Psychological medicine invited review

Title: Metropolis and Mental Health – challenges of 21th century urbanization

Authors: Lydia Krabbendam[a,b] , Mark van Vugt[c], Philippe Conus[d,] , Ola Söderström[e], Lilith Abrahamyan Empson[e], Jim van Os[b,f,g]**,** Anne-Kathrin J. Fett [a,b,h]

Affiliations:

[a] Department of Clinical, Neuro and Developmental Psychology, Faculty of Behavioral and Movement Sciences, and Institute for Brain and Behavior Amsterdam, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, NL

[b]Department of Psychosis Studies, King's College London, Institute of Psychiatry, Psychology and Neuroscience, 16 De Crespigny Park, London SE5 8AF, UK

[c] Department of Experimental and Applied Psychology, Faculty of Behavioral and Movement Sciences, and Institute for Brain and Behavior Amsterdam, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, NL

[d] Institut de Géographie, Université de Neuchâtel, Espace Louis-Agassiz, 2000 Neuchâtel, CH

[e] Department of psychiatry CHUV, Lausanne University, Switzerland

[f] Department of Psychiatry, UMC Utrecht Brain Center, Utrecht, The Netherlands,

[g] Department of Psychiatry and Psychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Centre, Maastricht, The Netherlands,

[h] Department of Psychology, City, University of London, Northampton Square, London EC1V 0HB, UK

Corresponding author:

Lydia.Krabbendam@vu.nl

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Abstract

Twenty-first century urbanization poses increasing challenges for mental health. Epidemiological studies have shown that mental health problems often accumulate in urban areas, compared to rural areas, and suggested possible underlying causes associated with the social and physical urban environments. Emerging work indicates complex urban effects that depend on many individual and contextual factors at neighbourhood and country level and novel experimental work is starting to dissect potential underlying mechanisms. This review summarizes findings from epidemiology and population- based studies, neuroscience, experimental, and experience-based research and illustrates how a combined approach can move the field towards an increased understanding of the urbanicity-mental health nexus.

Introduction

Urbanization is a relatively recent cultural phenomenon, starting about 10.000 years ago with the change from human hunter-gatherer existence to intense agriculture. Cities have been on the rise and today 55% of the world's population lives in urban areas. Further urbanization is expected (UN, 2018). Living in a city may offer benefits, such as access to cultural offers and healthcare, but epidemiological studies have frequently shown that mental health problems accumulate in urban areas (e.g. Vassos *et al.* (2018), Vassos *et al.* (2012)). This suggests adverse influences of urban environments, to which humans may not be equipped given their short exposure in the evolutionary history (*Evolutionary Mismatch Hypothesis*, see Li *et al.* (2017) for an overview). According to the biophilia hypothesis, human beings have an innate love for the natural world and a universal tendency to seek connections with other forms of life, which result at least in part from our genetic makeup and evolutionary history (Kellert and Wilson, 1995),. Based on the evolutionary perspective, two theoretical frameworks have been proposed to explain the effects of natural versus urban encounters on the human psyche. According to Attention Restoration Theory (ART; (Kaplan and Kaplan, 1989)), urban life taxes cognitive resources, particularly directed attention, to a much greater extent than the environment our ancestors were used to in our past. Being present in nature helps to replenish this voluntary cognitive resource, because the sensory qualities of natural environments trigger non-effortful processes, particularly involuntary attention. The other framework, which may be complementary rather than exclusive, is Stress Reduction Theory (SRT, (Ulrich *et al.*, 1991)), which emphasizes unconscious effects on the autonomous nervous system to explain how nature may reduce stress, especially the natural landscapes which were in our collective past beneficial for survival.

Investigating how the environment is associated with mental health and well being, requires a definition of the different components that constitute a natural or an urban environment and that may impact the human psyche. A plausible set of urban influences may lie in social characteristics, such as high population density, low social cohesion, repeated transgressions of personal space, and high socioeconomic deprivation (for reviews see (Galea and Vlahov, 2005, Heinz *et al.*, 2013)). Further risk may be conveyed by physical characteristics of cities, such as lack of green-space or environmental pollution (Attademo and Bernardini, 2017, Rautio *et al.*, 2018) and elements globally referred to as "urban stress". Understanding these influences requires studies that document spatial variation and investigate to what extent social and material situations are aetiologically relevant (March *et al.*, 2008); to enable urban designs that mitigate risk and enhance protections (Adli *et al.*, 2017). This selective review aims to illustrate how interdisciplinary research from epidemiology, experimental psychology, neuroscience and social sciences is instrumental in achieving this goal and to suggest directions for future research.

