFC and TPJ during positive social interactions in patients compared to controls. Previously, in healthy subjects, associations of increased urbanicity with altered activity in brain areas involved in

Figure 1. Graphical overview of the trust game. The top row represents the visual stimuli in the experimental trust game trials; the middle row indicates the separate phases including their durations; the bottom row represents the visual stimuli in the control trials. Trust game trials started with an investment cue (2 seconds); the investment period where participants made their choice followed; here a number line appeared, with the cursor initially set on 5 (4 seconds, regardless of reaction times); the invested amount was shown (2 seconds), followed by a waiting period (jittered, 2–4 seconds), and a fixation cross (500 ms). Finally, the returned amount (3 seconds) and the final totals of both players (jittered, 2.5–4.5 seconds) were displayed, followed by a fixation cross (500 ms). In the control trials, participants were told to move the cursor to a number between 0 and 10, indicated by a red arrow. The design and duration of the control trials were identical to those of the experimental trials, but without the element of choice. Every trial lasted 18.5 seconds.



Source: Taken with permission from Lemmers-Jansen et al. (2017).

stress and reward processing (pACC, insula and amygdala) were reported (Lederbogen et al., 2011). Therefore, we expected to find altered activity in the pACC, insula and amygdala in patients. To generate hypotheses for future research, we explored possible interactions between urbanicity and symptom severity in patients, as a combination of these factors could increase difficulties in trust and learning from social feedback.

Methods

Subjects

In total, 47 adolescents and young adults with psychotic symptoms were recruited in the Amsterdam and the Hague area. The patient group consisted of 29 FEP and 18 CHR, who were grouped together to increase the power of the analyses, and included to reduce possible biases resulting from long-lasting stigma and institutionalized living, which may be present in chronic patients. They displayed equal levels of current positive symptoms, and FEP displayed slightly (non-significantly) higher levels of negative symptoms. Patients were contacted through their treating clinician at the Academic Medical Center Amsterdam, the Amsterdam early intervention team psychosis and the mental health center PsyQ in the Hague. Healthy controls were randomly recruited at schools for secondary vocational education and matched based on urbanicity level, gender, education and age. Exclusion criteria were an IQ < 80, any contraindications for scanning and additionally for the healthy control group, a (family) history of psychopathology, which was assessed with self-report, and by a systematic interview with questions regarding past and present mental help seeking, symptoms of depression and psychosis, and medication use. All participants had sufficient command of the Dutch language. Seven controls, seven FEP and one CHR were excluded due to missing or invalid scanning data. The final sample consisted of 39 patients and 30 controls (mean age = 21.5, standard deviation [*SD*] = 2.9). The research was approved by the Ethics Committee of the VU Medical Center Amsterdam.

Measures

Trust game. Participants played the role of investor in two consecutive, counterbalanced, multi-round trust games. They were told that their anonymous counterpart, the trustee, was connected to them via the Internet. In reality, they played against a programmed computer, responding in either a cooperative or an unfair way. Each game consisted of 20 experimental and 20 control trials (see Figure 1). At the beginning of each experimental trial, participants started with €10. Any amount between

€0 and €10 could be invested. The invested money was tripled and the trustee (i.e. the computer) then made a repayment. In the control trials, participants were told to move the cursor to the number between 0 and 10, indicated by a red arrow. The design and duration of the control trials were identical to those of the experimental trials, but without the element of choice. Game trials were contrasted with control trials to eliminate confounding neural (visual and motor) activity. Every trial started with an investment cue (2 seconds); the investment period where participants made their choice followed, where a number line appeared, with the cursor always on 5 (4 seconds, regardless of reaction times); the invested amount was shown (2 seconds), followed by a waiting period (jittered, 2–4 seconds), and a fixation cross (500 ms). Finally, the returned amount (3 seconds) and the final totals of both players (jittered, 2.5–4.5 seconds) were displayed, followed by a fixation cross (500 ms). Every trial lasted 18.5 seconds.

