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## Environmental neuroscience unravels the pathway from the physical environment to mental health

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Genes, as well as the environment, are known to affect mental health. However, the effects of the physical environment on mental health are not well understood. The emerging field of environmental neuroscience aims to fill this gap. Here we present an outline of different areas of research that need to be undertaken in this field. These range from identification of the 'active ingredients' of the physical environment (for example, terpenes, air pollutants and low-level visual features), the investigation of which human senses are most strongly involved in processing those active ingredients, and a description of the brain-based mechanisms. The long-term goal and potential application of this new research field is to build knowledge for evidence-based urban and landscape planning to foster salutogenic environments that prevent and alleviate mental health problems. The identification of active ingredients may help to preserve our environment in the face of disturbances such as urbanization and climate change.

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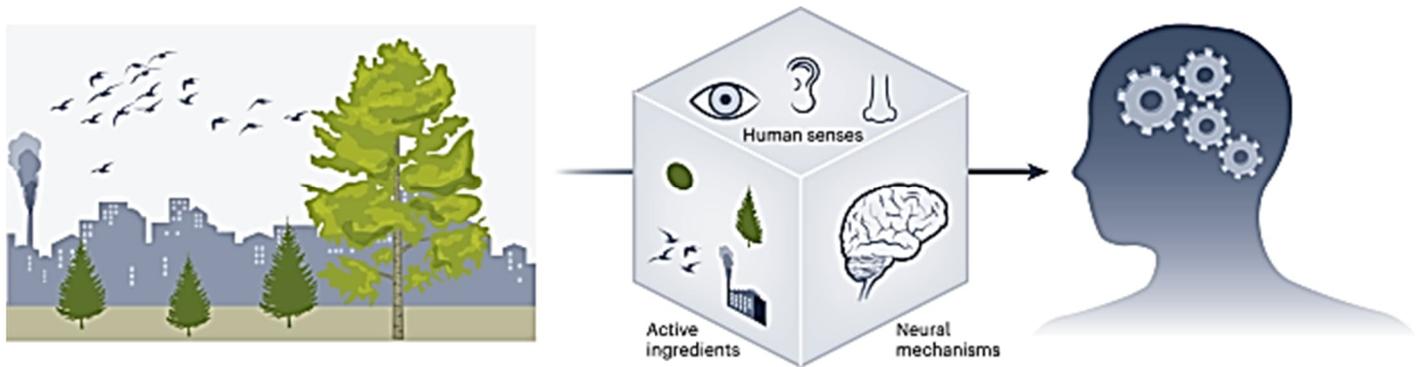
Urbanization processes are on the rise around the globe, leading to more and more individuals living in cities and not rural areas. The consequent potential effects on human health need to be better understood, in particular because climate change is already affecting and will likely challenge our living environments even more in the future. Increasing temperatures, extreme drought and precipitation will, in the long run, dramatically affect both rural and urban environments. In this Perspective, we summarize what is already known about the effect of the physical environment on mental health and in particular the pathways and brain-based mechanisms that link the two.

With respect to the development of mental health problems, the 'nature versus nurture' debate is a classical one. Nature reflects the influence of genetics, which is present from the moment of conception and thus inherited. Nurture, in contrast, encompasses acquired influences and the results of experiences and exposures after conception. Traditionally, most research has focused on the inherited predictors of psychiatric disorders, most likely because these internal factors are stable and can be objectively quantified. By contrast, measuring the external, environmental nurture factors seems to be more difficult and less frequently undertaken.

In psychiatric research, investigation of the effect of the environment on mental health has mostly comprised epidemiological research comparing prevalence rates of psychiatric disorders in urban and rural living populations. These studies have shown that mental health problems typically accumulate in urban areas<sup>1-3</sup>. This seems to be especially true for schizophrenia, affective and anxiety disorders, and autism, while the evidence for substance use disorders seems to be mixed<sup>1</sup>. For most disorders, the living environment during early upbringing (<15 years of age) seems to be most relevant, but, in the USA, this seems to be restricted to Black individuals<sup>4</sup>. However, for some mental disorders, such as anxiety and depression<sup>2,5</sup>, the current living environment is also predictive. There are also reports that do not note this higher prevalence of mental disorders in larger cities<sup>6</sup>. Another exception to the prevalent negative effect of city living seems to become apparent later in life, when cognitive performance has actually been reported to be higher in urban areas<sup>7</sup> and cognitive disorders such as dementia are less frequently observed<sup>8</sup>. Similarly, recent research suggests that bigger cities, in particular, may provide social networks that may act as a buffer against depression<sup>9</sup>.

