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Chapter 7

Neural correlates of urban risk environments

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Abstract

Epidemiological studies suggest that the association between urbanicity and psychosis might be explained by social deprivation, lack of social capital, cohesion and trust, and being part of a minority group. Besides, urbanicity is also associated with pollution, noise, and lack of green space, which have a negative impact on health outcomes. This chapter reviews the neuroimaging literature on brain function, structure, and connectivity in relation to urbanicity. Research in patients with psychosis has shown associations of urbanicity with brain functioning, rather than structure or connectivity. Neuroimaging research in healthy individuals supports altered social stress processing as a possible explanatory mechanism. Altered reward processing associated with urbanicity supports the possible influence of urbanicity on dopamine disregulation and the pathogenesis of psychosis. Mentalising and sensory gating deficits are discussed as alternative mechanisms that could account for the negative effects of the city on mental health.

Keywords:

Urbanicity, fMRI, social stress, reward processing, mentalising, sensory gating

Introduction

The association between urbanicity and non-affective psychosis has been supported by many epidemiological studies. Both current and early life urbanicity are of influence, however, given the neurodevelopmental nature of psychosis, urban upbringing seems to have the stronger effect (Krabbendam & Van Os, 2005; Marcelis, Takei, & Van Os, 1999; Pedersen & Mortensen, 2001). Different factors of urban life may impact on health risks in an interplay with genetic pre-dispositions in so called gene-environment interactions. Clearly, not all urban residents develop psychosis, and not all individuals who are affected by psychosis were brought up in urban areas. Therefore, it is important to understand which factors act together to increase the risk for psychosis, and to identify protective factors that may increase resilience (Heinz et al., 2013).

Living in a city is associated with benefits like better (access to) health care, more employment opportunities, and better schools. Besides these benefits, city life also has disadvantages affecting physical wellbeing, as well as mental health and cognitive functioning (Attademo et al., 2017; Gouin et al., 2015; Lambert et al., 2015; Stansfeld & Clark, 2015). Densely populated areas suffer from pollution, noise, and lack of green space (Attademo et al., 2017; Savale, 2014; Van den Berg et al., 2015). Also, the frequency and intensity of social contacts differ between rural and urban dwellers (Korte, 1980; White & Guest, 2003; Witt, 1989). This may be problematic for patients with psychotic disorders because of their deficits in social cognition and social interactions (Couture et al., 2006; Fett et al., 2011). It could be hypothesised that encounters with unknown people in urban environments overstrain patients' social capacities, suggesting that the association between urbanicity and psychosis could partly originate in social interactions [see also, (Weiser et al., 2007)].

In this light, urbanicity is often defined as a proxy for other social stressors, such as social deprivation (O'donoghue et al., 2016), lack of social capital, cohesion and trust (Drukker et al., 2006), disintegration of family networks and increased competition for resources (Zammit et al., 2010), being part of a minority group, perceiving group discrimination (Cantor-Graae & Selten, 2005; Kirkbride et al., 2007; Veling et al., 2008; Zammit et al., 2010), or feelings of being inferior (or different) to another person. The stress associated with this perceived inequality, especially when the situation seems unchangeable, is in concordance with the social defeat hypothesis (Selten & Cantor-Graae, 2005; Selten, Van der Ven, Rutten, & Cantor-Graae, 2013). Similar problems are also reflected in socioeconomic status (SES), a major predictor of physical and psychological outcomes, particularly during early development (Chiao, 2010). In addition, physical components of urbanicity could impact on (mental) health, for

instance pollution (Attademo et al., 2017), and lack of green space (Maas, Verheij, Groenewegen, De Vries, & Spreeuwenberg, 2006).