Urbanicity. Data of residences from birth to age 15 were obtained from all participants. The Dutch Central Bureau of Statistics (CBS) provides 'density of addresses', information about the number of inhabitants per km^2 of all Dutch towns and neighborhoods (CBS, 2014), reflecting the mean number of addresses within a circle with a radius of 1 km on 1st January of the reference year. The following reference years were used: 1995 (the first year available), 1997, 1999, 2003, 2005, 2007, 2009, 2011, 2013 (the final reference year, given that data collection for this study took place between April 2013 and March 2015); the column 'density of addresses' was not provided in the 2001 dataset. For participants born before 1995, the population density of this year was used for all previous years. For each number of years a participant lived at a specific address, the average population density for that address was based on the average of the reference years within that period and multiplied by the number of years.[1] All scores were added and then divided by 15, resulting in a weighted average over the period between birth and age 15. For addresses in other countries where only a town was mentioned, mean density for the town was calculated (three FEP, one CHR and two controls). Initially, outcome values were divided across five levels (CBS urbanicity rating; cf. Frissen et al., 2014), ranging from rural to very urban. Due to the skewed distribution of levels of urbanicity within groups (with most participants in the higher levels), we used a dichotomous division in the current analysis, representing lower (<2500/km^2) and higher ($\geqslant 2500$/km^2) urbanicity.

Positive and Negative Syndrome Scale. The 30-item Positive and Negative Syndrome Scale (PANSS) semi-structured interview was used for rating symptoms in the 2 weeks prior to testing (Kay et al., 1987). The PANSS distinguishes between positive, negative and general symptoms and was only administered to patients. For analysis, the positive and negative subscales were used. PANSS data were unavailable for four CHR.

Wechsler Adult Intelligence Scale. To control for group differences in verbal knowledge, we included the vocabulary subscale of the Wechsler Adult Intelligence Scale (WAIS) because the trust game has a strong verbal component (Wechsler, 1997). This subscale consisted of 33 words that had to be defined or described by the participants (e.g. winter, catastrophe).

Other measures. The trust game was followed by a questionnaire to investigate participants' opinions on the behavior of their counterpart and to check if they believed that they were playing a real person (see Supplementary Questionnaire S1-Q1). Four patients and three control participants did not believe the manipulation.

Procedure

All participants signed an informed consent. For participants under the age of 18, additional consent of one of the parents was obtained. First, participants completed several pen-and-paper questionnaires, including an assessment of postal codes of all former addresses. If unknown to the participant, parents were asked to provide additional information. Participants played several practice rounds of the trust game, to ensure understanding of the game, and were subsequently scanned for about an hour. First, they performed the trust game, followed by the structural scan, during which they could watch a movie. A second task, unrelated to the current research question followed (Lemmers-Jansen et al., 2018b). Scanning sessions ended with a resting-state scan. After scanning, participants were debriefed and received an image of their structural brain scan, 25€ for participation and travel cost reimbursement.

Functional magnetic resonance imaging data acquisition

Functional magnetic resonance imaging (fMRI) data were obtained at the Spinoza Center Amsterdam, using a 3.0-T Philips Achieva whole-body scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. A T2* echo-planar imaging (EPI) sequence (repetition time [TR] = 2.31 s, echo time [TE] = 27.63 ms, flip angle [FA] = 76.1°, field of view [FOV] = 240 mm, voxel size = $2.5 \times 2.5 \times 2.5$, 40 slices, 0.3-mm gap) was used, which resulted in 8 images per trial and 325 images per condition. A T1-weighted scan was obtained for anatomical reference (TR = 8.2 s, TE = 3.8 ms, FA = 8°, FOV = 240×188 mm^2, voxel size = $1 \times 1 \times 1$, 220 slices).

Data analysis

Behavioral data. Demographic and behavioral data were analyzed using Stata 14 with linear regression analyses and chi-square tests. To test our first hypothesis, assuming a

moderating effect of urbanicity on behavioral outcomes of trust, and patient and control group differences in this effect, we analyzed urbanicity-by-group interactions on the first investment (baseline trust), using linear regression analyses, with the main effects of urbanicity and group in the model. We report effect sizes in terms of beta. Second, we analyzed the association of urbanicity with development of investments (changes in trust) across repeated interactions (learning from feedback) as indicated by investments over trial number with both game partners. To investigate the development of trust over trials, we used multilevel mixed-effects linear regression analyses with random intercepts and random slopes ([XTMIXED]; investments [level 1]; within participants [level 2]) and report unstandardized coefficients and confidence intervals (CI). Group, urbanicity level and trial number were added as regressors to investigate the changes of investments over trials, rather than the mean investments, by group and urbanicity. To test our second hypothesis, linear regression analyses were used to investigate the effect of urbanicity on neural activation. For the exploratory analyses, investigating the association between urbanicity and symptoms on learning over trials, multilevel mixed-effects regression analyses were used. All group comparisons were controlled for WAIS vocabulary score to avoid potential confounding effects of group differences in WAIS, and age and gender were added as a priori confounders.