Based on these epidemiological studies, it remains unclear whether environmental exposures are causing the rise in prevalence

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**Fig. 1: Illustration of the black box between the physical environment and mental health as an outcome.** Three research questions are proposed to open the black box. (1) What are the active ingredients of the physical environment? (2) Which human senses are most strongly involved? (3) What are the neural mechanisms?

rates (breeder hypothesis), which would correspond to the nurture aspect, or whether individuals with a certain vulnerability or existing mental health problems deliberately choose a particular living environment (selective migration and drift hypothesis), which would correspond to a larger effect of nature. Polygenic risk score studies have indeed shown that individuals with a higher risk for mental disorders might be drawn to living in urban areas<sup>10,11</sup>. However, this nature pathway seems to explain only a small part of the observed association between the living environment and mental disorders<sup>12</sup>. In studies on healthy participants, moving into greener living areas led to an improvement of self-reported mental health<sup>13</sup>, which is supportive of the nurture pathway.

Another potential impediment of the present research is that the results are often interpreted as indicating that urban living results in higher prevalence rates of mental health problems due to environmental factors that are detrimental, such as crowding, higher levels of air pollution or more night light exposure. However, the pattern of results can likewise be interpreted as rural living environments providing salutogenic influences that protect individuals from developing mental health problems<sup>14</sup>. Those salutogenic factors could consist, for example, of the presence of terpenes, the sight of the color green or a higher concentration of negative ions. To address the question of whether urban living is detrimental or nature exposure is salutogenic, longitudinal studies would be helpful to enable us to disentangle which environment indeed has a salutogenic or detrimental effect on mental health. Solving this question could lead to more specific descriptions of how environments should be designed to prevent or relieve mental health problems. 'Green prescriptions' have been suggested<sup>15</sup>, in which patients with mental health problems receive the recommendation to spend time in green spaces on a regular basis. However, the scientific evidence is still not sufficient to justify a widespread application.

Previous research agendas have focused on the effects of nature on mental health<sup>16,17</sup>, without paying much attention to the exact pathways and mechanisms. From our point of view, the field needs a more thorough understanding of the pathways and working mechanisms that link the physical environment to mental health. This is addressed by the field of 'environmental neuroscience', a new discipline that seeks to utilize neuroscientific methodology to unravel the neural mechanisms linking the physical environment and human behavior<sup>18,19</sup>. The goal is to open the black box between the physical environment and the outcome of interest.

In contrast to the focus of a previous comment paper<sup>18</sup> that concentrated on translational work, we would like to propose that the research endeavor of environmental neuroscience can be divided into three sub-questions that put work on humans at the center. (1) What are the 'active ingredients' of the physical environment? (2) Which human senses are most strongly involved? (3) What are the neural mechanisms? Figure 1 provides an illustration.

### What are the active ingredients of the physical environment?

By active ingredients we are referring to the actual features of the physical environment that elicit the respective bodily processes and result in the mental health outcomes of interest. For example, if we think about the proclaimed positive mood and stress-reducing effects of spending time in forests<sup>20</sup>, these might actually be elicited by the presence of the color green<sup>21</sup>, low-level visual features such as fractals<sup>22,23</sup> or edge density<sup>24,25</sup>, the terpenes (essential oils) emitted by trees<sup>26</sup>, the songs of birds or sounds of other animals<sup>27</sup>, or the higher presence of negative ions<sup>28</sup>. There might be cases in which this type of nature exposure needs to be supplemented, for example in times of pandemics, for older adults and patients not able to spend time in a real forest or at times when forests might have become so rare that access is limited. In this case, knowledge on which particular elements need to be part of this supplementation is crucial. Visual presentation of a forest<sup>29,30</sup>, by means of virtual reality, might not be sufficient and might need to be enhanced by the presentation of odors and/or sounds. There are relevant summaries of the effects of certain landscape types (for example, parks, gardens and forest<sup>31</sup>), qualities of landscapes<sup>32</sup> or different types of blue space on mental health<sup>31</sup>. However, we believe that these types of landscape are not yet specific enough to allow a conclusion as to what is actually the driving factor of the observed effects.