The human brain and physiology are shaped by these experiences, and the effect may be larger in those with a genetic susceptibility to psychosis. The risk for psychosis increases due to an altered stress response of the hypothalamic–pituitary–adrenal (HPA) axis and augmented dopamine [DA; (Tost et al., 2015)]. Changes in these systems are thought to arise through sensitisation, a process causing increased dopamine release in response to repeated stressors (Heinz & Schlagenhauf, 2010; Myin-Germeys et al., 2005; Van Winkel, Stefanis, & Myin-Germeys, 2008). In sensitd individuals, even exposure to moderate levels of stress is associated with an excessive DA response (Kapur, 2003; Kirkbride et al., 2007; Meyer-Lindenberg & Tost, 2012; Myin-Germeys et al., 2005). These changes influence cognitions and neural processing. Investigating the association between urbanicity and psychosis at a neural level can therefore give insight into the nature of these altered processes. Yet to date, few studies have systematically studied the neural mechanisms of urbanicity in patient populations with psychotic disorders.

In this chapter we first review the literature on functional brain activity associated with urbanicity. Second, we discuss the association of urbanicity and brain structure and functional connectivity. We then review neuroimaging studies on the effects of air and noise pollution, and lack of green space, followed by the neural signature of possible social factors underlying the association between urbanicity and psychosis (see Figure 1). Some of the reviewed studies come from the animal literature, others were performed in individuals with psychosis, a majority however, was performed in the general population. We conclude with a summary of the presented data and suggestions for future research.

Urbanicity and brain function

Stress-related disregulation of the HPA axis and the mesocorticolimbic dopamine system may play an important role in the development of psychosis. Stress stimulates the HPA axis, altering hippocampal activity, which in turn affects the mesolimbic dopamine system. This is thought to lead to aberrant salience, where patients attribute meaning to otherwise irrelevant stimuli (Heinz & Schlagenhauf, 2010). The limbic system and dopamine are key to reward processes that are necessary for motivated behaviour and learning, for example in social interactions. These processes may thus be relevant for understanding the urban effect.

An influential study investigated the association between urbanicity and stress in healthy individuals, at whole brain level, and within regions of interest (ROI), using the

Montreal Stress Imaging Task (MIST) task that induces stress with arithmetical calculations (Lederbogen et al., 2011). Current city living was associated with higher activation of the amygdala during the stress paradigm, suggesting greater sensitivity to threat and negative emotions in city dwellers. Urban upbringing on the other hand, was associated with increased activity of the perigenual anterior cingulate cortex (pACC). The pACC is part of the limbic stress regulation system that is implicated in processing chronic social stressors (LeDoux, 2000), such as social defeat, and modulates amygdala and HPA axis activity. These data were linked to schizophrenia, through previous findings of reduced cingulate grey matter, and connectivity abnormalities of the pACC with the amygdala during processing of affectively negative stimuli.

Krämer et al (2017) used the Desire-Reason-Dilemma (DRD) paradigm, a task that distinguishes between conditioned reward processing, and top-down suppressing of reward signals to investigate reward and urbanicity in healthy participants. In this paradigm, participants first learn that specific stimuli are associated with reward. Subsequently, they have to suppress the reward signal to achieve a superordinate goal. ROI analyses showed that during both processing and suppression of reward, current city living was associated with reduced activation in the left ventral tegmental area (VTA), a dopaminergic region modulating the midbrain DA system. Furthermore, city living was associated with increased activity in the amygdala, medial orbital cortex and pACC during reward processing. This work shows that not only in stress processing, but also in reward processing, urbanicity is associated with differences in DA activation and modulation (Krämer et al., 2017), supporting the possible role of urbanicity and DA disregulation in the pathogenesis of psychosis.

Only one study has directly associated brain function in psychosis with urbanicity. Urbanicity was defined as the population density during the first 15 years of life, dichotomised as higher and lower urbanicity. This study used a social interactive trust game (TG), tapping into real-time social behaviour and social reward processing, in psychotic disorder (Lemmers-Jansen, Fett, Veltman, & Krabbendam, in revision). Trust is an important factor when it comes to building social capital and cohesion, and the reduction of social stress in healthy individuals (Takahashi et al., 2005). In the TG, the first player, the investor, may give a certain amount of money (e.g., between 0-10 units) to the second player, the trustee. The amount given is tripled, and then the trustee can decide to give (part of) the money back to the investor, or to keep it all and return nothing. In iterative games, participants played either a cooperative partner (always returning more than invested) or an unfair partner (returning less), and both the moment of investment decision and return of the repayment were studied. Baseline trust, or the initial trust placed in an anonymous other, and changes of trust over