Imaging data. Imaging data were analyzed using Statistical Parametric Mapping (SPM) 8. Functional images for each participant were preprocessed using the following steps: realign and unwarp, coregistration with individual structural images, segmented for normalization to an MNI (Montreal Neurological Institute) template and smoothing with a 6-mm Gaussian kernel (full width at half maximum [FWHM]). First, an event-related general linear model was used to construct individual time courses for the investment and repayment phase per condition. For each trial, the investment period was defined from stimulus onset to the moment of investment, and the repayment phase as the period during which the partner's return was displayed (Lemmers-Jansen et al., 2017). Trials from both the cooperative and unfair conditions were contrasted with control trials in the first level, to eliminate confounding neural activity. In the second level, two full-factorial models were used, one for cooperative and one for unfair interactions, with event (investment or repayment), urbanicity level during development and patient status as the defining factors.

A priori regions of interest (ROIs) were derived from trust game literature in psychosis patients, urbanicity and social stress processing literature. The following seven ROIs were used: mPFC (MNI coordinates: –3, 65, 25), right TPJ (52, –57, 26) and right caudate (10, 9, 5) derived from Gromann et al. (2013); pACC (–6, 40, 21) from Lederbogen et al. (2011); bilateral insula (34, 21, 0 and −32, 20, –6) and bilateral amygdala (27, –1, –19 and −24, –2, –19) derived from Achterberg et al. (2017). All ROIs were defined as a 10-mm sphere around the given coordinates, except for the caudate and bilateral amygdala, where a 5-mm sphere was used. We tested group differences using MarsBaR 0.43. An adjusted *p*-value for multiple comparisons was calculated, taking the correlation between the contrast estimates into account using the Simple Interactive Statistical Analysis Bonferroni tool,[2] resulting in an adjusted *p*-value of 0.023 for the cooperative and 0.021 for the unfair condition (see Table 2 and Lemmers-Jansen et al., 2018a). For the main effects of task, the standard Bonferroni correction in MarsBaR was used. We analyzed ROI activation during the investment and the repayment phase of the game in one full-factorial model, and separate per game partner.

All behavioral and neural analyses were replicated in the FEP-only sample. Results were essentially similar to the analyses in the full sample and are reported in the Supplementary Material (S3).

Exploring interactions between urbanicity and symptoms on trust. To generate hypotheses for future research, regression analyses were also performed in patients only, investigating urbanicity-by-symptom severity interactions on baseline trust, the development of trust and on neural outcomes (contrast estimates of the significant ROIs, averaged over all voxels). The PANSS positive and negative subscales were used as continuous variables. One patient reported extremely high positive symptoms (>3 SD). In all analyses, this outlier value was adjusted to the nearest value within 2 SD from the mean (from 31 to 23).

Results

Participant characteristics

Participant characteristics are displayed in Table 1. There were no significant gender or age differences between the patient and control groups. On the WAIS vocabulary subtest, patients scored significantly lower than controls. Four patients and three controls did not believe that they played a human counterpart. All analyses have been replicated without these participants, yielding similar results.

Behavioral results

Results pertaining to the trust game have previously been reported in a largely overlapping sample (Lemmers-Jansen et al., 2018a). Associations with urbanicity are novel in this research.

Baseline trust. Patients displayed lower baseline trust than controls (M=5.56 vs 7.13, β=–0.27, p=0.03); however, group differences in baseline trust were not moderated by

Table 1. Participant characteristics.

	Patients ($N=39$)	Controls ($N=30$)	Statistics
Age, *M* (*SD*)	21.58 (2.8)	21.37 (3.0)	$\beta=-0.037$, $p=0.76$
Gender—male, *n* (%)	21 (54)	18 (60)	$\chi^2=0.26$, $p=0.61$
WAIS, *M* (*SD*)	36.5 (12.03)	44.37 (11.3)	$\beta=-0.32$, $p<0.007$*
Urbanicity, low–high (*n*)	19–20	20–10	$\chi^2=2.23$, $p=0.1$
PANSS symptoms—total (*SD*)	60.43 (13.78)		
Positive, *M* (*SD*)	1.90 (.86)		$b=-0.02$, 95% CI = [–0.53, 0.48], $p=0.93$
CHR–FEP, *M*	1.91–1.98		
Negative, *M* (*SD*)	2.27 (.77)		$b=0.5$, 95% CI = [–0.04, 1.04], $p=0.07$
CHR–FEP, *M*	1.96–2.45		
Medicated, *n* (%)	24 (62)		
Atypical antipsychotics	13 (54)		
Participants with job, *n* (%)	12 (31)	25 (83)	$\chi^2=18.1$, $p<0.001$**
Education level (secondary/vocational), *n*	8/30	8/22	$\chi^2=6.85$, $p=0.3$
Education carrier (stopped/finished/still studying), *n*	4/10/23	1/9/18	$\chi^2=2.05$, $p=0.56$
Parental unemployment, *n* (%)	2 (5)	0	$\chi^2=1.63$, $p=0.20$