To identify important active ingredients it is not sufficient to compare urban and rural living based solely on population density as the defining factor, as is often done in epidemiological studies. More recent studies have increasingly made use of geographic information systems (GIS) approaches in which the home address of participants is utilized to extract geographic information in a predefined area around the living environment. For example, there are studies showing an association between air pollution and schizophrenia prevalence<sup>33</sup> or the presence of green space and depression and anxiety<sup>34</sup>. A meta-analysis attempted to summarize these findings with a focus on psychological distress as the outcome and reported a relevant role for the amount of green space, land-use mix, industry activity and traffic volume, among other less defined variables such as neighborhood quality<sup>35</sup>. However, the majority of the studies conducted with GIS methodology typically focus on only one or maximally a small number of predictor variables. This is problematic when the goal is to identify the most important predictors or active ingredients, as it may simply be the case that the actual relevant predictors have not even been included in the model. Therefore, future studies should set out to quantify a

comprehensive list of environmental variables and investigate their importance in the presence of all others. This should include both potentially detrimental influences of urban living such as air pollution, noise pollution, (night) light exposure, temperature and population density, but also potentially salutogenic factors such as the presence of the color green, low-level visual features such as fractality, terpenes, negative ions, biodiversity, visibility of sky, and so on. One way to do this could be by using feature selection algorithms developed in the field of machine learning and by utilizing large-scale datasets from existing cohort studies.

First, the key active ingredients should be identified in multiple observational cross-sectional studies—ideally replicated across different datasets and across different geographical regions. Experimental intervention studies are then needed to verify that the identified environmental factors are indeed causally involved in mental health symptoms in healthy participants or psychiatric populations. Laboratory studies that randomly assign participants to certain exposure conditions (for example, traffic noise, terpenes and virtual reality visual scenery) will be needed.

### **Which human senses are most strongly involved?**

Based on the identified active ingredients that play a major role in the observed effects of the physical environment on mental health, one may directly derive which human senses have to be involved in the pathway. Let us assume that essential oils emitted by trees (terpenes) turn out to be a relevant active ingredient that is also verified by laboratory experiments in which participants are exposed exclusively to these substances. It is then very likely that smell is the route by which the ingredient is perceived. However, it might still be that a more holistic multimodal exposure—for example, the odor being provided while observing pictures of a forest—might actually lead to supra-additive effects on mental health. So far, these interaction effects have not received sufficient attention in scientific research, but it would be helpful to determine which active ingredients and also which human senses need to be activated to promote the positive effects on mental health.

Moreover, it would be relevant to investigate whether stimuli need to be consciously accessed to provide potential effects on mental health or whether it is also sufficient to unconsciously perceive them. For example, do the terpenes in the air have to be recognized by the individual? Is it necessary that the individual is able to identify the odor as originating from a natural source/from trees? Here, the use of implicit tests such as the implicit association task<sup>36</sup> or the approach avoidance task<sup>37</sup> can be helpful, as these assess rather unconscious processes. Using these implicit tests, we showed that healthy participants have a tendency to approach nature pictures more quickly than urban pictures (approach avoidance task), that their attention was drawn more strongly to the side of the nature pictures (dot probe task), and they associated the nature pictures more strongly with the concept of 'approach' than 'avoidance'<sup>38</sup>. This pattern is in line with the so-called biophilia hypothesis<sup>39</sup>, which states that humans have an innate tendency to seek connection with nature.

In addition, it would be important to determine whether the associations that accompany the assumed source of the consciously perceived stimulus play a role in the salutogenic effects. Thus, what accompanying thought/affect does it elicit when an individual realizes the presence of the terpene odor and ascribes it to originate from trees? Does it make the person reflectively feel relaxed when memorizing the last forest walk, or does it unknowingly elicit fear due to childhood memories of some dangerous dark forest, out of fairy tales for example? This potentially semantic route to an affective response to natural environments would be in line with a recently proposed theory called conditioned restoration theory<sup>40</sup>. Conditioned restoration theory posits that urban citizens usually experience nature during leisure time and therefore associate positive cognitions and relaxation with nature, whereas urban settings are usually paired with work and chores and therefore with stressfulness.