repeated interactions were investigated. Reduced baseline trust was unrelated to urbanicity. However, during repeated interactions, lower urbanicity exposure during upbringing was associated with increased learning reflected by a stronger increase from positive feedback (high returns) in patients, but not controls. This suggests that learning from social feedback in individuals with psychosis may be sensitive to the effects of urbanicity exposure (Lemmers-Jansen et al., in preparation).

Using ROIs analysis of areas implicated in social decision-making, mentalising, reward and stress processing, showed that high urbanicity was associated with differential activation of the bilateral amygdalae in patients compared to controls. During cooperative investments, patients who were exposed to higher urbanicity during upbringing showed a stronger reduction of activation in the left amygdala than lower urban patients. Controls showed a similar, albeit less pronounced difference. In the right amygdala, during cooperative repayments, higher urban patients displayed increased activation compared to lower urban patients. The reverse was found in controls. This study mainly found decreased activation of the amygdala with higher urbanicity during cooperation, whereas in the Lederbogen study, current city living was associated with increased amygdala activation (Lederbogen et al., 2011). No associations with urbanicity were found in mentalising and reward related areas, suggesting these were not affected by urbanicity. Furthermore, the results implied a conditional interaction between negative symptoms and urbanicity, e.g., the presence of both factors yielding a cumulative impact on positive feedback learning (Heinz et al., 2013; Peeters, Gronenschild, et al., 2015).

Variation in brain activation during functional MRI with urbanicity exposure has also been linked to genetic variables. The neuropeptide S receptor 1 variant rs324981 interacted with urban upbringing on the amygdala stress response during an acute stress task (Streit et al., 2014), showing that amygdala responses are influenced by urban upbringing, via a gene-environment interaction. A similar interaction was found during the n-back working memory task, where the catechol-O-methyltransferase (COMT) gene showed an interaction with urbanicity on prefrontal functioning. COMT-Met individuals showed efficient, COMT-Val individuals inefficient prefrontal activation, suggesting that urbanicity interacts with DA pathways, affecting cortical function (Callicott et al., 2015).

Urbanicity and brain structure

Following up on the Lederbogen study, Haddad and colleagues studied possible morphological correlates of urban upbringing in healthy subjects. Urbanicity was defined as urban upbringing, with three categories (rural, town, city). With increasing urbanicity during upbringing, dlPFC volume was decreased and pACC volume was decreased, but only in men (Haddad et al., 2014). The findings tentatively suggest that urbanicity affects brain structures, some of which are specific to males. However, it remains unclear which urban factors would have a stronger influence on males and why.

Recently first steps have been taken to investigate associations between urban upbringing and the brain in patients with schizophrenia (Frissen et al., 2017; Peeters, Gronenschild, et al., 2015; Peeters, Van de Ven, et al., 2015). Several studies have been published on the Dutch Genetic Risk and Outcome in Psychosis (GROUP) dataset, a large sample of more than 1000 non-affective psychosis patients, 1100 non-affected siblings, 900 parents, and 600 healthy controls. Urban upbringing was unrelated to cell atrophy and structural differences in white matter. Cortical thickness was found to be reduced in patients compared to siblings and controls, however, urban upbringing did not have significant associations with cortical thickness. Also no gender effects were found with respect to urban upbringing, contradicting Haddad et al (Haddad et al., 2014), but it should be noted that the studies used different brain structural outcomes. Resting state functional connectivity of the PCC, a seed region of the default mode network (DMN), and of the nucleus accumbens (NAcc), a seed region for dopamine regulation within the mesocorticolimbic (MCL) system, did not reveal significant associations with urban upbringing either (Peeters, Gronenschild, et al., 2015; Peeters, Van de Ven, et al., 2015). The DMN consists of the mPFC, the posterior cingulate cortex and the precuneus, the lateral parietal and temporal cortex, hippocampus and parahippocampal gyrus and is active during rest and deactivated during goal-directed behaviour. The DMN is associated with many different processes, mainly with episodic and autobiographical memory, self-monitoring and social cognitive processes regarding the self and other (Supekar et al., 2010). In the MCL system, dopamine transmission is regulated in top-down and bottom-up processes. Both siblings and patients showed reduced connectivity compared to controls, but again there was no evidence for a differential impact of urban upbringing (Peeters, Gronenschild, et al., 2015; Peeters, Van de Ven, et al., 2015).

