Social interactions in health and psychosis

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2019

document version
Publisher's PDF, also known as Version of record

Part III:

Urbanicity

Chapter 6

Trust and the City

linking urban upbringing to neural mechanisms of trust in psychosis

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In revision

Abstract

Objective: Elevated prevalence of non-affective psychotic disorders is 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: Thirty-nine 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. Urban exposure during upbringing (0-15 years) was defined as higher-urban (>2500 inhabitants/km2) or lower-urban (<2500 inhabitants/km2).

Results: Patients displayed lower baseline trust (first investment) than controls, regardless of urbanicity exposure. During cooperative interactions, lower-urban patients showed increasing of investments. Higher urbanicity was associated with decreased activation of the left amygdala in patients and controls, and with increased activation of the right amygdala in patients only. In unfair interactions, no associations of brain activation and urbanicity were found.

Conclusion: Urbanicity was unrelated to baseline trust. Patients appear to be more susceptible to urbanicity effects than controls. Higher-urban patients failed to compensate for the initial distrust during repeated cooperative interactions. Urbanicity was linked to differential amygdala activation, suggesting altered feedback learning. However, this could not explain behavioural differences. Replication studies are needed.

Keywords:

Psychotic disorder, urbanicity, trust, fMRI, amygdala

Introduction

The association between urbanicity and non-affective psychosis, psychotic symptoms and experiences has been established by many epidemiological studies [for a review, see (Heinz et al., 2013)], showing elevated incidence rates in densely populated urban areas. An increased incidence of non-affective psychosis has been linked with urban birth, urban upbringing, and current city living. There is some support for the hypothesis that part of the association may be due to selective migration, suggesting that individuals at genetic risk for schizophrenia may move to (or remain in) urban areas (Colodro-Conde, Couvy-Duchesne, Whitfield, & et al., 2018). The effects of the population density in the living area seem, however, particularly pronounced during upbringing (Heinz et al., 2013; Pedersen & 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., 2008; Kirkbride et al., 2007; Michail & Birchwood, 2009; O'donoghue et al., 2016; Van Os, Kenis, & Rutten, 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, Viechtbauer, Penn, Van Os, & Krabbendam, 2011). A key component of low social capital and cohesion is the lack of trust and reciprocity (Magson, Craven, & Bodkin-Andrews, 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 behavioural 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, the investor receives an endowment of €10. The investor can give any amount between €0 and €10 to the counterpart, the trustee. The given amount is tripled and the trustee then can return any part of this amount to the investor. Any investment requires trust that a fair repayment will be made. An iterative trust game with the same partner allows for the investigation of baseline trust towards unknown others (i.e., first investment), and the development of trust or distrust based on either cooperative or unfair returns from the partner (Fett, Gromann, et al., 2014; Fett et al., 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; Fett et al., 2016).

Additionally, 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, Fett, et al., 2018).

Two key processes can be distinguished in the trust game: reward learning (Fehr & Camerer, 2007; King-Casas et al., 2005; Rilling & Sanfey, 2011) and mentalising (Fett, Gromann, et al., 2014; Sripada et al., 2009; Van den Bos et al., 2011). 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 signalling if a repayment is better (or worse) than expected (Delgado & Dickerson, 2012; King-Casas et al., 2005), and in an iterative trust game participants learned to predict the counterpart's response (King-Casas et al., 2005). Chronic patients showed reduced caudate activation in response to cooperative interactions (Gromann et al., 2013). Mentalising is essential for learning about the trustworthiness of others. During both giving and receiving trust, healthy participants showed activation of mentalising areas, the medial prefrontal cortex (mPFC) and the temporo-parietal junction (TPJ). Chronic schizophrenia patients showed reduced TPJ activation in both cooperative and unfair interactions (Gromann et al., 2013), CHR showed increased TPJ activation during investments in the unfair condition (Lemmers-Jansen, Fett, et al., 2018). No differences in mentalising areas were found in FEP compared to controls (Lemmers-Jansen, Fett, et al., 2018).

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, Delespaul, & Van Os, 2005). In another functional neuroimaging study, city living was additionally associated with altered activation and modulation of the brain regions involved in reward processing [i.e., ventral tegmental area, medial orbital cortex; (Krämer et al., 2017)]. These studies show that functional neuroimaging may help to elucidate the mechanisms of risk associated with urbanicity, and point to altered regulation of stress and reward as possible underlying mechanisms.

To our knowledge, this is the first neuroimaging study investigating the association between urbanicity and trust in patients with psychotic symptoms. Based on previous findings using the trust game and given an increased sensitivity to stress in psychosis, we hypothesised that higher urbanicity levels during upbringing in patients compared to controls would be associated with reduced baseline trust towards unknown others and with decreased sensitivity to cooperative, and possibly also to negative feedback from the trustee. Furthermore, we hypothesised that urbanicity would be associated with altered activation in the reward-related caudate, and in mentalising 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 stress and reward processing (pACC, insula, and amygdala) were reported (Adolphs, 2010; Lederbogen, Haddad, & Meyer-Lindenberg, 2013). Therefore we expected to find altered activity in the pACC, insula, and amygdala in patients. Patients seem to be more susceptible to the influence of urbanicity than controls, especially during negative social interactions, given evidence of increased sensitivity to negative social stimuli (Myin-Germeys et al., 2005). To generate hypotheses for future research, we explored possible interactions between urbanicity and symptom severity in patients, as symptoms in combination with higher urbanicity could have an added effect on trust and learning from social feedback.