M: mean; *SD*: standard deviation; WAIS: Wechsler Adult Intelligence Scale; PANSS: Positive and Negative Syndrome Scale; CHR: clinical high-risk patients; FEP: first-episode psychosis patients; CI: confidence interval.
Parental unemployment was coded as unemployed if both parents were reported as unemployed.
*Significant at $p<0.01$; **significant at $p<0.001$.

urbanicity, indicated by a non-significant urbanicity-by-group interaction ($\beta=-0.09$, $p=0.7$). After removing the interaction from the model, no significant main effect of urbanicity was found ($\beta=-0.19$, $p=0.12$).

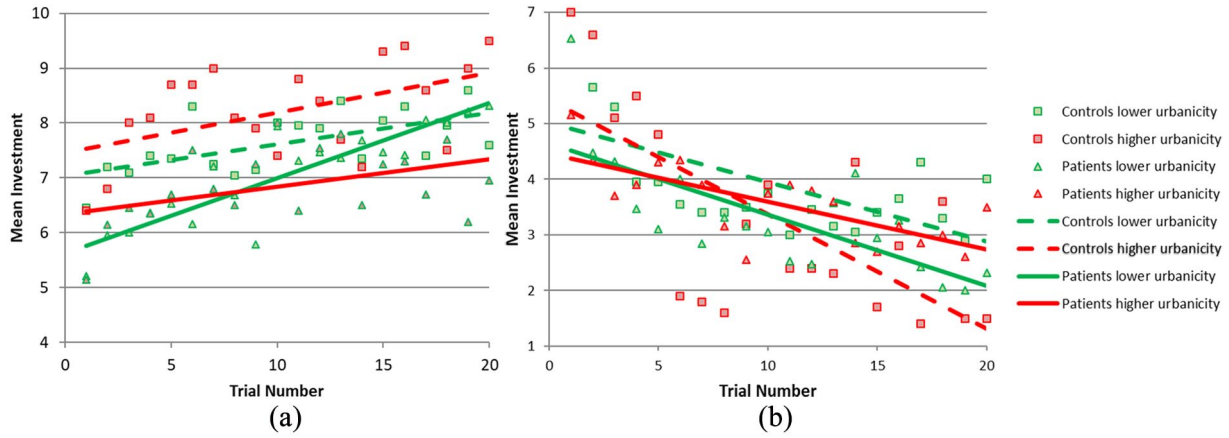
Cooperative interactions. The interaction between group, trial number and urbanicity on investment was trending toward significance ($b=-0.10$, 95% CI = [–0.22, –0.01], $p=0.08$), tentatively suggesting that the association between urbanicity and learning over trials differed between patients and controls (see Figure 2(a)). In patients the interaction between urbanicity and trial number on investment was significant ($b=-0.09$, 95% CI = [–0.17, –0.006], $p=0.04$), whereas in controls it was not ($b=0.02$, $p=0.67$). Further within-group analyses showed that patients brought up in lower-urban areas adjusted their investments in response to positive feedback more than patients brought up in higher-urban areas ($b=0.14$, 95% CI = [0.080, 0.194], $p<0.001$, and $b=0.05$, 95% CI = [–0.007, 0.11], $p=0.09$, respectively).

Unfair interactions. The interaction between group, trial number and urbanicity on investment in repeated unfair interactions (see Figure 2(b)) was non-significant ($b=0.08$, $p=0.19$). Removing this three-way interaction from the model, a significant group-by-trial number interaction was found ($b=0.07$, 95% CI = [0.01, 0.13], $p=0.002$), showing that, regardless of urbanicity, patients adjusted their investments less than controls. No interactions with urbanicity, nor a main effect of urbanicity, were found (all p's >0.74).