Neural correlates of possible urbanicity related environmental and social mechanisms

In this section we discuss neuroimaging studies that focus on environmental factors inherent in urban areas, namely pollution, noise, and lack of green space. We then review the available literature on neural correlates of social factors that have been associated with urban life, such as social capital, social exclusion, and deprivation.

Pollution

Being exposed to pollution during early development might partly explain the association between urbanicity and psychosis. City living is associated with a higher exposure to toxic substances in the air and sound pollution. Functional connectivity, brain structure and brain activation during a sensory task, where the children were presented with visual–auditory stimulation (viewing faces and listening to fast music) were assessed in a large sample of school children in Barcelona [8-12 years, (Pujol et al., 2016)]. Higher pollution (i.e., amount of elemental carbon and nitrogen dioxide inside and outside the classroom) was associated with weaker functional DMN connectivity, between mPFC and angular gyrus (TPJ), and stronger connectivity with the frontal operculum at the lateral boundary of the DMN, indicating weaker segregation of the network boundaries. Structural brain changes were not significantly associated with pollution. Research in children in Mexico City (Calderón-Garcidueñas et al., 2008; Calderón-Garcidueñas et al., 2012), where the air quality in among the worst in the world, showed increased white matter hyperintensities (WMH). WMH indicate white matter damage that is linked to vascular oxidative stress, older age, dementia, risk for strokes, and inflammation (Debette & Markus, 2010). WMH has also been associated with schizophrenia, with loss of connectivity and reduced information processing efficiency (Hofman, Krabbendam, Vuurman, Honig, & Jolles, 2000). Rodent studies support the evidence in humans, showing a causal effect of air pollution on altered midbrain functioning and hippocampal structure, resulting in changed affective responses, and cognitive impairment (Fonken et al., 2011; Levesque, Surace, McDonald, & Block, 2011).

Sound pollution is exposure to noise. The intensity of the sound is of influence on the perceived negative associations, but mainly the persistence (long-term exposure) and the information conveyed by the noise are of relevance (Savale, 2014). Chronic noise induces stress and neurochemical alterations in the brain (Ravindran, Devi, Samson, & Senthilvelan, 2005), and is associated with mental health problems like anxiety, depression, hostility, and reduced quality of life (Akan, Yilmaz, Özdemir, & Korpinar, 2012; Stansfeld, 1992). However, not all people are equally susceptible for noise. Noise sensitive individuals are more likely to experience negative emotions from

unwanted sounds and they show greater susceptibility to adverse effects of noise on health. Noise sensitivity is associated with sensory gating processes (Kliuchko, Heinonen-Guzejev, Vuust, Tervaniemi, & Brattico, 2016). The inability to ignore unimportant noise, and sensory filtering or gating problems are known features of psychotic disorders (Tregellas, Smucny, Eichman, & Rojas, 2012). During rest, hearing noise induced greater activation of the hippocampus in patients with schizophrenia compared to controls. During a spatial selective attention task, where sounds deviating from the regular presented sound (250 Hz higher) had to be identified, in healthy controls noise was associated with reduced activation in the bilateral insula, cingulate gyrus, right TPJ, left dlPFC, and cerebellum, representing problems in the recruitment of task-related networks in response to the distracting noise. Patients showed increased activity in the TPJ and ACC during task performance, and increased activity in the left hippocampus in response to noise compared to silence (Tregellas et al., 2012), possibly indicating patients' problems to engage the ventral attention network. In summary, there is a negative impact of noise on attention and task performance in patients with schizophrenia.