Methods

Subjects

Forty-seven 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 for the current study grouped together to increase the power of the analyses. Both patient groups were included to reduce possible biases resulting from long lasting stigma and institutionalised living, that may be present in chronic patients. They displayed equal levels of current positive and FEP displayed slightly (but 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, mainly in the Amsterdam area. The control group was 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 or 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 anxiety during or before scanning, missing or invalid data. The final sample consisted of 39 patients and 30 controls (mean age 21.5, SD = 2.9). The research was approved by the Ethical Committee of the VU Medical Center Amsterdam.

Measures

Trust game

Participants played the role of investor in two counter-balanced 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 computer, programmed to respond in a cooperative or unfair way. For a detailed description of the paradigm, see (Fett, Gromann, et al., 2014; Fett et al., 2016; Gromann et al., 2013; Lemmers-Jansen et al., 2017). Each game consisted of 20 experimental and 20 control trials. 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 any given number between 0-10, indicated by a red arrow. The design and duration of the control trials were equal to the experimental trials, but without the element of choice. Every trial lasted 18.5 seconds. Results pertaining to the trust game have previously been reported in a largely overlapping sample (Lemmers-Jansen, Fett, et al., 2018).

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 squared kilometer of all Dutch towns and neighbourhoods (Netherlands, 2014), reflecting the mean number of addresses within a circle with a radius of one kilometer on January 1st of the reference year. The reference-years used were 1995, 1999, 2005, 2010, 2013, and 2014. In case of more than one density value for a particular postal code, an average was calculated. For foreign addresses, where only a town was mentioned, mean density for the town was calculated (three FEP, one CHR, and two controls). Average population density was defined across five levels [CBS urbanicity rating, cf. (Frissen et al., 2014)], ranging from rural to very urban (1 ≤ 500/km^2; 2 = 500–1,000/km^2; 3 = 1,000–1,500/ km^2; 4 = 1,500–2,500/km^2; 5 ≥ 2,500/km^2). Mean urbanicity exposure over 0-15 years of age was used for analyses. Due to unequal distribution of levels of urbanicity within groups (with most participants in the higher

levels,), we used a dichotomous division, representing lower (< 2,500/km^2), and higher (≥ 2,500/km^2) urbanicity.

Positive and Negative Syndrome Scale [PANSS (Kay et al., 1987)]

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

Wechsler Adult Intelligence Scale [WAIS (Wechsler, 1997)]

To control for group differences in verbal knowledge, we included the vocabulary subscale of the WAIS, because the trust game has a strong verbal component. This subscale consisted of 33 words that had to be defined or described by the participants (e.g. winter, catastrophe, reckless). Answers were coded as fully correct (2 points), partially correct (1) or wrong (0).

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. Subsequently participants were 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, Krabbendam, et al., 2018). Scanning sessions ended with a resting state scan. After scanning, participants were debriefed, and they received an image of their structural brain scan, 25€ for participation, and travel cost reimbursement.

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* EPI sequence (TR = 2.31, TE = 27.63, FA = 76.1º, FOV 240mm, voxel size 2.5 x 2.5 x 2.5, 40 slices, 0.3 mm gap) was used, which resulted in 325 images per condition. A T1-weighted scan was obtained for anatomical reference (TR = 8.2, TE = 3.8, FA = 8º, FOV 240*188mm, voxel size 1 x 1 x 1, 220 slices).

Data analysis

Behavioural data

Demographic and behavioural data were analysed using Stata 14 with regression analyses and chi-square tests. To test our first hypothesis, assuming a moderating effect

of urbanicity on behavioural outcomes of trust, and group differences in this effect, we analysed urbanicity-by-group interactions on first investment, regardless of condition (baseline trust), using linear regression analyses. The main effects of urbanicity and group were included in the model. We report effect sizes in beta's. Second, we analysed 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 each game partner (cooperative and unfair). To investigate this development of trust over trials, we used multilevel random regression analyses [(XTREG); investments (level 1); within participants (level 2)] and report unstandardised coefficients and confidence intervals. Trial number was added as regressor, because we were interested in the changes of investments over trials, rather than the mean investments. 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 random regression analyses (XTREG) 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 analysed using Statistical Parametric Mapping (SPM) 8. Functional images for each participant were pre-processed using the following steps: realign and unwarp, co-registration with individual structural images, segmented for normalization to an MNI template and smoothing with a 6 mm Gaussian kernel (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, we defined the investment as the period of 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. At second level, a full-factorial model was used, with urbanicity level and patient status as defining factors.

A priori regions of interest (ROIs) were derived from trust game literature in psychosis patients, the urbanicity, and social stress processing literature. Talairach coordinates were converted to Montreal Neurological Institute (MNI) space with the tal2mni converter under MatLab. 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 ; bilateral insula (34, 21, 0 & -32, 20, -6), and bilateral amygdala (27, -1, -19 & -24, -2, -19) derived from Achterberg et al. (2017).

We tested group differences using MarsBaR (version 0.43; see http://MarsBaR.sourceforge.net). An adjusted *p*-value for multiple comparisons was calculated, taking the correlation between the contrast estimates into account by using the Simple Interactive Statistical Analysis Bonferroni tool (http://www.quantitativeskills.com/sisa/calculations/bonfer.htm), resulting in an adjusted p-value of .04 for the investment phases and .03 for the repayment phases (see Table 2) in the group comparisons, [see (Lemmers-Jansen, Fett, et al., 2018; Woudstra et al., 2013)]. For the main effects of task, the standard Bonferroni correction in MarsBaR was used. We analysed ROI activation during both the investment and the repayment phase of the game.

All behavioural 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.