Symptoms. Exploratory analyses showed that, within patients, urbanicity-by-symptoms interactions on baseline trust were significant for negative symptoms ($\beta=-1.38$, $p=0.02$) but not for positive symptoms ($\beta=-0.48$, $p=0.50$). Post hoc linear regression within the same model showed that the significant interaction was driven by a negative non-significant association between negative symptoms and baseline trust in higher-urban patients ($\beta=-0.68$, $p=0.07$) and a similarly strong association in the opposite direction in lower-urban patients ($\beta=0.61$, $p=0.12$, see Supplement Figure S2-F1).

Interactions of urbanicity with positive and negative symptoms on changes in investment in cooperative and unfair interactions were non-significant (all p's >0.52).

Figure 2. Associations of urban upbringing and trust over trials by group. The figure shows the regression lines and data points of changes of investment during the trust game in cooperative and unfair interactions in patients and controls, brought up in lower- (<2500 inhabitants per km²) and higher-urban environments (≥2500 inhabitants per km²). Mean investments per group were calculated per trial: (a) cooperative interactions and (b) unfair interactions.



Imaging results

ROI analyses were performed with eight predefined ROIs (see section 'Imaging data'). First, the main effects of task of the trust game for the whole sample were analyzed (see Table 2). The pACC and mPFC were activated in the investment phases of both conditions, and the TPJ was activated during repayments in both conditions. The bilateral insula was consistently activated throughout conditions and game phases, except during the cooperative investments. The caudate was only active during unfair investments.

Second, interactions of urbanicity with group were investigated. In the cooperative investment phase, an interaction of urbanicity and group on left amygdala activation was found at trend level (Figure 3(a)), whereas in the cooperative repayment phase an interaction was found on right amygdala activation (Figure 3(b)) and in the left amygdala at trend level (Figure 3(c)). During investments, higher urbanicity was associated with a decrease in left amygdala activation, which was more pronounced in patients than in controls. During repayments, patients brought up in higher-urban areas showed increased activation of the right amygdala compared to the control condition of the task, whereas controls brought up in higher-urban areas showed decreased activation. In the unfair condition, no group-by-urbanicity interactions were found. In the ROI showing significant group-by-urbanicity interactions, we additionally investigated interactions of investment, symptoms and urbanicity on the contrast estimates, but these associations did not reach significance.

For completeness, whole-brain main effects of task are reported in Supplementary Table S4, showing prefrontal and temporal activation in almost every condition. Whole-brain group-by-urbanicity interactions yielded no significant results surviving family-wise error correction.

Discussion

This study set out to investigate the association between urbanicity and trust in healthy individuals and patients with psychotic symptoms. Contrary to our expectation, urbanicity was unrelated to baseline trust. In patients, but not in controls, urbanicity exposure was associated at trend level with differential learning from positive social feedback, with a steeper increase in investments in lower-urban compared to higher-urban patients. During cooperative interactions, higher urbanicity exposure was associated with differential activation of both amygdalae in patients compared to controls. In previous research in healthy subjects (Lederbogen et al., 2011), higher urbanicity was associated with greater amygdala activation, a finding our results could not confirm. We found increased amygdala activation only in patients during cooperative repayment. The task conditions, however, are not comparable (Lederbogen et al., 2011), using a stress paradigm, whereas the trust game condition of cooperation does not reflect a stressful situation.

Consistent with existing trust game data in psychosis patients (Fett et al., 2012, 2016; Gromann et al., 2013; Lemmers-Jansen et al., 2018a), patients showed reduced baseline trust. However, this initial trust toward unknown others was not affected by urbanicity. In contrast, throughout repeated interactions with the cooperative game partner, associations with urbanicity became apparent, albeit at trend level and different than hypothesized. The group-by-urbanicity interaction on increases of investment was explained by the lower starting point (baseline trust), followed by the steep increase in investment in lower-urban patients (Figure 2(a)), rather than, as expected, by decreased learning of patients who grew up in higher urbanicity. Similar patterns of steep

Table 2. ROI activation during the trust game.