Lack of green space

Being in nature has a positive effect on well-being, as indicated by self-report. This positive effect lasts several hours after the contact with nature (Bakolis et al., 2018). One of the earliest studies on EEG responses to urban versus nature pictures found that viewing green natural (vegetation) scenes elicited alpha activity in the central parietal cortex. A lower alpha amplitude while viewing urban pictures, was associated with high arousal and feelings of anxiety (Ulrich, 1981). The author concluded that "subjects felt more 'wakefully relaxed ' while viewing the vegetation, as opposed to urban scenes", suggesting that nature calms the brain. The first MRI study on the effects of green space on the brain found increased activation of temporal and parietal lobes in the rural condition, while the frontal and occipital lobes were more active during urban scenery viewing. Rural scenes elicited positive affect, whereas urban pictures elicited negative affect, and this was accompanied by increased basal ganglia versus (para)hippocampal activity respectively (Kim et al., 2010). Subjective ratings of the scenes matched the neural outcomes, however, direct correlations were not assessed in this study. These findings suggest a protective, regenerative characteristic of green, natural environments (Maas et al., 2006), which is supported by lower levels of cortisol, lower heart rate, muscle tension, and blood pressure, less arousal (Roe, Aspinall, Mavros, & Coyne, 2013; Ulrich et al., 1991), and by activation of protective hormones and of the immune system (Kuo, 2015). A 90-minute walk in a natural as opposed to an urban environment has been shown to reduce rumination and subgenual prefrontal cortex

(sgPFC) activation. The sgPFC is linked to self-focused behavioural withdrawal and rumination, supporting a restorative effect of nature, positively by distracting participants from depressed mood (Bratman, Hamilton, Hahn, Daily, & Gross, 2015).

In summary, brain areas associated with exposure to air and sound pollution suggest stress may explain (part of) the association between urbanicity and psychosis. Yet, causal links cannot be inferred from correlational research, and other factors may also underlie the findings. Furthermore, an epidemiological study has suggested that exposure to air pollution is less likely to explain the association with urbanicity and schizophrenia risk as the association with population density was much stronger than the distance to the nearest main road (Pedersen & Mortensen, 2006). Viewing nature, directly and on photographs has benefits on wellbeing and cognitive processes. Research suggests that this immediate effect of viewing urban and rural images is unaffected by whether people grew up or currently lived in a rural or urban environment (Van der Wal, Schade, Krabbendam, & Van Vugt, 2013).

Social exclusion

To investigate the effect of social exclusion in humans, interactive games have been developed. The most frequently used paradigm is a ball-tossing game, Cyberball, where the participant throws a ball with two other players, and at a certain point is excluded from the game, while the other two players continue to throw the ball to each other. Studies in healthy participants showed that social exclusion elicits feelings of negative mood, and loss of control, belonging, and self-esteem, even when participants knew that the other players are computerised (Zadro, Williams, & Richardson, 2004). These behavioural effects are accompanied by activation in several regions associated with negative emotions, such as the subgenual ACC, middle temporal gyrus (MTG), and regions associated with emotion regulation (Goldin, McRae, Ramel, & Gross, 2008), such as the bilateral anterior insula, dorso-medial and ventral (lateral) prefrontal cortex (PFC), cuneus, and in the reward related ventral striatum [VS; (Eisenberger, Lieberman, & Williams, 2003; Falk et al., 2014; Masten et al., 2009)]. During exclusion, parts of the DMN have shown increased activity, suggesting questioning the motives of other players, or rumination on the situation (Bolling et al., 2011). Only one study used this paradigm comparing schizophrenia patients and healthy controls (Gradin et al., 2012). Healthy controls showed increased medial prefrontal cortex (mPFC) activation during exclusion, whereas patients exhibited a reduced mPFC response. Many studies have associated mPFC functioning with emotional and social information processing, and monitoring and updating of social values to plan future behaviour. The authors suggested that differences in mPFC activation as a result of social exclusion could indicate a dysfunction of social valuation processes. The magnitude of abnormality in

mPFC responses correlated with the severity of positive symptoms, and not with antipsychotic medication, showing more impairment with increased illness severity (Gradin et al., 2012).