The urban environment and mental health

Living in or growing up in an urban environment has been associated with the elevated prevalence of mental disorders (Peen *et al.*, 2010). Most research in this realm has focussed on disorders in the schizophrenia spectrum. However, particularly in the last decade investigations of other mental health conditions have emerged. Compelling evidence supports the urbanicity and non-affective psychosis link (OR 1.72 (Krabbendam and Van Os, 2005); meta-analytic IRRs of 1.68 (Vassos *et al.*, 2018) and 2.25 (Castillejos *et al.*, 2018)). Findings are most robust for urban residence at birth and during childhood, suggesting an important impact of urban factors on the developing organism (March *et al.*, 2008, Paksarian *et al.*, 2018, Toulopoulou *et al.*, 2017). Urban birth and provincial city upbringing have also been associated with bipolar disorder (IRR 1.18 (Marcelis *et al.*, 1998)) , 1.21 and 1.23 (Pedersen and Mortensen, 2006); and urban birth and current urbanicity have been associated with prevalence and incidence of unipolar mood disorders (e.g. IRR 1.16 (Vassos *et al.*, 2018); pooled OR of 21 studies 1.39 (Peen *et al.*, 2010), for a review with mixed results see Rautio *et al.* (2018)). Associations with current urbanicity have also been found for anxiety disorders (pooled OR of 12 studies 1.13 (Peen *et al.*, 2010)). Urban residence at birth and during childhood have been associated with autism spectrum disorders (IRRs birth: 2.28; childhood: 2.85 (Lauritsen *et al.*, 2014), birth: 1.41 (Vassos *et al.*, 2018)). The evidence for substance use is mixed, depending on geographic region and substance (IRRs 1.76-2.47 (Peen *et al.*, 2010, Vassos *et al.*, 2018)), pooled OR of 13 studies 1.31 (Peen *et al.*, 2010)). Links between urbanicity and eating disorders were mostly, but not always inconclusive (e.g. (Mitchison and Hay, 2014), Mulders-Jones *et al.* (2017), Penkalla and Kohler (2014), Vassos *et al.* (2018)).

Some epidemiological studies suggest that the risk of urbanicity is increased in those with a genetic liability for mental health conditions, as in the case of psychosis (Krabbendam and Van Os, 2005, van Os *et al.*, 2010).

At the same time, those at higher risk might be drawn towards living in urban or deprived areas (i.e., selective migration (Colodro-Conde *et al.*, 2018, Sariaslan *et al.*, 2016)), but such mechanisms can only explain a small part of the urbanicity effect (Paksarian *et al.*, 2018). Given that hereditary risk for mental health disorders involves multiple common genetic variants of small effects, future studies could investigate how urbanicity interacts with polygenic risk scores. Using this approach for other environmental exposures, recent results from the EU-GEI study suggested that both early life adversity and cannabis use interacted with molecular genetic risk state in the development of psychosis (Guloksuz *et al.*, 2019).

Importantly, emerging evidence shows geographic variation in the relation between urbanicity and psychosis. For instance EU-GEI showed no significant overall association between current urbanicity and psychosis, with opposite effects in the United Kingdom and the Netherlands (IRRs = 1.17 and 1.89) and France, Spain and Italy (1.01; 1.01; 0.72) (Jongsma *et al.*, 2018). A study of low- and middle-income countries showed higher psychosis rates with urbanicity in Estonia, but opposite patterns in Mali, Senegal and the Philippines (DeVylder *et al.*, 2018). For affective psychosis, some reported a lower incidence with urbanicity (Kelly *et al.*, 2010, Kirkbride *et al.*, 2017) and living in higher unit density neighbourhoods has been associated with a lower incidence of depression and anxiety in Peru and the United States (Loret de Mola *et al.*, 2012, Miles *et al.*, 2012). This variation in risk for different disorders, time of exposure (e.g. developmental vs. current), and geographic region stresses the need for systematic research that assesses periods of risk in conjunction with multiple individual (e.g. polygenic risk) and contextual factors (e.g. specific risk attributes of urban environments).

Risk attributes of the urban environment

Urban risk does not only lie in population density, but arises from an accumulation of social and environmental stressors (Galea, 2011, Rapp *et al.*, 2015), see Box 2.

