How much does the environment shape one's developing, or developed brain, and impact a person's mental health?

Environmental Influence in the Brain, Human Welfare, and Mental Health.
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The environments in which we find, or place, ourselves offer many opportunities for social interactions, all of which impact mental health. " The nature of how these social experiences are imbedded into the environment may be crucial." The sophisticated part of the brain that regulates feedback, the hypothalamic-pituitary adrenal (HPA) axis, directly links "excessive social adversity" with physical and mental health and can have additional impact if the brain is still developing as in children and adolescents. Parts of the brain are reprogrammed when exposed to severe and chronic stress and alter the way in which the HPA responds, thus, altering ones' physical and mental health.

- Childhood is a critical period of neurodevelopment and exposure to stress may not be apparent until much later or in adulthood. New research indicates the most detrimental changes to the brain, related to stress, happen in middle childhood (6-12), not early childhood or adolescence.
- The hippocampus (the part of the brain thought to be the center of emotion, memory and the autonomic nervous system) is critical to physical and mental health, can experience a pronounced decrease in volume for those who experience trauma or stress.
- The quality of human social bonds influences various health-related factors including positive affect, self-esteem, morbidity, longevity, recovery, and risk for mental illness.
- Urban environments impact neural development; fast-paced urban environment, air pollution, lack of green space or access to nature.

So, what are the implications for education? How do we ensure school is not one of the stressors that alters neural development?

- Create safe space for students to socialize and recharge. Where can students go during the day to practice imbedding themselves in the school community? How does the school facilitate and teach these skills?
- Create a classroom culture of inclusion with respect to student collaboration and communication that embodies the research and the need for acceptance and participation to promote healthy brain development.
- Promote opportunities for students to connect with and spend time in nature. Research indicates this can result in stronger brain development, reduced stress, and increased physical well-being.

Enjoy the article! What conversations have you been part of that involve reducing stress for students in school to minimize negative the impact on brain development?

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Editorial

Commentary

Perspective

Reviews

Environmental influence in the brain, human welfare and mental health

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Abstract

The developing human brain is shaped by environmental exposures—for better or worse. Many exposures relevant to mental health are genuinely social in nature or believed to have social subcomponents, even those related to more complex societal or area-level influences. The nature of how these social experiences are embedded into the environment may be crucial. Here we review select neuroscience evidence on the neural correlates of adverse and protective social exposures in their environmental context, focusing on human neuroimaging data and supporting cellular and molecular studies in laboratory animals. We also propose the inclusion of innovative methods in social neuroscience research that may provide new and ecologically more valid insight into the social-environmental risk architecture of the human brain.

Subject terms: Psychiatric disorders Schizophrenia Social behaviour Stress and resilience

Introduction

Environmental exposures shape the developing and developed brain and affect human health. Recent years have seen a strong growth of interest in how social influences can, much like 'classic' environmental exposures such as toxicological or nutritional factors, have enduring effects on brain circuits and human behavior[1]. Although the environment affects all aspects of health and well-being, our focus will be on mechanisms related to mental health outcomes, which make up a significant and increasing proportion of the burden of disease worldwide[2].

Research in this area has typically focused on the identification of adversity-related factors and their neural underpinnings, as suggested by an implicit medical model of illness, risk and mitigation. Less attention has been paid to salutary experiences that may promote resilience and the capacity of the human brain to adapt to or buffer adverse environmental influences[3]. In this Review we will highlight work that begins to define convergent neural systems of risk and resilience related to the social environment in a developmental perspective. Although we take our point of departure from human imaging experiments, this requires incorporating aspects of the animal, molecular genetic and epidemiological work on which these studies are built. Specifically, the integration of animal data allows for critical insights into the molecular and cellular mechanisms of environmental influences that noninvasive human research cannot provide.

We approach this topic from three angles, discussing (i) neuroendocrine mediators of the lasting effects of social environment and some of their epigenetic mechanisms, (ii) neuroscience data on social-environmental exposures that arise from different levels of analysis and (iii) novel methods that may enable ecologically more valid study of these influences in the future. We highlight selected exposures, systems, methods or mechanisms, as we aimed for a broad scope on the topic, and space limitations prevent discussing all aspects in depth. Notably, the discussion of the levels of analysis does not follow a classical biological order (for example, genes-cells-neural systems). The human neuroscience literature still tends to focus on the neural underpinnings of related social influences in isolation, so we organized the discussion along a gradient, from more proximal, concrete influences to more distal, abstract ones (i.e., from dyadic to group to societal to area-level exposures). Not surprisingly, risk- and resilience-related influences do not operate in isolation but interact within and across these levels of abstraction—as, for example, in the case of urban upbringing and ethnic minority status[4] or social status and parental caregiving[5]. The neurobiology of these additive and/or interactive influences is barely addressed in the current literature and is therefore also underemphasized in this review. Importantly, many relevant social modifiers with lasting neural effects are currently best viewed as broader proxy markers for poorly understood causal exposures in real-life social or physical environments (for example, 'urban upbringing'). A finer dissection of the precise environmental components of these social exposures is crucial, as it may provide important

mechanistic entry points for preemptive interventions and the promotion of societal well-being. Here we argue that neuroscience can have a role in this endeavor and that there are novel approaches that may enable a better and more mechanistic definition of the social subcomponents of complex social risk and resilience factors.