Social capital

Social capital refers to networks of relationships among people who live and work in a particular society. For effective social interactions trust, reciprocity, and cooperation are essential. These constructs can be operationalised in interactive neuroeconomic games. Participants are to make decisions about allocation of money between themselves and an unknown other. In order to make these social decisions, social cognition is required, including mentalising abilities and empathy. Furthermore, trusting behaviour is influenced by the rewarding effects of social cooperation. Patients, their first degree relatives, and patients at clinical high-risk encounter deficits in social cognition and reward processing, as reflected in altered activation of the social brain, and the related DMN (Fett, Shergill, et al., 2015). Reduced trust could be explained by aberrant sensitivity to the rewarding propensity of social contact, and by impaired mentalising skills (Fett et al., 2012; Gromann et al., 2014; Lemmers-Jansen, Fett, et al., 2018). These deficits might add to the instantiation and maintenance of psychotic symptoms. Initial research suggests that, despite the association between reward and urbanicity in healthy individuals (Krämer et al., 2017), urbanicity is not associated with the neural mechanisms of trust (social reward processing and learning, and mentalising), but instead with social stress processing [see above Urbanicity and brain function, (Lemmers-Jansen et al., in revision)].

Social deprivation

Due to ethical restrictions in humans and primates, research on social deprivation is mainly performed in rodents. Rodent studies provide evidence that social deprivation, operationalised as post-weaning isolation, is associated with morphological changes, e.g., reduced dendritic length in the prefrontal cortex (PFC) and nucleus accumbens (NAcc), areas associated with (conditioned) learning and motivated behaviour (McGinty & Grace, 2007). Rats normally live in social groups, and young rats are frequently engage in social behaviour. Social isolation produces aberrant behaviour such as hyperactivity in response to a novel environment. This behaviour is also found in rats with hippocampal lesions (Alquicer, Morales-Medina, Quirion, & Flores, 2008), suggesting that social isolation and hippocampal lesions may involve similar mechanisms. Isolation rearing resulted in elevated DA levels and psychotic-like symptoms such as hyper-reactivity to novel environments, cognitive impairment, and deficits in sensorimotor function (King, Seeman, Marsden, & Fone, 2009). Other research validated isolation

rearing as a neurodevelopmental model of a "schizophrenia-like" state, further showing deficits in sensorimotor gating and reduced (m)PFC volume, both often found in schizophrenia (Day-Wilson, Jones, Southam, Cilia, & Totterdell, 2006; Schubert, Porkess, Dashdorj, Fone, & Auer, 2009). Isolation and gating deficits might possibly explain social dysfunction in schizophrenia.