Social and economic factors, such as deprivation/poverty and social fragmentation, lack of social capital, cohesion and trust may explain urban risk (Castillejos *et al.*, 2018, Drukker *et al.*, 2006, Galea *et al.*, 2007, O'donoghue *et al.*, 2016, Zammit *et al.*, 2010), for reviews see De Silva *et al.* (2005), Ehsan and De Silva (2015), McKenzie (2008)). Yet, some contradictory evidence shows higher social cohesion and incidence of distress and common mental health disorders in rural areas (Loret de Mola *et al.*, 2012). Similar rates of poverty and social exclusion have been reported in urban and rural European areas, yet higher inequality has been found in cities (Eurostat, 2014). This is interesting, as perceived social inequality has been suggested to increase the risk for mental distress, especially when the situation is unchangeable (*Social Defeat Hypothesis* (Selten *et al.*, 2013)). Social defeat could explain elevated risk in low SES/higher inequality neighbourhoods, which might be more typical, yet not specific to cities (Blumenthal and Kagen, 2002). Further, densely populated urban areas are characterized by a high frequency of social encounters. These may contribute to negative urban effects for individuals with a liability for mental health conditions through increased stress sensitivity (Myin-Germeys *et al.*, 2005) and/or, as in case of psychosis and depression, deficits in social cognition (Green *et al.*, 2015, Weightman *et al.*, 2014).

A factor that has frequently been investigated in the context of urban risk is migration, which is thought to increase risk through social instability (Bhugra, 2004, Cantor-Graae and Pedersen, 2013, McKenzie, 2008, Price *et al.*, 2018). However, migrant status is not a risk per se and its effects vary between countries and ethnic groups (Jongsma *et al.*, 2018, Kirkbride *et al.*, 2017, Schofield *et al.*, 2017). Social support structures, shared social history, positive identification with one's own ethnic group (Anglin *et al.*, 2018, Veling *et al.*, 2010) and low discrimination appear to render individuals more resilient, (Schofield *et al.*, 2017, Veling *et al.*, 2008) showing that effects of individual characteristics (e.g. migrant status) depend on context. Finally, it is important to consider that the perception of the social stress associated with the urban environment is also influenced by the mental health and wellbeing of the individual (Corcoran *et al.*, 2017). For example, a large population study in adolescents showed that those who perceived higher levels of threat in their neighbourhood were more likely to have psychotic experiences (Newbury *et al.*, 2018). This effect remained after accounting for levels of crime, individual disorder, neighbourhood- and family-level SES, suggesting that the subjective perception of the urban environment is an important target for research and possibly intervention.

An important *physical factor* through which cities could impact mental health may be lack of green space (Bratman *et al.*, 2012, Fong *et al.*, 2018, Gascon *et al.*, 2015, Lee and Maheswaran, 2010, van den Berg *et al.*, 2015). Low compared to high green space presence was associated with a 1.52-fold increased schizophrenia risk in a Danish case registry study (Engemann *et al.*, 2018), with most profound effects for low green space presence during early childhood. Individuals with psychosis also have been found to reside in less green areas than the general population (Boers *et al.*, 2018). Lack of green space has also been associated with the prevalence of anxiety and autism spectrum disorders (de Vries *et al.*, 2016, Wu and Jackson, 2017), but findings are mixed with for mood and substance use disorders (Banay Rachel *et al.*, de Vries *et al.*, 2016).

As flipside to reduced green space, the features of urban environments (e.g., noise, light, social encounters) may lead to cognitive overload for attention, memory or cognitive control (Bratman *et al.*, 2012) and salience processing in general *(Winton-Brown et al., 2014)*. Some evidence linked urbanicity to reduced cognitive development in children (Gouin *et al.*, 2015). Schizophrenia risk has been associated with lower cognitive functioning and urbanicity, possibly indicating reduced coping ability with the eventfulness of cities (Weiser *et al.*, 2007). Noise pollution or noise-induced stress have also been associated with measures of annoyance, displaced aggression, reduced wellbeing and cognitive functioning (Dzhambov and Dimitrova, 2014, Goines and Hagler, 2007, Ohrstrom, 2004, Wright *et al.*, 2014). In line with the biophilia hypothesis (Kellert and Wilson, 1995), these findings may pinpoint impaired relaxation (e.g. SRT) or cognitive restoration (e.g. ART), which are associated with nature sights and sounds or reduced cognitive load (Berto, 2014, Bratman *et al.*, 2012). Often exposure to noise occurs simultaneous to exposure pollutants from road or air traffic, which might be an independent mechanism that transduces urban risk (e.g. exposure to ultrafine particles, heavy metals as lead and cadmium, or nitrogen oxide (Buoli *et al.*, 2018, Newbury *et al.*, 2019)), which affect particularly individuals with lower SES in urban areas (Cesaroni *et al.*, 2010, Laurent *et al.*, 2007). Though, a recent review suggested that pollution only accounts for a small part of risk for mental health problems, at least in psychosis (Attademo *et al.*, 2017).