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 was found to be an outlier, with extremely high positive symptoms (>3SD). 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 large nor significant gender or age differences between the groups. On the WAIS vocabulary subtest, patients scored significantly lower than controls.

Behavioural results

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

Table 1

Participant Characteristics

	Patients (39)	Controls (30)	Statistics
Age, Mean (*SD*)	21.58 (2.8)	21.37 (3.0)	β = -.037, p = .76
Gender, *n* Male (%)	21 (54%)	18 (60%)	χ^2 = .26, p = .61
WAIS, Mean (*SD*)	36.5 (12.03)	44.37 (11.3)	β = -.32, p < .007*
Urbanicity low - high (*n*)	19 - 20	20 - 10	χ^2 = 2.23, p = .1
PANSS symptoms Total (*SD)*	60.43 (13.78)		
Positive, Mean (*SD*)	1.90 (.86)		
CHR - FEP Mean	1.91 - 1.98		b = - .02, 95%CI-.53 - .48, p = .93
Negative, Mean (*SD*)	2.27 (.77		
CHR - FEP Mean	1.96 - 2.45		b = .5, 95%CI -.04 - 1.04, p = .07
Medicated, *n* (%)	24 (62%)		
Atypical antipsychotics *n* (%)	13 (54%)		

* Significant at p < .01

Note: WAIS = Wechsler Adult Intelligence Scale; PANSS = Positive and Negative Syndrome Scale: CHR = clinical high-risk patients: FEP = first episode psychosis patients.

Baseline trust

Patients displayed lower baseline trust than controls (mean 5.56 vs. 7.13, β = -.27, p = .03), however group differences in baseline trust were not moderated by urbanicity, indicated by a non-significant interaction of urbanicity and group (β = -.09, p = .7). After removing the interaction from the model, no significant main effect of urbanicity was found (β = -.19, p = .12).

Cooperative interactions

The group-by-urbanicity interaction on investment over repeated trials was significant (b = - .10, CI95% -.19 to -.02, p = .02 showing that the association between urbanicity and learning over trials differed between groups (see Figure 1a). In patients the interaction between urbanicity and trial number on investment was significant (b = - .09, CI95% -.14 to -.083, p = .002), whereas in controls it was not (b = .02, p = .64) Further analyses within group 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 = .14, CI95% .097 to .177, p < .001, and b = .05, CI95% .012 to -.088, p = .012, respectively).

Unfair interactions

The interaction between group, trial number, and urbanicity on investment in repeated unfair interactions (see Figure 1b), was non-significant (b = .08, p = .1). Removing this three-way interaction from the model, a significant group-by-trial number interaction was found (b = .07, CI95% .03 to .12, p = .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 > .68).

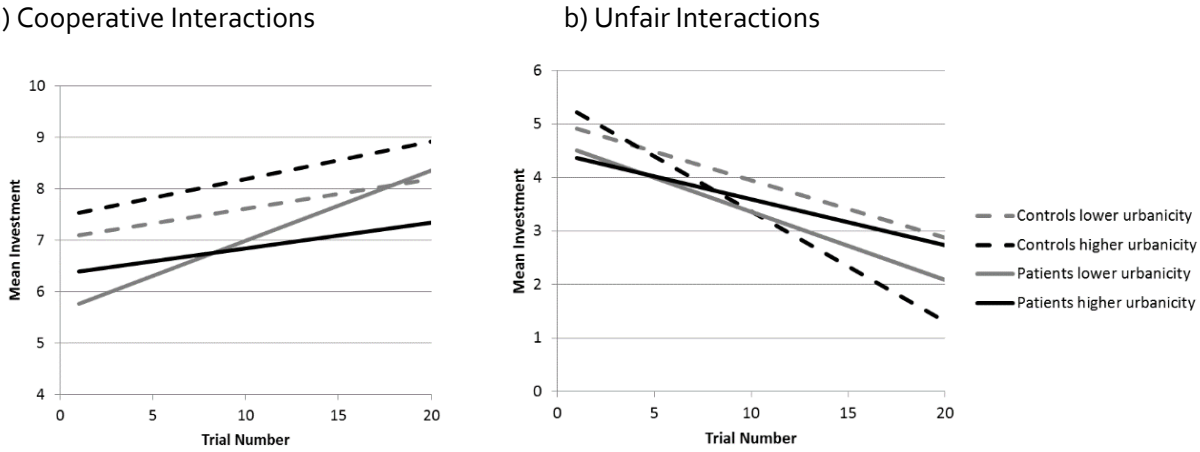


Figure 1 Associations of Urbanicity and Trust over Trials by Group

Symptoms

Exploratory analyses showed that within patients, interactions of urbanicity and symptoms on baseline trust were not significant for positive symptoms (β = -.48, p = .50). For negative symptoms, however, a significant interaction was found (β = -1.38, p = .02), see Figure 2. Post-hoc linear regression within the same model, showed that the interaction was driven by a negative non-significant association between negative symptoms and baseline trust in higher-urban patients (β = -.68, p = .07), and a similarly strong association in the opposite direction in lower-urban patients (β = .61, p = .12).

Interactions of urbanicity with positive and negative symptoms on changes in investment in cooperative and unfair interactions were non-significant (all p's > .38).

Imaging results

Region of interest analyses were performed with eight predefined ROIs (see Data analysis, Imaging data). First, the main effects of task of the trust game for the whole sample were analysed (see Table 2). The pACC was activated in the investment phases

of both conditions, and in the repayment phase of the cooperative condition. The bilateral insula was consistently activated throughout conditions and game phases, except during the cooperative investment phase. The caudate was only active during unfair investments, and the TPJ was activated during repayments in both conditions.