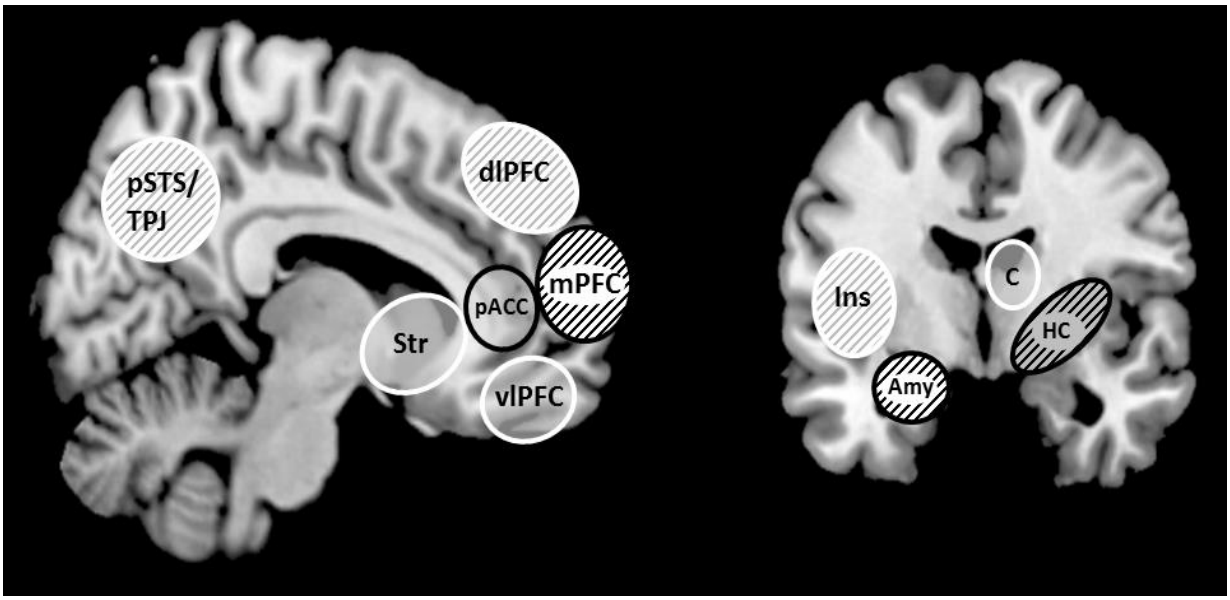

Figure 1 Brain Areas Associated with Urbanicity Effects

Brain areas implicated in the three possible mechanisms explaining the association between urbanicity and psychosis. In white the social brain, in black the stress processing network and in grey areas associated with sensory gating deficits. Striped patterns indicate that the area is implicated in the two mechanisms with corresponding colours. Amy = amygdala; C = caudate; dlPFC = dorsolateral prefrontal cortex; HC = hippocampus; Ins = insula; mPFC = medial prefrontal cortex; pACC = perigenual anterior cingulate cortex; pSTS/TPJ: posterior superior temporal sulcus/ temporo-parietal junction; Str = striatum; vlPFC = ventrolateral prefrontal cortex.

Summarising, interpersonal social factors are associated with aberrant activation of the DMN during social exclusion and reduced activation in the mPFC, dlPFC, and mentalising areas in patients. The neural results are consistent with the idea of increased social stress. Alternative or even complementary mechanisms could be mentalising and sensory gating. Many patients with a psychotic disorder show deficits in mentalising, that might be more pronounced when brought up in urban areas, but this remains to be investigated. If a patient has problems identifying other people's emotions and intentions, the continuous confrontation with many unknown people around him/her could induce positive symptoms. This confrontation might also increase amygdala activity, that reduces HPA activity, which in turn induces maladaptive behaviour that may lead to social conflict (Tost et al., 2015).

Conclusion and future directions

While city living has been associated with greater health, possibly due to the availability of resources and economic factors for some (Dye, 2008), for mental health, and psychosis in particular, the effects appear to be adverse (Amodio, 2010). The existing literature on urbanicity, psychosis and the brain is still scarce despite a recent surge of interest in the neural correlates of urban exposure (Amodio, 2010; Bakolis et al., 2018; Kuo, 2015). Various mechanisms may explain this effect of the city [for a review see (Kuo, 2015)]. Yet, the primary idea is that urban upbringing and/or city living increase the sensitivity to stress, with a downstream impact on mesolimbic dopamine pathways (Lieberman, Sheitman, & Kinon, 1997; Tost & Meyer-Lindenberg, 2012), through exposure to risk-attributes of densely populated urban environments. Factors that could explain the association between urbanicity and psychosis, are pollution, social capital and sensory gating deficits (see Figure 1). The different risk attributes may lead to (subtle) morphological brain changes, but predominantly changes seem to be reflected in differential cognitive mechanisms (e.g. anxiety, competition, trust), reflected by fMRI. So far, the available evidence from fMRI studies assessing urbanicity in conjunction with (social) reward or stress tasks in healthy controls and patients highlighted the amygdala, mPFC, insula and pACC as areas where the city exerts its effects (Krämer et al., 2017; Lederbogen et al., 2011; Lemmers-Jansen et al., in revision). These results tentatively support the urbanicity-stress sensitization hypothesis, although some key-regions that are affected by changes in the HPA axis, such as the hippocampus have not shown differential activation. Findings are contradictory with regard to dopamine-related reward processing, leaving the sensitization of the reward systems by the city a matter of debate.