Other, possibly related, salutogenic effects of natural environments could include better immune function, lower blood pressure, and/or health behaviours, such as physical and social activity, which directly affect individuals and unborn offspring (Ebisu *et al.*, 2016, Fong *et al.*, 2018, James *et al.*, 2015, Kuo, 2015, Maas *et al.*, 2009, Rook, 2013, Rook *et al.*, 2013, Twohig-Bennett and Jones, 2018). Interestingly, visiting green spaces appears to affect mental health of city dwellers positively (Alcock *et al.*, 2014, Bratman *et al.*, 2015). Lack of green space during upbringing and adult life could be due to various SES-related factors, but low use of green space could lie in reduced motivation and withdrawal from activity that accompanies mental health conditions (Van den Berg *et al.*, 2016), highlighting the potential importance of activating interventions.

In sum, studies on urban upbringing and current urban living show that a variety of individual and context-related factors of the urban environment increase the risk for mental ill-health. A common denominator of urbanicity risk appears to lie in the presence of stressors and the lack of opportunity for stress relief associated with specific social and physical characteristics of the urban environment (Gong *et al.*, 2016). Importantly, the urban environmental risk factors may cluster and have additive, if not synergistic effects (Kuepper *et al.*, 2011, Morgan *et al.*, 2014), which require further systematic investigation of the interplay of social, environmental and person characteristics.

The urban environment and the brain

Neuroscientific studies may contribute to our understanding of the neurobiological processes mediating the effect of urban living on mental health (Meyer-Lindenberg and Tost, 2012). For instance, neuroimaging can investigate hypothesized emotional and cognitive brain mechanisms or brain areas and connections that are susceptible to urban effects. The social stress hypothesis is supported by an initial functional neuroimaging (fMRI) study that probed the blood-oxygen-level-dependent (BOLD) brain to stress as a function of urban upbringing and current city living. In healthy individuals, current city living was associated with higher activation of the amygdala during social stress. Urban upbringing moreover was associated with increased activity of the perigenual anterior cingulate cortex (pACC), which connects to frontal and limbic brain areas and has been implicated in emotional processing, contingency learning and cognitive control (Francis L. Stevens *et al.*, 2011, Palomero-Gallagher *et al.*, 2018). In another study, current city living was associated with higher activation of the amygdala, medial orbital cortex and pACC during a task measuring reward activation and modulation (Krämer *et al.*, 2017). The results indicate a fronto-limbic hypersensitivity during stress and reward processing. The finding is in line with the hypotheses derived from experimental and epidemiological studies, which suggest that exposure to urban (social) stress leads to neural sensitization and sensitization of physiological stress systems as the hypothalamus-pituitary-adrenal axis (Selten and Cantor-Graae, 2005, Selten *et al.*, 2013, Steinheuser *et al.*, 2014). In addition, urban upbringing has been associated with more inefficient prefrontal processing during a working memory task, suggesting the involvement of cognitive control processes (Reed *et al.*, 2018). Although the evidence is still limited, structural neuroimaging associated urban upbringing with reduced dlPFC and (in men only) pACC volumes (Akdeniz *et al.*, 2017, Haddad *et al.*, 2014), reduced cortical thickness in frontal and temporal-parietal cortices and increased volume of the precuneus (Besteher *et al.*, 2017, Lammeyer *et al.*, 2019), as well as white matter changes in the left superior longitudinal fasciculus (Lammeyer *et al.*, 2019). However, few studies have linked urban living to brain phenotypes in disorder. In males with a psychotic disorder, urban upbringing was associated with reduced grey matter volume (Frissen *et al.*, 2018), but not with cortical thickness (Frissen *et al.*, 2017), or functional connectivity (Peeters *et al.*, 2015). Importantly, it is largely unclear what accounts for these neural alterations. Initial studies, which discussed in the following paragraph, focused on social stressors and green/blue space as potential explanatory factors of structural and functional brain changes.

An important new direction is the study of gene-urbanicity interactions for brain phenotypes. In a subgroup of the sample studied in Lederbogen *et al.* (2011), a functional variant of the neuropeptide S receptor 1 interacted with urban upbringing on the amygdala stress response during the social stress task (Streit *et al.*, 2014). Urban upbringing also interacted with dopamine genes in altering prefrontal function during a working memory task, a finding that was replicated in two independent samples (Reed *et al.*, 2018). Future studies of gene-urbanicity interaction could capitalize on the identification of polygenic risk scores for the disorder as an index of molecular genetic risk, rather than focusing on single nucleotide polymorphisms.