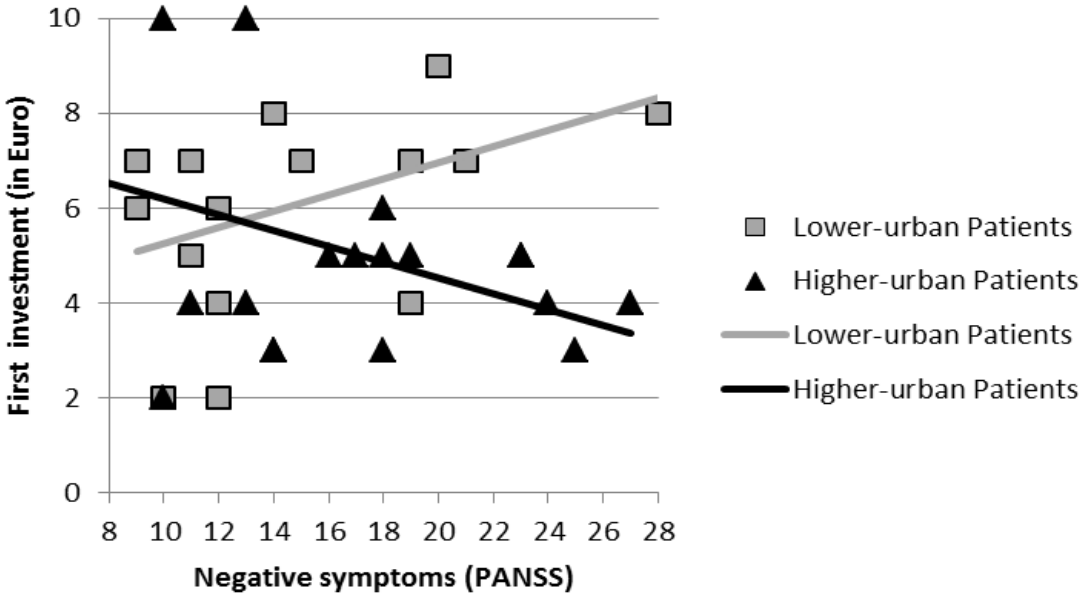


Figure 2 Association Between Negative Symptoms and Urbanicity on Baseline Trust During Cooperative Interactions, in Patients.
PANSS = Positive and Negative Syndrome Scale

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 (Figure 3a), whereas in the cooperative repayment phase an interaction was found on right amygdala activation (Figure 3b). 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 symptoms and urbanicity on the contrast estimates, but these associations did not reach significance.

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	4.67	< .001
	Insula left	-32, 20, -6	2.82	.03
Cooperative repayment	Insula right	34, 21, 0	4.80	< .001
	Insula left	-32, 20, -6	4.08	< .001
	pACC	-6, 40, 21	2.46	.06
	TPJ	52, -57, 26	3.10	.01
Unfair investment	pACC	-6, 40, 21	6.07	< .001
	mPFC	-3, 65, 25	3.20	.009
	Insula right	34, 21, 0	3.88	.001
	Insula left	-32, 20, -6	5.55	< .001
	Caudate right	10, 9, 5	3.34	.006
Unfair repayment	Insula right	34, 21, 0	5.83	< .001
	Insula left	-32, 20, -6	3.88	.001
	TPJ	52, -57, 26	2.97	.02
Interactions of urbanicity and group				
Cooperative investment *	Amygdala left	-24, -2, -19	1.99	.03
	Amygdala right	27, -1, -19	1.50	.07†
Cooperative repayment *	Amygdala right	27, -1, -19	1.90	.03
	Amygdala left	-24, -2, -19	1.66	.05†

* = adjusted significance levels for multiple comparisons, calculated based on the internal correlation of the contrast estimates, resulting in an adjusted threshold of $p = .04$ for the investment phase and $p = .03$ for the repayment phase

† = interaction at trend level

Note: ROI = region of interest; MNI = Montreal Neurological Institute; pACC = perigenual anterior cingulate cortex; TPJ = temporo-parietal junction; mPFC = medial prefrontal cortex.

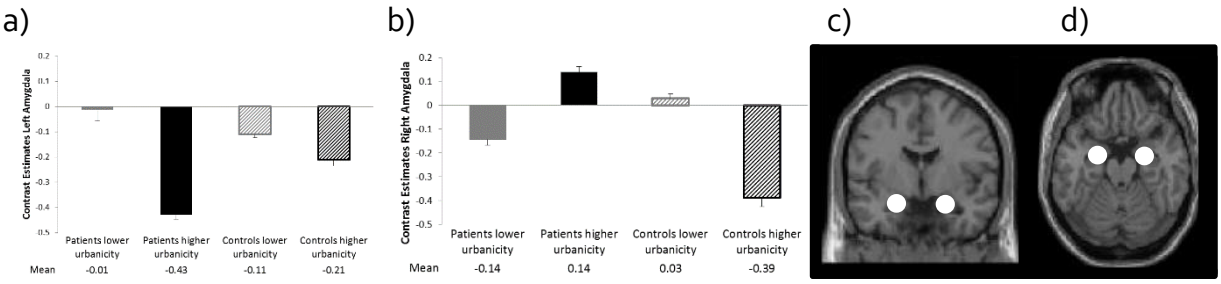


Figure 3 Contrast estimates showing urbanicity-by-group interactions

Note: Bar graphs with standard errors for the urbanicity-by-group interaction on ROI contrast estimates: a) in the left amygdala during cooperative investment; b) in the right amygdala during cooperative repayment. The right panels display the location of the bilateral amygdalae, showing the c) coronal and d) transversal section.