Condition—main effect of task (Bonferroni corrected)	ROI	MNI (*X*, *Y*, *Z*)	*t*	*p*
Cooperative investment	pACC	–6, 40, 21	5.32	<0.001
	mPFC	–3, 65, 25	2.59	0.04
	Insula left	–32, 20, –6	3.31	0.005
Cooperative repayment	Insula right	34, 21, 0	4.67	<0.001
	Insula left	–32, 20, –6	3.38	0.003
	TPJ	52, –57, 26	3.22	0.006
Unfair investment	pACC	–6, 40, 21	8.74	<0.001
	mPFC	–3, 65, 25	3.50	0.002
	Insula right	34, 21, 0	3.72	0.001
	Insula left	–32, 20, –6	5.44	<0.001
	Caudate right	10, 9, 5	3.42	0.003
Unfair repayment	Insula right	34, 21, 0	6.10	<0.001
	Insula left	–32, 20, –6	3.89	<0.001
	TPJ	52, –57, 26	2.66	0.03
Interactions of urbanicity and group				
Cooperative investment[a]	Amygdala left	–24, –2, –19	1.67	<0.05[b]
Cooperative repayment[a]	Amygdala right	27, –1, –19	2.07	0.02
	Amygdala left	–24, –2, –19	1.77	0.04[b]

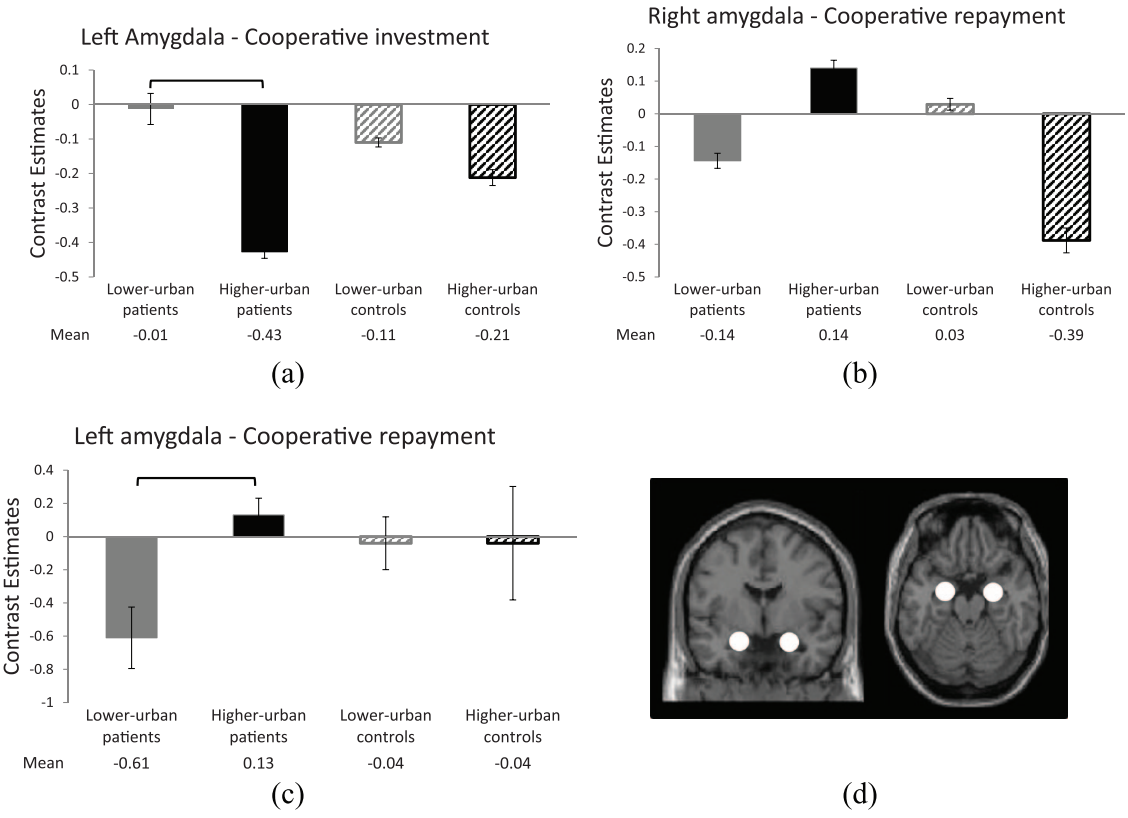
ROI: region of interest; MNI: Montreal Neurological Institute; pACC: perigenual anterior cingulate cortex; mPFC: medial prefrontal cortex; TPJ: temporo-parietal junction.
[a]Adjusted significance levels for multiple comparisons, calculated based on the internal correlation of the contrast estimates of $r = 0.73$ for the ROI in the cooperative condition and $r = 0.69$ for the unfair condition. This resulted in an adjusted threshold of $p = 0.023$ for the cooperative and $p = 0.021$ for the unfair condition.
[b]Interaction at trend level.