In sum, initial evidence links urbanicity to changes in neural activation and structure. While tentatively supporting existing theories, the findings need to be interpreted with great caution given their correlational nature. It will be important for future research to draw upon insights from the animal literature and to directly investigate the impact of different urban attributes on the brain in experimental and experience-based studies. Initial studies that attempted to directly unravel the effects of the city will be discussed in the following.

Risk attributes of the urban environment and the brain

Many studies have investigated social phenomena that are relevant to the hypothesized mechanisms of urbanicity, although not explicitly framed in this context. For example, low childhood SES has been associated with a range of brain structural and functional changes (Farah, 2017, McDermott *et al.*, 2019), with the strongest effects in the most disadvantaged children (Noble *et al.*, 2015). A quantitative meta-analysis of social environmental stressors based on 54 studies and 3044 participants concluded that the experience of social environmental stress was associated with altered BOLD response across several brain regions. Increased BOLD of the right amygdala was a robust finding across multiple studies (Mothersill and Donohoe, 2016). This effect was similar for the (n = 34) studies including adults and those including children / adolescents (n = 21). The meta-analysis included different types of social stressors, some of which are not relevant to urban social risk (e.g., childhood trauma), but is nevertheless informative on the key role for the amygdala in the neural effects of the social environment. Finally, recent evidence linked psychosocial stressors (childhood adversity, migration and urban living) in healthy volunteers to reduced volume of the amygdala (Weissman *et al.*, 2019) and increased connectivity between striatal and cortical regions involved in salience and reward processing (McCutcheon *et al.*, 2019). Interestingly, recent evidence from the animal literature shows that repeated social defeat is associated with sensitized neurons and microglia over several weeks (Weber *et al.*, 2019). Such changes at cell level might drive higher-level changes in brain structure, and could contribute to various mental health conditions that have been associated with stress sensitization and reward processing deficits (Gerin *et al.*, 2019, Weissman *et al.*, 2019, Whitton *et al.*, 2015).

Future studies could apply more detailed methods to assess experience of social stress in urban and rural neighbourhoods, as it is already done in epidemiological studies (e.g., Binbay *et al.* (2012)), allowing for a comparison of groups that differ on well-defined social dimensions of residential environments. Social cognitive neuroscience has developed validated paradigms that could be used in conjunction with this approach to study how individuals with different urban social experiences respond to social stressors. For example, the experience of social exclusion, social inferiority or transgression of personal space can be experimentally induced and studies using these paradigms have reliably associated negative social experiences with activation in brain areas that are involved in the processing of negative emotions and cognitive control (Kennedy *et al.*, 2009, Kishida *et al.*, 2012, Zink *et al.*, 2008).

Recent studies have started to investigate the associations between urban physical factors and the brain. Kühn *et al.* (2017) used data on green and blue space from the European Urban Atlas in conjunction with structural brain imaging, and reported that older adults who lived close to forests had increased amygdala integrity, based on three different neuroimaging sequences of grey and white matter density (voxel-based morphometry, mean diffusivity from diffusion tensor imaging, and magnetisation-transfer ratio). The study also investigated associations with urban green, water and wasteland and additional regions of interest, the pACC and DLPFC, for which volume reductions have previously been linked to urban upbringing (Akdeniz *et al.*, 2017, Haddad *et al.*, 2014). However, none of the other associations was significant, suggesting that neuro-regenerative effects of nature are specific to (non-urban) green space and primarily working on brain regions that are implicated in emotional (threat) processing, rather than those related to cognitive control. It is possible that non-urban green space is a proxy for personal space (i.e., low social exposure), which is likely to act positively on the brains' threat system. Although, others showed that lifelong access to residential greenness (using satellite-based normalized difference vegetation index) was positively associated with grey and white matter volume in prefrontal and premotor areas and the cerebellum in school-aged children (Dadvand *et al.*, 2018), possibly relating to neural plasticity and regeneration. Interestingly, the regions that were associated with greenness were also positively associated with working memory and inversely associated with inattentiveness, suggesting that impaired structural integrity could underlie the previously discussed cognitive effects of urban environments (e.g. (Reed *et al.*, 2018)). Others found that in children between 8-12 air pollution exposure was mainly associated with reduced functional connectivity in the default mode network activity and stimulus-driven mental operations (Pujol *et al.*, 2016) rather than structure or membrane metabolites, which might point toward stress related mechanisms. Neurotoxicity related structural changes, as supported by animal studies (Fonken *et al.*, 2011, Levesque *et al.*, 2011), could appear further down the line of development.