For completeness, whole brain main effects of task are reported in S2_Supplementary Table, showing prefrontal and temporal activation in almost every condition. Whole brain group-by-urbanicity interactions were investigated, but 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 with differential learning from positive social feedback, with a steeper increase in investments in lower compared to higher-urban patients. On the neural level, 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 receiving a higher amount than invested does not reflect a stressful situation.

Consistent with existing trust game data in psychosis patients (Fett et al., 2012; Fett et al., 2016; Gromann et al., 2013; Lemmers-Jansen, Fett, et al., 2018), baseline trust was lower in patients than controls. However, this difference in baseline trust was unaccounted for by urbanicity. In other words, urban exposure did not seem to affect the initial trust towards unknown others. In contrast, throughout repeated interactions with the cooperative game partner, associations with urbanicity became apparent, albeit different than hypothesised. 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 patients with lower urbanicity (Figure 2a), rather than, as expected, by decreased learning of patients who grew up in higher urbanicity. Increases of investments of the latter group resembled increases observed in controls. Similar patterns of steep increases of trust in patients with lower urban upbringing 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, Fett, et al., 2018), in contrast to chronic patients who did not respond to positive feedback (Fett et al., 2012; Strauss et al., 2013). 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 behaviour) of others counteracted initial distrust. This possibly compensatory mechanism was absent in patients who grew up in higher-urban areas (Lemmers-Jansen, Fett, et al., 2018). Contrary to our expectations, no associations with urbanicity were present for unfair interactions. In the unfair interactions the effect size was similar to the cooperative condition, but the results lacked statistical precision. Urbanicity seems to have a

stronger influence on positive social interactions and trust building than on negative interactions, where trust needs to be reduced. Impaired learning from positive social feedback suggests that urbanicity is a proxy for social stress, fostering distrust. Alternatively, these differences might be due to the increased genetic risk levels for psychosis in participants with high-urban upbringing, due to selective migration (Colodro-Conde et al., 2018). 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.

Furthermore, we hypothesised that urbanicity would be associated with altered activation in the reward-related caudate, and in mentalising areas such as the mPFC and TPJ during positive social interactions in patients compared to controls. 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, based on increased sensitivity to negative social stimuli (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 mentalising processes. Our findings differed in several aspects from previous research, which could be due to differences in methodology (using city living, and a task that required processing and suppressing of reward) and to the selection of the ROI [reward system: ventral tegmental area; (Krämer et al., 2017)].

In line with our hypothesis, aberrant activation of the amygdalae was present in higher-urban patients. In the left amygdala higher-urban patients showed stronger reduction of activation than lower-urban patients. Controls showed a similar, albeit less pronounced difference. 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 contra-lateral amygdala showed similar trend-level associations with urbanicity, suggesting that there was no clear hemispheric dominance in either condition. The amygdala is implicated in a series of functions like emotion processing, reward learning, memory, reward, and stress responsiveness (Adolphs, 2010; Davis, 1992; Paton, Belova, Morrison, & Salzman, 2006; Phelps, 2006; Roozendaal, McEwen, & Chattarji, 2009; Ruff & Fehr, 2014; Wassum & Izquierdo, 2015). In addition, it plays a central role in valence processing (Vrticka, Sander, & Vuilleumier, 2013), in encoding socially threatening stimuli (FeldmanHall et al., 2018), and in social behaviour, and dysfunction of this area can results in a lack of social apprehension (Bickart, Dickerson, & Barrett, 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 study, increased amygdala activation was associated with more urban city living during a social stress task (Lederbogen et al., 2011), 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. Given the behavioural findings, it can be hypothesised that the altered activation of the amygdalae in higher-urban versus lower-urban patients is associated with differences in social feedback learning [cf; (Adolphs, 2010; Paton et al., 2006; Phelps, Delgado, Nearing, & LeDoux, 2004; Roozendaal et al., 2009; Wassum & 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 behaviour (Adolphs, 2010). Further research is needed to elucidate the association between urbanicity, amygdala functioning, and trust, suggesting additional measures of 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 behavioural 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 increasing number of risk factors or traumata (Shevlin, Houston, Dorahy, & Adamson, 2007; Van Os, Pedersen, & Mortensen, 2004), it seems that within patients, exposure to high urbanicity during upbringing in combination with a more severe symptom profile might be associated with more severe difficulties with social interactions. However, this warrants further investigation.

Limitations and future directions

This study is the first to investigate the association of urbanicity and social interactions in patients with psychotic symptoms. Epidemiological studies have shown an association between psychosis and urbanicity. Brain structure and connectivity in patients do not explain this association (Frissen et al., 2017; Peeters, Gronenschild, et

al., 2015; Peeters, Van de Ven, et al., 2015). We extended the existing studies by providing insight in the functional neural mechanisms during social interactions, showing that depending on urbanicity during upbringing, the amygdala shows differential activation between patients and controls in social interactions in the trust game. This differential activation possibly underlies the behavioural dif-ferences in learning from social feedback during the trust game. Several limitations must be considered. Firstly, our patient sample was not homogeneous, including both FEP and CHR. CHR patients are already in care for other psychopathology (mainly an-xiety and depression), reporting psychotic symptoms, but have not experienced full-blown psychosis, unlike FEP (Van Os & Linscott, 2012; 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 & Reininghaus, 2016). However, despite their similar levels of psychotic symptoms, different mechanisms might underlie behavioural and neural outcomes before and after transition to psychosis. In line with these considerations, additional analyses in a FEP only sample con-firmed the main behavioural and neural findings (see Supplement). 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 = .4) and enough power for the investigation of medium effect sizes in baseline trust. For the detection of small effects and in the 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 interactions of urbanicity with symptoms. Additionally, half of the FEP (33% of all patients) was on antipsychotic medication, which might have enhanced their responsivity to feedback compared to non-medicated patients (Insel et al., 2014; Nielsen et al., 2012). We did not control for medication, due to collinearity effects. 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 big cities around the world, where population density is higher. 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, and preferably in different countries, to increase generalizability of the findings. 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 (Johnson & Mislin, 2011; Vlaev, 2012).