Another important issue to disentangle would be to define the impact of conscious beliefs. For example, is it important that the individual has the explicit assumption that forest exposure enhances mood and/or cognitive functioning, and what impact does it have if a person believes the forest will have a negative effect on mental health? To investigate the impact of beliefs it could be interesting to manipulate the beliefs of participants by giving them excerpts to read that promote a certain direction. Alternatively, one can use ambiguous stimuli, that is, stimuli that can either be interpreted as originating from nature or man-made contexts. In a previous study, for example, participants were presented with pink noise that could either be interpreted as originating from a waterfall or from traffic noise<sup>41</sup>, which in turn could influence how the auditory presentation impacted mental health parameters. Disentangling effects that are caused by the active ingredients themselves from effects that are elicited by beliefs on the effects of those ingredients is an important means to understanding how the physical environment influences mental health and to open the black box described above.

### **What are the neural mechanisms involved?**

Related to knowing which human senses are involved in processing the physical environment, it is likewise important to understand which brain regions are involved.

On the one hand, knowledge on which brain areas are affected by the different active ingredients may be utilized to predict which environments could be health promoting for specific psychiatric disorders, based on the respective structural and functional alterations in the brain with which the respective disorder is associated. For example, patients with schizophrenia often present frontal and hippocampal deficits<sup>42</sup> that might benefit from environments that foster frontal and hippocampal brain structure, such as green spaces<sup>43</sup> and rural regions during upbringing<sup>44</sup>.

On the other hand, it is important to determine whether the observed effects are more pronounced in brain areas responsible for affective or for cognitive processes. This would provide answers to an ongoing debate in environmental psychology as to whether the positive, restorative effects of nature exposure are more strongly driven by affective or cognitive processes. This debate has revolved around two partly complementary theories: (1) attention restoration theory<sup>45</sup>, which highlights the cognitive route by positing that attentional resources become depleted over time when individuals are exposed to urban contexts and that those resources can be restored by exposure to nature, and (2) stress recovery theory<sup>46</sup>, which highlights the affective route by focusing on the alleviating effects of nature exposure on the arousal and stress levels of individuals. The cognitive route could comprise regions such as the lateral prefrontal cortex, anterior insula and the posterior cingulate cortex, and the affective route would most likely be assumed to involve brain regions such as the amygdala, orbitofrontal cortex, ventral striatum and anterior cingulate cortex. However, this dichotomy is artificial to some extent, as complex cognitive–affective behaviors probably have their basis in dynamic coalitions of networks of brain areas<sup>47</sup>. In the future, research may want to investigate the time course of brain activity across different brain regions using electroencephalography (EEG) or magnetencephalography. This is interesting, because stress recovery theory and attention restoration theory could be read as implying a different order in affective and cognitive processes, with stress recovery theory suggesting that affective processes should come first and attention restoration theory indicating that cognitive effects should occur first. Also, the acquisition of physiological data, such as electrodermal activity, heart rate, heart rate variability and/or blood pressure<sup>48,49</sup> could be helpful to disentangle the potential differential engagement of affective and

cognitive processes in the human response to the physical environment. Furthermore, physiological data may help to unravel to what extent the observed effects of nature are mediated by stress or immunological responses

Interestingly, a more recent theoretical notion, put forward by Valtchanov<sup>50</sup>, posits an association between the restorative response to nature and activation of the reward pathway (for example, the ventral striatum). This theory is mostly based on existing evidence of an association between preference/pleasantness ratings in different domains, such as photographs, music, odors and food<sup>51</sup> and specifically for visually presented scenes<sup>52</sup>, and brain activation in reward regions. It furthermore assumes that bottom-up information such as the fractality of visual stimuli may trigger this reward processing. Another recently proposed theoretical framework, the goal discrepancy account<sup>53</sup>, attempts to provide an umbrella for the affective and cognitive effects of restorative nature by positing that both arise from discrepancy reduction. According to this account, nature essentially helps individuals to reduce discrepancies between their current situation and their goals.

Identifying the most prominent neural route that nature exposure or the different aforementioned active ingredients specifically modulates may help to decide between the existing environmental psychological theories and could provide insight into how the positive effects on mental health come about. In addition, nature prescription could be especially indicated in patients with mental health problems, depending on the predominance of affective or cognitive symptoms.