The initial neuroimaging studies suggest stress sensitisation through environmental stressors, neurotoxicity and neuro re- and degeneration as possible neurobiological pathways that mediate urbanicity effects on cognitive functioning and mental health. Future studies need to systematically investigate multiple mechanisms that could underlie the urban effect on the brain (e.g. exposure to toxic or noise pollution, social stressors). Longitudinal research will be necessary to unravel developmental effects. To improve our insight into which specific urban features are involved, experimental and experience-based studies that investigate immediate responses to specific physical and social characteristics of urban environments will be indispensable.

Experimental and experience-based studies – testing causality of urban factors

Experimental studies use randomized designs to investigate the psychological or psychophysiological effects of nature/urban related experimental stimuli or short-term experience of nature or urban environments. Drawing on ART and SRT, these studies have included cognitive outcomes as well as outcomes related to mental health and psychophysiology. Studies differ in type (e.g., images versus actual presence) and duration (e.g., minutes to hours) of the nature versus urban experience, but overall systematic reviews confirmed the positive effects of nature on mental wellbeing and cognition, although some studies yielded inconclusive findings (Bowler *et al.*, 2010, Bratman *et al.*, 2012, Ohly *et al.*, 2016). The effects on psychophysiological indicators, such as blood pressure and heart rate variability are less well-studied (Bowler *et al.*, 2010). However, there are individual studies that suggest that a brief experience of nature changes physiological health markers (Li *et al.*, 2011, Park *et al.*, 2010), an effect that may extend to simulated environments (i.e., viewing nature vs urban scenes) (Brown *et al.*, 2013). Moreover, positive effects on mood and cognition of a short walk in nature versus urban environments have been observed in individuals with major depression (Berman *et al.*, 2012). The experimental approach has also been applied to study the effects of specific urban environments. For example, passing through a deprived urban environment increased anxiety and reduced trust in patients with persecutory delusions (Ellett *et al.*, 2008), as well as in healthy individuals (Nettle *et al.*, 2014). In patients with persecutory delusions, going out in a busy shopping area had similar effects (Freeman *et al.*, 2014).

Recently, studies also started to investigate the direct neural effects of short-term urban vs. nature experience. Healthy participants underwent resting state fMRI before and after a 90-minute walk in a nature as opposed to an urban environment (Bratman *et al.*, 2015). The walk in nature reduced self-reported rumination and activation in the sub-genual prefrontal cortex (sgPFC), whereas the urban walk did not. The sgPFC is linked to self-focused behavioral withdrawal and rumination, supporting a restorative effect of nature, positively by distracting participants from negative feelings. It is important to note that the exposure conditions should be carefully matched for characteristics that are not directly related to nature or urban environments, such as pleasantness or level of threat. That is, unpleasant nature scenes may well have marked negative effects (Pretty *et al.*, 2005), just as beautiful urban scenes may have positive effects (Seresinhe *et al.*, 2019). A solution for this problem would be simulated exposures that are matched for such characteristics. Virtual Reality has successfully been applied to study the effect of social environmental stress in psychosis, and may combine experimental control with good ecological validity (Veling *et al.*, 2008), for a systematic review see (Valmaggia *et al.*, 2016).

In sum, there is convincing evidence for positive effects of short-term experience of nature on wellbeing and cognition, which may occur through largely unconscious processes affecting attention and autonomous nervous system activity. The experimental approach may be instrumental in identifying specific associations between elements of natural or urban environments and outcomes that are relevant to mental health. At the same time, not all relevant elements of natural or urban environments lend itself to experimental designs with human participants (e.g., pollution) and it is unclear how short-term effects relate to effects of years of exposure. Within these constraints, future research could set out to systematically delineate the optimal duration and type of the nature experience (e.g., (Barton and Pretty, 2010, Bratman *et al.*, 2012). Furthermore, it would be relevant for experimental studies to systematically incorporate individual differences in sensitivity to the natural or urban environment, for example related to baseline mental health, as epidemiological research points to person-environment interactions. It has also been postulated that explicit cognitions (e.g., connectedness to nature) may mediate the beneficial effects of nature experiences on attention and mental health (Mayer *et al.*, 2008). Zooming in on the conscious experience of natural or urban environment to understand the impact of the environment on the psyche is at the focus of the experience-based approach that is discussed next.