Neuroendocrine mediators of social-environmental exposures

Hypothalamic-pituitary-adrenal axis.

Psychosocial challenges are robust activators of the hypothalamic-pituitary-adrenal (HPA) axis, the complex feedback-regulated neuroendocrine system controlling cortisol secretion and physiological stress responses in mammals[6]. In the short term, HPA axis activation facilitates successful adaptation of the organism to imminent threats by shifting the physiological priorities from sustenance (i.e., digestion and reproduction) toward functions supporting defensive behaviors (i.e., energy supply, perfusion, ventilation and cognition)[7]. A large body of literature highlights the cumulative burden of excessive social adversity and HPA axis activation for physical and mental health, in particular when the exposure coincides with ongoing neural development[8]. Of particular importance are gene-environment interactions on the development of brain systems that feed into the HPA axis and facilitate emotional responses, including the hippocampus, amygdala and prefrontal cortex (PFC). HPA axis activation releases adrenal glucocorticoids, which interact with glucocorticoid receptors (GRs) that are highly expressed in limbic regions, act as transcription factors and modulate the structural and functional organization of the neural circuitry that underlies the behavioral response to stress. As a consequence, severe and chronic stress exposure during sensitive neurodevelopmental periods induces a reprogramming of prefrontal and limbic systems with lasting alterations in region-specific gene expression, neural plasticity, neuroendocrine function and behavioral response to subsequent stressors[9]. In humans, a wide range of social-environmental risk factors for mental health have been associated with enduring changes in the reactivity of the HPA axis, including childhood maltreatment[10], social exclusion[11] and urban upbringing[12], but little is known about the potential specificity of different psychosocial stressors for subcircuits of the prefrontal-limbic system.

Dopamine.

The rodent literature supports converging effects of environmental influences and HPA axis reprogramming on the development of the mesocortical and mesolimbic dopamine system, which arises from the ventral tegmental area[13]; targets the nucleus accumbens, limbic regions and the PFC; and influences a broad range of motivated behaviors including reward seeking, anxiety and associative learning[14]. Dopaminoceptive neurons highly express GRs[15], and repeated exposure to aggression has been shown to result in a GR-mediated activation of the dopaminergic system that facilitates lasting stress-related behaviors such as social avoidance[16]. In contrast, inactivation of *Nr3c1*, which encodes a glucocorticoid receptor, in dopaminoceptive neurons results in region-specific elimination of GRs and a profound decrease in cocaine self-administration, a mechanism relevant for the understanding of stress-related clinical phenomena such as addiction relapse. Social isolation in adolescent transgenic mice modeling a genetic risk factor for schizophrenia in *DISC1* (encoding disrupted in schizophrenia 1) results in a significant elevation of corticosterone levels and related, regionally specific hypermethylation of the gene encoding tyrosine hydroxylase in dopaminergic efferents of the ventral tegmental area to the frontal cortex[17]. These data underscore the role of HPA axis activation and GR function in the lasting reorganization of dopaminergic pathways in the context of social stress.

Oxytocin.

For salutary experiences promoting resilience to stress, basic research points to another convergent effector system that may involve oxytocin, a peptide hormone and neurotransmitter produced in the supraoptic and paraventricular nucleus of the hypothalamus. The oxytocin system is evolutionarily conserved and involves peripheral release as a pituitary hormone with a role in parturition and lactation. Central dendritic release modifies a variety of social behaviors, including maternal care, social recognition, social bonding and the emotional and somatic expression of fear, anxiety and aggression[18]. Although the precise expression of oxytocin receptors in the human brain remains to be clarified[19], oxytocin is believed to modulate, directly or indirectly, brain functional circuits crucial for motivation, emotion and stress response. These include the amygdala, anterior cingulate cortex (ACC), lateral septum, ventral tegmentum and nucleus accumbens[18], which overlap with circuits that control and are shaped by HPA axis function.

Several lines of evidence support a role for oxytocin in prosocial behaviors that attenuate the adverse effects of psychosocial stress (for example, sensitive caregiving and social support). In lower mammals, oxytocin release modulates maternal nurturing activities, mother-infant bonding, parental care and social recognition. In humans, oxytocin signaling facilitates interpersonal gaze to the eye region, emotional understanding of others, interpersonal trust[20], social support[18] and maternal care[21]. Oxytocin further attenuates amygdala fear responses, buffers physiological stress responses of the HPA axis and sympathetic nervous system and enhances sensitive maternal behaviors in mothers exposed to psychosocial stress[18, 20, 22, 23]. Supportive caregiving also stimulates central oxytocin release in the infant, which may represent a crucial neuroprotective mechanism for the buffering of early adverse life events[22], although more direct evidence for this proposal is needed. These data support the idea of a social neural resilience mechanism that affects the ability to form stable social bonds and to profit from the beneficial effects of social support in the context of stress-related psychosocial challenges.