Next, we will provide an overview of the emerging field of environmental neuroscience to describe the relationship between physical environment and the brain<sup>18</sup>. Given the small number of neuroscientific studies involving psychiatric patients, we will start with evidence from healthy participants. We will subdivide the research into the neural effects of long-term exposure to certain living environments at and around the home address, short-term exposure (such as a trip to or walk in a certain environment) and acute exposure effects. We selected this order, based on the fact that the first studies in this field took a long-term perspective.

### Effects of long-term environmental exposure on the brain

Initial studies in the field of environmental neuroscience were mostly cross-sectional in nature and compared the brain signatures of individuals living (or having been brought up) in cities, towns or rural regions, defined on the basis of population density. In a seminal study, individuals performed a socially stressful mental calculation task (Montreal imaging stress task, MIST) in a magnetic resonance imaging (MRI) scanner<sup>54</sup>. The results indicate that individuals living in cities at the time of the study showed higher amygdala activity, a brain region that has been linked to stress and fear processing<sup>55</sup>. The exposure to urbanicity during upbringing, namely the first 15 years of life, a particularly vulnerable period for the development of schizophrenia<sup>56</sup>, was associated with higher brain activity in the perigenual anterior cingulate cortex (pACC), likewise known to be involved in stress responses. Both results were interpreted as evidence for the detrimental impact of city living. This functional brain study was followed by several others investigating the associations between population density in the living environment of participants and brain structure. These studies reported a negative association between gray matter volume in dorsolateral prefrontal cortex and pACC (in men only) and urban upbringing during the first 15 years in life<sup>57</sup>, with two other cross-sectional studies confirming this prefrontal cortex finding<sup>58,59</sup>. Interestingly, all of these findings were interpreted as deficits due to the exposure to urban environments. However, because the data are cross-sectional in nature, and due to the gross assessment of urbanicity on the basis of a single dimension (population density), it is unclear whether the effects should be attributed to the presence of urbanicity or the absence of nature, as well as what urbanicity actually implies.

In a first attempt to characterize the respective living environments of participants in more detail, going beyond the classes 'urban' versus 'town' versus 'rural,' we used a GIS approach. Specific geographical characteristics around the home environment were extracted dimensionally in a 1-km radius—the approximate walking range of older adults—around the home address of older participants in the Berlin Aging Study II. We discovered a positive association between the extent of forest and structural amygdala features such as cell density and myelin content<sup>60</sup>. A similar attempt on a sample of children in Barcelona, Spain, revealed a positive association between green spaces in a 100-m radius around the home address and prefrontal cortex volume, also hinting at the potential salutogenic effects of nature exposure<sup>43</sup>. In addition, the researchers observed a positive association between gray matter volume in the prefrontal cortex and working memory as well as a negative association with inattentiveness. Interestingly, a recent re-analysis of the dataset of older adults from BASE II14 provides a first hint that urban green (parks, zoos and so on) around the home addresses of older people may indeed explain variance in brain structure in pACC above and beyond the explanatory power of urban fabric. This suggests that green space may be salutogenic above and beyond the negative effects of typical urban characteristics of the living environment.

However, it remains unclear which specific features of the physical environment are actually the driving factors, that is, whether air or noise pollution, the presence of green, nature sounds or other aspects are the active ingredients. Accordingly, studies with a more fine-grained assessment of the physical environment, ideally as well as longitudinal and interventional data, are needed to draw more specific and in particular much needed causal conclusions.

Moreover, it would be fruitful if more studies on the long-term effects of the physical environment on the brain would widen their focus to include potential behavioral effects, whether it be the main outcome or by verifying that the brain regions of interest do show the expected correlations with certain cognitive or self-reported phenomena, as for example in a comparison of adolescents' brains who have been exclusively raised in rural versus urban areas<sup>44</sup> or a study on air pollution effects on the cognitive and brain maturation of adolescents<sup>61</sup>. The study on adolescents who were exclusively raised in rural or urban areas, reports a structural difference in the left hippocampal formation (rural > urban) and superior spatial processing performance in adolescents raised in rural regions. At the same time the hippocampal volume was positively associated with performance in the spatial processing task.