Experience-based studies start from the notion that the urban or natural milieu is constructed in the mind of the individual, rather than an externally given entity. Therefore, the role of natural and urban environments in mental health needs to be understood as the result of people's actions and experience in context (Cresswell, 2014) . Such in situ experiences can be captured by studies in which individuals provide quantitative and/or qualitative information, while they walk through specific neighbourhoods or natural landscapes. This may provide a much more fine-grained insight into how the effects of urban stressors identified in epidemiological studies depend on specific contexts (Söderström *et al.*, 2016).

Corcoran *et al.* (2018) collected data on walkers' in situ judgements of threat and trust in two urban neighbourhoods, which differed in terms of deprivation. Perceptions of trust and threat were influenced by the perception of neighbourhood affluence, but also by the mental health and wellbeing of the walkers. Experience-based studies may further elucidate specific features of the urban environment that elicit stress in individuals with psychopathology. For example, a recent study used video recordings of patients' urban walks in conjunction with video-elicitation in patients with first episode psychosis and showed that situations of stress are related to demographic density, sensory environments (in places like shopping malls), obstacles to fluid pedestrian mobility and unchosen social interactions, whereas creating sensory 'bubbles', programming mobility and creating places of comfort were tactics used to handle urban stress (Söderström *et al.*, 2016, Söderström *et al.*, 2017). Other studies based on ethnographic data have shown that 'niches'(Bister *et al.*, 2016) (Bister *et al.*, 2016) or 'atmospheres' (Duff, 2016, Söderström *et al.*, 2016, Söderström *et al.*, 2017). Interestingly, density, a known stressor, served as a protective context for one individual with psychosis, because being in an anonymous crowd (in contrast to being with close friends and relatives) triggered feelings of belonging without being too exposed. Other studies based on ethnographic data have shown that 'niches' (Bister *et al.*, 2016) or 'atmospheres' (Duff, 2016) of recovery are important for urban mental health, despite urban changes which very often reduce such possibilities for economically precarious people. These findings converge with those of recent studies in psychology on the role of space in mental health (McGrath and Reavey, 2018).

Recently, the study of the experience of the city has been complemented by the use of Ecological Momentary Assessment (EMA; (Shiffman *et al.*, 2008)), which involves repeated sampling of current experiences in real-time and real-world contexts. EMA has high ecological validity because assessments are made in the natural flow of real life and in different situations, which makes it possible to understand the variability in mental states in relation to the environment, without explicit reflection on these relationships from the side of the individual. Applying EMA, Bakolis et al. (2018) observed that specific natural features of the built environment (i.e., seeing trees, hearing birds sing) were associated with higher levels of mental wellbeing, which lasted for several hours and which was more prominent in individuals with higher trait impulsivity (Bakolis *et al.*, 2018). EMA can be enriched with geographically explicit information (i.e., GEMA;(Kirchner and Shiffman, 2016)) through combination with global positioning systems (GPS) and geographic information systems (GIS). By linking subjective experiences with objective measures of mobility and place, GEMA can reveal continuous and dynamic interactions between people and place. For example, focusing on the relation between location and stress in adolescents, a recent GEMA study suggested that being around urban green space was associated with lower stress (Mennis *et al.*, 2018). This may point to the restorative effects of nature experience, or to the tendency to seek out urban green spaces at times of lower stress, or explicitly for purposes of stress reduction. Recent advances in portable neuroimaging greatly enrich the possibilities to experimentally investigate the neural correlates of nature and urban encounters, e.g. with mobile EEG devices while participants walk in urban versus nature environments and talk about their experiences, an approach which has recently successfully been piloted in older individuals (Tilley *et al.*, 2017).

In sum, the experience-based studies provide a richness of quantitative and qualitative detail about the interactions between contextual characteristics and individual reflective and reflexive experiences. Combined with measures that tap autonomous nervous system activity, or even brain electrical activity, this may contribute to a much more fine-grained understanding of the relation between presence in urban or nature environments and mental health. At the same time, these studies lack the rigour that is characteristic for experimental and neuroimaging studies, and may therefore be less suited to investigate the effects of isolated risk factors.