increases of trust have previously been reported in relatives of patients with psychosis (Fett et al., 2012) and in patients at clinical high risk for psychosis (Lemmers-Jansen et al., 2018a), in contrast to chronic patients who did not respond to positive feedback (Fett et al., 2012). The results tentatively suggest that low urban exposure during upbringing might act as a protective factor on the sensitivity to cooperation, where steep increases of trust in response to positive feedback (i.e. trustworthy behavior) of others counteracted initial distrust. This possibly compensatory mechanism was absent in patients who grew up in higher-urban areas (Lemmers-Jansen et al., 2018a). Contrary to our hypothesis, we did not find evidence for the hypothesis that urbanicity increases the sensitivity to negative social feedback. If so, this would have resulted in an even steeper decline of trust in response to negative feedback. Urbanicity seems to have a stronger influence on positive social interactions and trust building than on trust reducing negative interactions.

Furthermore, we hypothesized an association between urbanicity and altered activation in the reward-related caudate, and with mentalizing areas such as the mPFC and TPJ during positive social interactions in patients compared to controls. In addition, altered activity in brain areas involved in stress and reward processing (pACC, insula and amygdala; Adolphs, 2010; Lederbogen et al., 2013) in patients compared to controls were expected, especially during negative social interactions (Myin-Germeys et al., 2005). Contrary to our predictions, urbanicity was not associated with reduced activation of the reward-related caudate, nor with mPFC and TPJ during the cooperative condition in patients versus controls, suggesting intact reward and mentalizing processes.

In line with our hypothesis, aberrant activation of the amygdalae was present in higher-urban patients, albeit during cooperative rather than unfair interactions. In the left amygdala, higher-urban patients showed a stronger

Figure 3. Contrast estimates show urbanicity-by-group interactions. The figure shows bar graphs with standard error bars for patients and controls brought up in lower- (<2500 inhabitants per km²) and higher-urban environments (>2500 inhabitants per km²). The graphs display the mean contrast estimates (activation during game trials minus control trials, including marked main effects of urban upbringing within groups) in (a) the left amygdala during cooperative investments (significant at trend level), (b) the right amygdala during cooperative repayments and (c) the left amygdala during cooperative repayments (significant at trend level); (d) the location of the bilateral amygdalae (MNI coordinates: right 27, –1, –19; left −24, –2, –19), showing the coronal and transversal sections.



reduction of activation than lower-urban patients during investment and the reverse during repayment. Controls showed a similar, albeit less pronounced difference. Note that these interactions were at trend level. In the right amygdala, higher-urban patients displayed increased activation compared to lower-urban patients. A reverse pattern was found in controls. In both conditions, the contralateral amygdala showed similar but weaker associations with urbanicity, suggesting no clear hemispheric dominance in either condition. Engelmann et al. (2019) showed that threat-induced aversive affect disrupted functional connectivity between the TPJ and amygdala during decisions to trust. In our study, reduced amygdala activation was found both during investment and repayment in controls during cooperative investment and repayment, and also in higher-urban patients during cooperative investments. The amygdala is implicated in a series of functions like emotion processing, reward learning, memory and stress responsiveness (Adolphs, 2010; Phelps, 2006; Roozendaal et al., 2009; Wassum and Izquierdo, 2015). In addition, it plays a central role in valence processing (Vrticka et al., 2013), and dysfunction of this area can result in a lack of social apprehension (Bickart et al., 2014). An association of urbanicity and amygdala activation was previously observed by Lederbogen et al. (2011). Our study did not find increased neural activation with higher urbanicity in the healthy control sample, but this increased activation was observed in the patient population during cooperative repayments. In the Lederbogen et al. (2011) study, increased amygdala activation was associated with more urban city living during a social stress task, whereas we mainly found decreased activation with higher urbanicity. Using the same ROIs in a social task, we expected to find similarities in outcome. The trust game is not a priori a stress paradigm, which might account for the different findings. However, the fact that our results point into the opposite direction warrants further investigation. Reduced amygdala connectivity and activation has previously been found in the trust game in threat situations (Engelmann et al., 2019), suggesting that urbanicity might function as a social stressor. Given the

behavioral findings, it might also be hypothesized that the altered activation of the amygdalae in higher- versus lower-urban patients is associated with differences in social feedback learning (cf. Adolphs, 2010; Paton et al., 2006; Phelps et al., 2004; Roozendaal et al., 2009; Wassum and Izquierdo, 2015). Reduced amygdala activation during the feedback phase in lower-urban patients, in combination with the steep increase of investments, might reflect social approach behavior (Adolphs, 2010). Taken together, stress, urbanicity and aversive affect impact on amygdala functioning (Engelmann et al., 2019; Lederbogen et al., 2011). Further research is needed to elucidate the mechanisms underlying the association between urbanicity, amygdala functioning and trust, suggesting additional connectivity analyses, and measures of affect and arousal, such as skin conductance.