Summarising, 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 during 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.

Acknowledgements

We would like to thank Prof. Lieuwe de Haan and his team at the Amsterdam Medical Center (AMC), Prof. Mark Van der Gaag and Dr. Helga Ising at PsyQ, The Hague, Onno Ackema and the department of early psychosis of the AMC, and the VIP team for helping with recruitment of the patients; Tinka Beemsterboer and colleagues at the Spinoza Centre for Neuroimaging, Roeterseiland Amsterdam for their help during scanning and Margot de Gier for calculating population density scores for the participants.

Supplementary Material

S1 Replication of the analyses, based on the FEP sample only

S1_2.1 Subjects

Twenty-nine adolescents and young adults with non-affective psychosis and 28 age-matched healthy controls (mean age 19.6, SD = 1.6) were recruited in the Amsterdam area. Patients were contacted through their caregivers at the academic medical center Amsterdam, the Amsterdam early intervention team psychosis. Healthy controls were recruited at schools. Exclusion criteria were an IQ<80, any contraindications for scanning, and additionally for the healthy control group, a (family) history of psychopathology. All participants had sufficient command of the Dutch language. Seven patients and seven controls were excluded due to anxiety during or before scanning, missing urbanicity data, and invalid data. The final sample consisted of 22 patients and 21 controls. This research was approved of by the Ethical Committee of the VU Medical Center Amsterdam.

S1_3 Results

S1_3.1 Participant characteristics

Participant characteristics are displayed in S1_Table 1. There were no gender or age differences between the groups. On the WAIS vocabulary subtest, FEP scored significantly lower than controls.

S1_3.2 Behavioural results

Baseline trust

There was a trend towards lower baseline trust in FEP than controls (mean 5.45 vs. 7.19, β = -.33, p = .07), however group differences in baseline trust did not vary with urbanicity, indicated by a non-significant interaction of urbanicity and group (β = -.31, p = .6). After removing the interaction from the model, no significant main effect of urbanicity was found (β = -.22, p = .15). Within FEP, interactions of urbanicity and symptoms on baseline trust were not significant for positive symptoms and paranoia (β = -.61, p = .38 and β = -.26, p = .73, respectively). For negative symptoms, however, a significant interaction was found (β = -2.29, p = .05), showing that more severe negative symptoms were associated at trend level with reduced baseline trust in higher-urban FEP (β = -.57, p = .07), but not in lower-urban FEP (β = .31, p = .35).

Supplementary Material

S1_Table 1

Participant Characteristics

	FEP (22)	Controls (21)	Statistics
Age, Mean (*SD*)	19.88 (1.54)	20.41 (2.57)	β = -.13, p = .42
Gender, *n* Male (%)	14 (64%)	15 (71%)	χ^2 = .30, p = .59
WAIS, Mean (*SD*)	32.5 (10.3)	45.57 (8.75)	β = -.56, p < .001**
Urbanicity lower – higher (*n*)	11 – 11	12 – 9	χ^2 = .22, p = .64
PANSS symptoms			
- Positive, Mean (SD)	1.89 (.94)		
- Negative, Mean (SD)	2.45 (.86)		
- Paranoia, Mean (SD)	2.23 (1.41)		
Medicated, *n* (%)	16 (71%)		
- Atypical antipsychotics *n* (%)	11 (69%)		

** Significant at p < .001

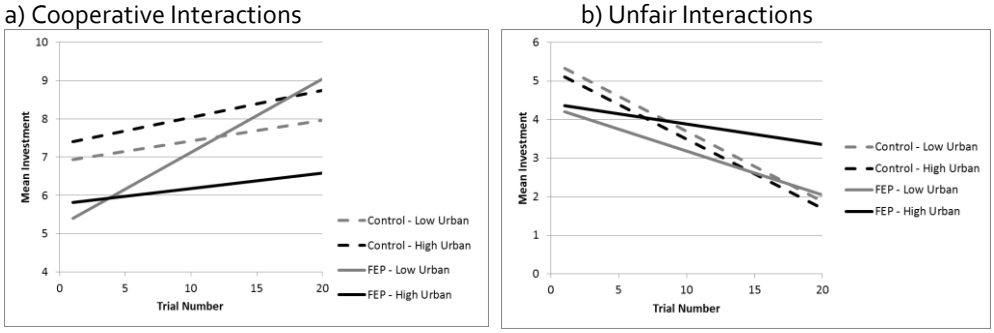
Note: FEP = first episode psychosis; WAIS = Wechsler Adult Intelligence Scale; PANSS = Positive and Negative Syndrome Scale

Cooperative interactions

The three-way trial number-by-group-by-urbanicity interaction on investment was significant (b = - .08, CI95% -1.37 to -.03, p = .002), showing that the association between urbanicity and learning over trials differed between groups (see S1_Figure 1a). In patients the interaction between urbanicity and trial number on investment was significant (b = - .15, CI95% -.22 to -.08, p < .001), whereas in controls it was not (b = .017, CI95% -.06 to .1, p = .68). Further analyses within urbanicity group (lower/higher) showed that patients brought up in higher urban areas did not significantly adjust their investments in response to positive feedback (b = .04, CI95% -.01 to .09, p = .11), whereas patients brought up in lower urban areas, adjusted their investments to levels similar to controls (b = .19, CI95% .14 to .24, p < .001). No interactions of urbanicity with negative, positive or paranoid symptoms on increases of investment were found (all p's > .68).