Conclusions and future directions

A vast epidemiological literature has investigated associations between urbanicity and mental health, linking urban birth, upbringing and current residency to adverse mental health outcomes. The fact that urbanicity affects outcome across diagnostic boundaries suggests that research in this area could benefit from applying a dimensional rather than a categorical approach to psychopathology (Galea *et al.*, 2011, Johnstone *et al.*, 2018). This echoes calls from other areas of research into the causes of psychopathology (Caspi *et al.*, 2014), for example psychiatric genetics (Selzam *et al.*, 2018, State and Levitt, 2011). The epidemiological studies further indicate that urbanicity is not universally negative (DeVylder *et al.*, 2018, Jongsma *et al.*, 2018). Mixed findings are emerging between north and south and high and middle/low income countries. However, comparisons between studies remain difficult given the variable operationalization of urbanicity in terms of population density or urban/rural categories (city, town and village). Progress in this area comes from studies that characterize the urban environment in more detail, i.e. not only in terms of population density, but also in terms of physical and social dimensions of the urban that may be relevant to mental health. Interdisciplinary approaches between psychiatry and the social sciences encourage research to move beyond the limits of epidemiology and of urban living reduced to the vague and general concept of urbanicity and "urban stress" (Söderström, 2019). These interdisciplinary endeavours do not necessarily have to resolve the plural epistemologies of the biological disciplines focusing on the individual and the social sciences on the relational perspective. Instead, they may use the difference to co-create research designs. This may, for example, inspire social geographers to move beyond social constructivism and include the dimension of mental health. It may help epidemiologists and neuroscientists to consider urban life as a series of situational phenomena that people encounter and actively assemble, rather than something that can be reduced to the notion of 'exposure' to an invariable environment (Söderström, 2019).

Neuroscientific studies use these insights to elucidate the neurobiological pathways that mediate the effects associated with these specific physical and social components of urban life. Although this literature is still in its infancy, studies have identified candidate brain phenotypes that offer initial neurobiological support for associations between urban factors and structure and function of several brain areas, including networks associated with stress and emotion processing and regulation.

Experimental studies may buttress the correlational findings from epidemiological and neuroscientific approaches by enabling causal inferences through randomized controlled designs. Studies using this approach have shown beneficial effects of nature compared to urban experience, and negative effects of deprived and busy urban environments. These studies may be further enriched by experience-based approaches that focus on in situ experience of the environment and capitalize on the notion that the way the city is lived is key to understanding the psychological and physiological responses it elicits. However, not all urban phenomena are suitable for experimental manipulation in humans (e.g., pollution), or open to introspective evaluation (e.g., immune function). In addition, experimental and experience-based studies are limited for the time being to outcomes that show immediate effects (i.e., changes in physiological and psychological parameters of stress, wellbeing, cognition), and whether these immediate effects translate to the effects of long-term urban living remains an open question. Environmental epigenetics suggest that urban characteristics (e.g. stress through exposure to pollution or social density) biochemically influence the phenotypical development and might help to understand delayed temporality and intergenerational urban effects in future research (Guthman and Mansfield, 2012).

Urbanicity effects are complex and while it is clear that there is no silver bullet, together these studies highlight the need for multi-method interdisciplinary collaborations to elucidate multiple interacting pathways and reciprocal relations of the urbanicity-mental health conundrum. This review largely focused on contributions from psychiatric epidemiology, experimental studies and neuroscience to the understanding of urbanicity effects on mental health, and illustrated how other disciplines, which aim to understand urban life and its effects of on humans, such as sociology, anthropology, urban planning or geography, will be important in future research collaborations and to create urban spaces that influence mental health positively. Understanding urbanicity effects requires a complex system approach to model multiple interacting processes at individual and social levels (Galea *et al.*, 2010). Specifically, agent-based models (ABM) are computer simulations which allow multiple interactions at the level of the individual or the agent (e.g., biological and behavioural characteristics, SES) and social factors (e.g., neighbourhood social and physical characteristics, mental health service facilities), that aggregate to create unexpected patterns of population health (Tracy *et al.*, 2018). ABM allow researchers to investigate how specific interactions between individuals generate a collective pattern and may be particularly helpful to model the effect of interventions that cannot easily be investigated experimentally in the real world. For example, Yang *et al.* (2011) used ABM to model walking behaviour in a city as a function of individual and environmental characteristics, and to investigate effects of potential interventions at the individual and city level. ABM may also be used to model the effects of simulated scenarios (e.g., specific individual or environmental interventions) and examine outcomes of these interventions under different conditions. There is still much conceptual and methodological work to be done to successfully apply ABM to urban mental health, for example in finding the balance between simplified and realistic models, and in estimating the model parameters using the available empirical data. However, epidemiological, neuroscientific, experimental and experience-based approaches may together with computational modelling advance our understanding of the impact of the metropolis on mental health, and ultimately develop evidence-based interventions towards a healthy environment (see Box 3).

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