Previous studies have reported associations between negative symptoms and reduced feedback and reward learning (Gold et al., 2012; Strauss et al., 2011). Explorative behavioral analyses including symptom severity show that in patients the combination of childhood urbanicity and negative symptoms was associated with reduced baseline trust. It is important to note that the association was non-significant and the interaction driven by the reverse association in lower-urban patients. However, this finding tentatively suggests a co-dependency between urbanicity and negative symptoms, reducing social functioning. Parallel to the cumulative risk for psychosis with an increasing number of risk factors or traumata (Shevlin et al., 2007; Van Os et al., 2004), it seems that, within patients, exposure to high urbanicity during upbringing in combination with more severe symptoms might be associated with more severe difficulties with social interactions. However, this warrants further investigation.

Limitations and future directions

Several limitations must be considered. First, our patient sample was not homogeneous, including both FEP and CHR. CHR are already in care for other psychopathology (mainly anxiety and depression), reporting psychotic symptoms, but have not experienced full-blown psychosis, unlike FEP (Velthorst et al., 2009; Woods et al., 2009). Recently, it has been argued that the presence of psychotic symptoms is possibly a more important feature for CHR than transition to psychosis, suggesting that it is valid to combine both groups in research (Van Os and Reininghaus, 2016). However, despite their similar levels of psychotic symptoms, different mechanisms might underlie behavioral and neural outcomes before and after transition to psychosis. In line with these considerations, additional analyses in an FEP-only sample confirmed the main behavioral and neural findings (see Supplementary Material S3). These findings suggest that the similarities between the two groups based on symptom severity are larger than the differences. Second, we found small to medium effect sizes ($d = 0.4$) and enough power for the investigation of medium effect sizes in baseline trust. For the detection of small effects and in the three-way interactions with trust over multiple trials, the study was underpowered. Larger samples are required to replicate our findings. In the patient sample, symptom severity was generally modest. A wider range of symptoms might have yielded different results, particularly with regard to urbanicity-by-symptoms interactions. In addition, half of the FEP (33% of all patients) was on antipsychotic medication, which might have modified their responsivity to feedback compared to non-medicated patients (Insel et al., 2014). We did not control for medication, due to collinearity with patient status. Furthermore, urbanicity was roughly defined in two categories, with a rather small high-urban control sample. Results might be different when measured in more extreme urban environments. Data were acquired in the Netherlands, but outcomes can be different in cities around the world (Fett et al., 2019). Furthermore, in low- and middle-income countries, risk factors for psychosis may be differently distributed between rural and urban areas, as compared to high-income countries (DeVylder et al., 2018). For future studies, it is recommended to include the full urbanicity range, equally distributed over groups, also allowing for analyses with urbanicity as a continuous variable. Including participants from different countries increases generalizability of the findings. On the basis of our data, we cannot exclude the possibility that genetic drift or selective migration, the tendency of people at risk for psychosis moving toward cities (Colodro-Conde et al., 2018), underlies the observed effects. Other confounders such as migration, social economic status, social deprivation and environmental factors associated with urbanicity (Heinz et al., 2013) could influence levels of trust, but were not investigated. Future studies should take these factors into account, in order to disentangle the mechanisms by which urbanicity impacts on social interactions and trust. A methodological limitation is that participants were not paid on performance in the trust game. Several studies have reported that this does not impact the results, but there also is evidence that real and hypothetical payments have different effects on decisions and related brain activity (Vlaev, 2012).

Summarizing, higher urbanicity in patients impacts on the ability to engage in positive social interactions. Patients seem to be more susceptible to the influences of urbanicity than controls, during positive but not negative interactions. At the neural level, urbanicity impacts on amygdala functioning during positive social interactions. We recommend studies of urbanicity in social paradigms to elucidate the consequences of urbanicity for daily-life interactions and to clarify associations with amygdala functioning.

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Supplemental Material

Supplemental material for this article is available online.

Notes

1. For example, if a person lived at address A from 1990 to 1996 and at address B until 2005, we calculated 5× the value for the reference year 1995, 1× the value for 1997 for address A, and 1× the value for 1997, 2× 1999, 4× 2003 and 2× the value for 2005 for address B.
2. http://www.quantitativeskills.com/sisa/calculations/bonfer.htm

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