### Effects of short-term environmental exposure on the brain

The first successful attempts at interventional studies to infer causality have been undertaken, where participants have been sent for a walk in different environments. A seminal study has shown that a 90-min walk in a natural environment in comparison with a group who walked in an urban environment instead, reduced self-reports of rumination and reduced neural activity during rest in the medial prefrontal cortex, an area that has been associated with repetitive thinking<sup>62</sup>. With a similar design we have recently examined the effects of a walk in a forest environment on stress-processing. In participants taking a one-hour walk in a forest, we found a reduction of amygdala activity in a fearful faces paradigm, compared to a group of urban walkers, where we found no change<sup>63</sup>. Interestingly, this effect seemed to generalize to a social stress task (MIST) in women, but not in men<sup>64</sup>. However, no effects were found in self-report measures, cognitive performance or physiological indicators of stress.

To assess the impact of day-to-day variations and their effects on brain structure and function, we conducted a longitudinal observational study<sup>65</sup> in which a small number of participants were assessed about 50 times using MRI over the course of about 6 months during their regular life. When examining daily variations in time spent out-doors in the 24 hours before the brain scan was taken, a significant

positive association with gray matter volume in the dorsolateral pre-frontal cortex was observed, suggesting that even these natural daily variations in short-term exposure can have an impact on brain structure, a measure that is usually assumed to be fairly stable over time<sup>66</sup>. This finding clearly highlights the importance of the day-to-day choices of the environments that we surround ourselves with and to which patients suffering from mental health problems are exposed.

### Effects of acute environmental exposure on the brain

At an even shorter timescale there is research that investigates the brain activity that is elicited during exposure to photographs, videos or virtual reality in the laboratory or real-life environments—this is what we mean by ‘acute exposure’. These studies have used a wide range of methodologies, including EEG<sup>67,68</sup>, functional near-infrared spectroscopy (fNIRS)<sup>69</sup> as well as functional MRI<sup>70,71</sup>. A recent review of these studies came to the conclusion that exposure to natural environments, compared to the urban environment, is associated with low-frequency brain waves and lower activity in frontal brain areas, along with self-reports of restorative-ness<sup>69</sup>. Urban environments, in contrast, were instead associated with higher activity in the amygdala and posterior cingulate cortex, which is associated with negative affect and effortful attention. Similar well-controlled laboratory studies are required in the future to identify the causal impact of the exposure to selective active ingredients and explore the associated neural mechanisms. Moreover, future research should also focus on the question of how these abovementioned timescales interact and integrate over time and whether functional brain activity elicited in an acute or short-term exposure setting may then accumulate into structural alterations in the same brain regions when individuals habitually live in the respective environment.

Unfortunately, there is not yet much evidence on the effect of the physical environment on the brain of psychiatric patient samples. The first study on patients with psychotic disorder and the siblings of patients did not show that the negative association between psychotic disorder and cortical thickness was moderated by urbanicity during upbringing<sup>72</sup>. Another study has shown a positive association between the neighborhood characteristic of average income and total gray matter volume, which was particularly pronounced in the prefrontal cortex of healthy participants, whereas this association was not observed in patients with schizophrenia. Conversely, the hippocampus was larger in affluent environments in patients compared to controls<sup>73</sup>. A functional MRI study revealed a group-by-developmental upbringing interaction in bilateral amygdala during cooperative interactions in a trust game<sup>74</sup>. However, more research is needed to pinpoint how the physical environment affects the development and maintenance of mental disorders.

The knowledge gained by the proposed research can be utilized to inform urban and landscape planning. It could guide evidence-based building practices with the aim to facilitate the exposure of the public to salutogenic environmental features. With continuously rising numbers of individuals with mental health problems, this could be a fairly indirect intervention approach that has wide reach and scalability.

### Conclusion

To better understand how the physical environment affects mental health, we propose that three main research questions need to be addressed. First, the active ingredients of the physical environment that elicit positive mental health effects need to be identified. Second, and related to the first point, the major human sensory pathways by which the active ingredients are perceived should be determined. Third, the neural mechanisms involved in processing the physical environment need to be discovered. The knowledge gained by environmental neuroscience may inform landscape and urban planning, as well as architecture, to make living environments more salutogenic. This knowledge would also help to identify the active ingredients of salutogenic environmental exposure that we need to preserve in the face of the environmental changes elicited by urbanization and climate change, to facilitate mental health.

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S.K. conceived and wrote the first draft. J.G. revised this draft.

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The authors declare no competing interests.

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