Supplementary Material

a) Cooperative Interactions b) Unfair Interactions

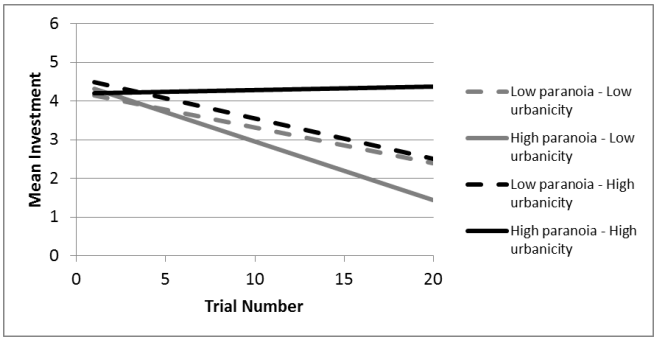


S1_Figure 1. Associations of Urbanicity and Trust over Trials by Group

Unfair interactions

The three-way interaction between group, urbanicity and trial number in the *unfair condition* was non-significant, although visual inspection suggested that the high-urban FEP group again showed less sensitivity to the feedback than the low-urban FEP (see S1_Figure1b, *b* = .03, CI95% -.03 to .09, *p* = .31). Removing the three-way interaction from the model, a significant group-by-trial number interaction was found (*b* = .05, CI95% .02 to .08, *p* < .001), 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* > .27).

Interactions of urbanicity with negative or positive symptoms on investments were non- significant. However, a trial number-by-urbanicity-by-paranoia interaction was found (*b* = .17, CI95% .03 to .32, *p* = .02), indicating that patients with the combination of high paranoia and higher urbanicity did not decrease their investments during the game, as patients with lower urbanicity, or higher urbanicity with low paranoia did (*b* = .11, CI95% .009 to .22, *p* = .03). Specifically, patients with lower levels of paranoia decreased investments over trials similar to controls regardless of urbanicity; patients with higher levels of paranoia showed no such adaptation if they grew up in higher urbanicity (see S1_Figure 2).



S1_Figure 2 Interaction of Urbanicity and Paranoia on Investment in Unfair Interactions

Supplementary Material

S1_3.3 Imaging results

Region of interest analyses were performed with seven predefined ROIs. First, the main effects of task of the trust game for the whole sample were analysed (see S1_Table 2). The pACC was activated in investment phases of both conditions. The bilateral insula was consistently activated throughout conditions and game phases, except during the cooperative investment phase. The caudate was only active during unfair investments.

S1_Table 2

ROI Activation During the Trust Game

Condition	ROI	MNI	t	p
Main effect of task (Bonferroni corrected)		X, Y, Z		
Cooperative investment	pACC	-6, 40, 21	2.75	.03
Cooperative repayment	Insula right	34, 21, 0	3.51	.004
	Insula left	-32, 20, -6	2.72	.03
Unfair investment	pACC	-6, 40, 21	6.07	<.001
	Insula right	34, 21, 0	3.21	.01
	Insula left	-32, 20, -6	3.43	.005
	Caudate right	10, 9, 5	2.37	.08
Unfair repayment	Insula right	34, 21, 0	5.32	< .001
	Insula left	-32, 20, -6	3.98	.001
Interactions of urbanicity and group				
Cooperative repayment *	Amygdala right	27, -1, -19	1.96	.03
Unfair repayment **	Insula right	34, 21, 0	1.95	.03
	Amygdala left	-24, -2, -19	2.47	.01

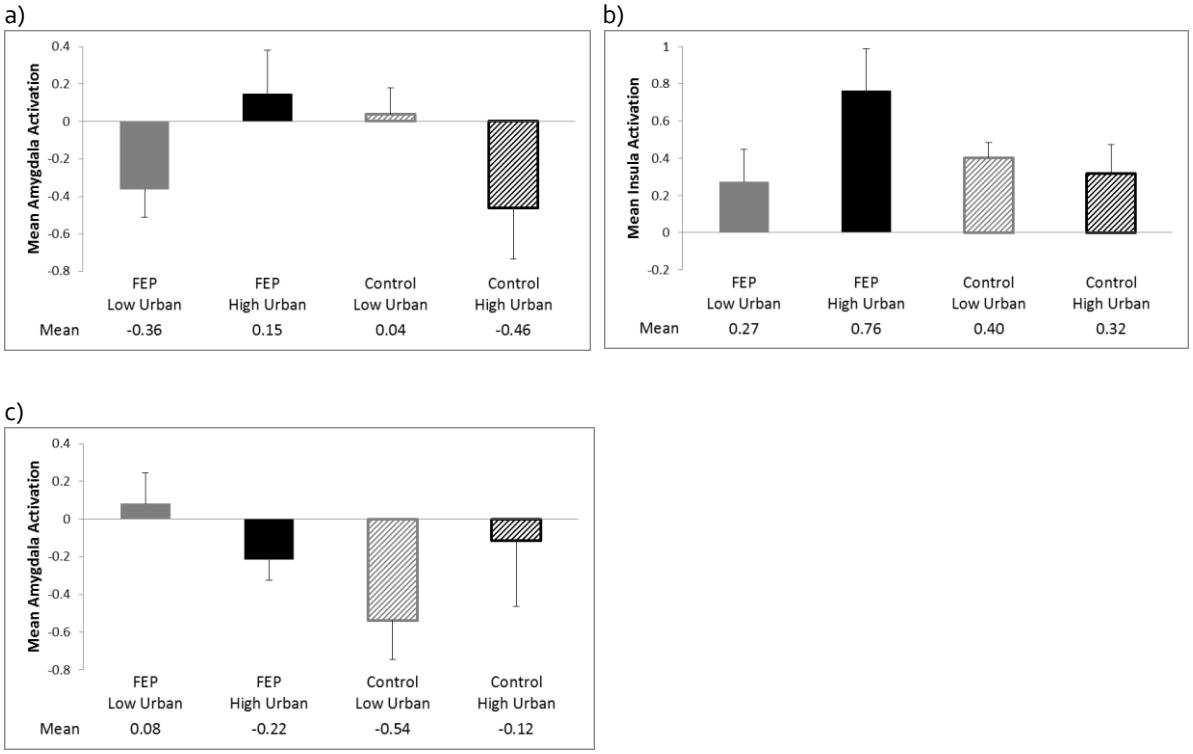
* = adjusted significance levels for multiple comparisons, calculated based on the internal correlation of the beta values, resulting in an adjusted p value of .025