With regard to functional connectivity, urbanicity could not account for the found differences between psychosis patients and healthy controls (Peeters, Gronenschild, et al., 2015; Peeters, Van de Ven, et al., 2015). The existing studies investigating brain structure yielded contradictory results. Using VBM analysis in healthy individuals Haddad et al. showed urbanicity effects on some regions of stress processing and mentalising (Haddad et al., 2014). While urbanicity related stress exposure early in life may have caused structural changes, this interpretation remains speculative. Others who investigated patients and controls did not report any urbanicity-mediated differences in cortical thickness using freesurfer analyses (Frissen et al., 2017). Future research comparing methodology, setting, and definition of urban-rural categories will be necessary to generate further evidence on whether, where and how urbanicity influences brain structure.

In cities, access to green space is limited and air quality is often poor (Maas et al., 2006; Van den Berg, Hartig, & Staats, 2007; Van den Berg, Jorgensen, & Wilson, 2014). Exposure to green space appears to relax the brain and to decrease rumination-related brain activation (Bratman et al., 2015; Ulrich, 1981; Ulrich et al., 1991), whereas urban stimuli increase activation of stress-related brain areas (Kim et al., 2010). The available evidence supports the urbanicity-stress hypothesis with respect to current city-living. Some of these effects might be partly due to the impact of pollution on the central nervous system, for example through neurochemical changes or neuro-inflammation (Block et al., 2012; Brockmeyer & D'Angiulli, 2016; Grandjean & Landrigan, 2014). Animal studies associated pollution with reduced cognitive performance and mood symptoms, as well as changes in hippocampal morphology (Fonken et al., 2011), and with structural changes in the brain. Initial evidence supports that in healthy individuals urbanicity-related exposure to toxins is associated with DMN connectivity and white matter changes. Future research is needed to elucidate the potential role of exposure to toxic environments in psychosis.

Urbanicity is often defined as a proxy for social risk-attributes of the city. We discussed several imaging studies that utilised paradigms that are of interest with regard to these social mechanisms. However, only one study examined the direct association with urbanicity and psychosis, making it an area of interest for future investigations. In addition, it is as yet unknown whether there are critical periods during the human life span where risk associates of urbanicity are particularly damaging. Together, this highlights the need for comprehensive and systematic assessments of the risk-increasing attributes of urban environments in future neuroimaging research, elucidating how these attributes act upon, and reinforce the vulnerabilities for psychosis.

Urban environments demand a lot of their inhabitants. Limited space has to be shared with many others. Physically this means crowded space, noise, polluted air, resulting in stress and a constant exposure to environmental and social stimuli. Urban residents are challenged with many social encounters, the majority with unknown, or slightly familiar others. For individuals with a vulnerability for psychosis, this poses daily challenges, and it might overstrain their capacities, causing (social) stress, possibly partly based on sensory gating deficits. Most of the above-discussed research supports the social stress hypothesis, but the mechanisms causing this stress remain a topic for further investigation.

Finally, some initial research on gene-environment interactions shows that effects of the city on the brain are modulated by genes related to dopamine and stress expression (Callicott et al., 2015; Streit et al., 2014). Thus, the city may only get into the

brain of certain predisposed individuals. Researchers in the field will need to combine measures of vulnerability with fine-grained measures of developmental and current urbanicity exposure in addition to assessments of social and environmental factors. Novel experimental methods such as virtual reality, in conjunction with skin conductance or heart rate measures for example, could offer a way to assess the effect of urbanicity on (stress)physiology and cognitive functioning in a more controlled way. Epidemiological studies and animal models may help to clarify the effects of environmental pollution. Multi-method neuroimaging investigations of the effects of specific components of urbanicity on the neural mechanisms of risk for mental, neurodevelopmental, and neurodegenerative diseases in general, and schizophrenia in particular, have promising potential to improve strategies for pre- and intervention.