** = adjusted p value of .03

Note: ROI = region of interest; MNI = Montreal Neurological Institute; pACC = perigenual anterior cingulate cortex; an additional ROI was used for analyses, but yielded no significant results: medial prefrontal cortex (mPFC): -3, 65, 25.

Second, interactions of urbanicity with group were investigated. In the cooperative repayment phase an interaction of urbanicity and group on right amygdala activation was found (S1_Figure 3a), and the unfair repayment phase showed interactions of urbanicity and group on right insula and left amygdala (S1_Figure 3b-c). Patients brought up in higher urban areas showed increased activation of the right amygdala

during cooperation compared to the control condition of the task, whereas controls brought up in higher urban areas showed decreased activation. The insula during unfair repayments also showed highest activation in patients brought up in higher urban areas, with no difference in high and low urban controls. In the left amygdala during unfair repayments patients with low urban upbringing showed activation compared to the control condition of the task, whereas the other groups activated more in the control condition. Controls with high urbanicity activated more than low urban controls, and high urban FEP activated less than low urban FEP. Interactions of symptoms by urbanicity on ROI activation did not reach significance.



S1_Figure 3 Contrast Estimates Showing Interactions of Urbanicity and Group and Urbanicity and Positive Symptoms

Note: Bar graphs with standard errors for the interaction of urbanicity and group on ROI contrast estimates: a) in the right amygdala during cooperative repayment; b) in the right insula during unfair repayment; c) in the left amygdala during unfair repayment.

Supplementary Material

S2_Supplementary Table

Whole brain Main Effects of Task

Condition	Region	MNI-coordinates	Cluster size	Z-value
Cooperative investment	Superior mPFC	-3, 26, 40	177	6.71
	OFC	-33, 56, 8	18	5.28
	ACC	2, 43, 23	29	5.19
	Lingual gyrus	2, -80, 0	46	5.84
Cooperative repayment	mPFC	5, 33, 43	131	7.35
	vlPFC	55, 18, 30	1072	inf
	vlPFC	-41, 6, 33	635	6.81
	OFC	-46, 48, -3	44	5.66
	Middle cingulate cortex	5, 6, 28	19	5.64
	Insula	35, 23, -3	35	5.68
	Temporal middle gyrus	-51, -35, -5	31	5.7
	TPJ	-31, -60, 45	588	inf
	Precuneus	7, -70, 43	89	6.11
	Hippocampus	20, -30, -3	13	5.91
	Hippocampus	-23, -32, 0	8	5.68
	Inferior occipital lobe	40, -77, -15	4575	inf
Unfair investment	mPFC/ACC	-1, 31, 38	797	inf
	dlPFC	-43, 48, 3	50	5.84
	vlPFC	42, 31, 33	129	5.79
	vlPFC	-41, 26, 30	54	5.4
	OFC	35, 23, -13	26	5.51
	Insula	-38, 21, -8	22	5.92
	TPJ	52, -37, 53	141	5.46
	Inferior parietal gyrus	-33, -62, 45	83	5.37
	Lingual gyrus	-8, -82, -10	156	6.47
	Precuneus	-6, -70, 38	58	5.39
	Caudate	-11, 13, 0	7	5.17
Unfair repayment	Superior mPFC	5, 23, 43	297	7.31
	vlPFC	45, 38, 20	1010	inf
	vlPFC	-43, 8, 31	477	7.3
	Precentral gyrus	-31, -2, 50	19	5.68
	Precentral gyrus	35, 3, 50	7	5.61
	Insula	40, 21, -8	133	6.71
	Temporal middle gyrus	-51, -35, 0	14	5.92
	Inferior parietal lobe	-31, -57, 48	9277	inf
	Hippocampus	22, -30, 3	59	6.47
	Hippocampus	-21, -27, -5	35	6.14

Note: Main effects of task were performed on all participants, with a significance level of $p = .05$, Family wise error (FWE) corrected. For brevity reasons, large clusters were only represented with the strongest peak value. mPFC = medial prefrontal cortex; OFC = orbitofrontal cortex; ACC = anterior cingulate cortex; vlPFC = ventrolateral prefrontal cortex; TPJ = temporo-parietal junction; dlPFC = dorsolateral prefrontal cortex; inf = infinite.