Studies in rodents highlight the role of the social environment in shaping the oxytocin system, with implications for stress resilience[24]. For example, the density of oxytocin receptors in brain regions associated with maternal behavior in rats (such as the medial preoptic area) is increased by estrogen, thereby facilitating behavioral requirements for high maternal responsiveness, such as lower levels of aversion and increased attraction toward pup-related stimuli[25]. The intensity of maternal care experienced is transmitted from females of one generation to those of the next by an epigenetic mechanism that regulates DNA and histone methylation in the promoter region of the gene encoding estrogen receptor (*Esr1*) in the medial preoptic area during sensitive periods of neural development[26]. In prairie voles, cohabitation of a mating pair leads to increased histone acetylation of the gene encoding oxytocin receptor (*OXTR*) in the nucleus accumbens of females, which facilitates pair bond formation and alloparental behavior[27, 28]. A critical intermediate of these effects is the dopaminergic system, which is sensitive to the long-term epigenetic effects of early social experiences[29] and interacts with the oxytocin system in the formation of prosocial phenotypes[30]. Taken together, these data highlight the complex interaction of different

neuroendocrine systems and provide a molecular framework for the understanding of the lasting effects of social influences on behavioral phenotypes that can, in turn, amplify or mitigate the effects of the environment in conspecifics.

Levels of analysis of environmental exposures

Social support in childhood: parents and caregivers.

Childhood is a critical period of neurodevelopment, with dynamic social interactions between caregivers (particularly parents) and infants. Parenting behavior has long-lasting effects on development: acts that result in harm or pose a threat to the child increase the risk for learning disabilities, behavioral and emotional abnormalities and a broad range of disorders including depression, borderline personality disorder, post-traumatic stress disorder (PTSD), anxiety and schizophrenia[31]. In contrast, stable, loving and supportive caregiver behavior promotes attachment security and the ability to form trusting and empathetic social relationships and buffers the detrimental effects of adverse life events[32].

Studies in laboratory rodents have elucidated the molecular mechanisms that are shaped by the quality of parent-infant interactions, with a particular focus on systems involved in stress reactivity. Exposure to prolonged periods of maternal separation results in increased reactivity of the HPA axis and high hypothalamic vasopressin (AVP) levels[33]. The enduring effects on this neuropeptide system are mediated by developmental changes in the epigenetic state of the promoter region of the gene encoding AVP[33]. Similarly, paradigms that induce increased fragmentation of maternal care toward offspring enhances corticotrophin-releasing factor (CRF) receptor signaling in the hippocampus, resulting in impaired neural plasticity and enhanced stress reactivity in adulthood[34, 35]. The experience of abusive caregiving has a lasting impact on functioning of the prefrontal cortex, and epigenetic modulation of brain-derived neurotrophic factor (BDNF) may account for the within- and across-generation effects of this form of early life adversity[36]. In contrast, highly nurturing maternal care during postnatal development can attenuate HPA axis responses to stress, enhance neural plasticity, promote the development of mesolimbic dopaminergic pathways and enhance social and reproductive behaviors[26, 29, 37, 38]. Molecular changes in genes encoding hypothalamic and hippocampal steroid receptors may coordinate these broad neurobiological effects[26, 39]. These studies indicate a sensitive period during postnatal development during which the brain can be changed by the experience of variation in maternal care[26, 39]. Though paternal influence on these cellular and molecular pathways has been less frequently explored, evidence among biparental species increasingly points to an enduring effect of parental absence of the development of striatal, hippocampal and cortical circuits[40, 41]. Interestingly, though impaired functioning is typically observed in response to adverse early rearing environments, functioning can be enhanced through subsequent exposure to chronic stressors, suggesting the capacity for adaptive responses[42, 43].

In humans, the neural correlates of childhood sexual abuse, severe physical punishment, emotional abuse and institutional deprivation have been examined with neuroimaging. Despite a sizeable number of studies, the data need to be interpreted with caution. Owing to the difficulties in obtaining data from the same individuals over decades the studies often involve adults, retrospective self-reports on maltreatment experiences and cross-sectional study designs with a limited causal interpretability of the data. Further limitations arise from the focus on individuals with psychiatric comorbidities, which makes it difficult to separate the unique correlates of adverse caregiving from influences associated with a disorder itself or medication confounds[44]. Considerable attention has been directed to the hippocampus, mainly owing to its involvement in the glucocorticoid-mediated feedback control of the HPA axis and established morphological sensitivity to stress[45]. Meta-analyses suggest a significant reduction in hippocampal volume in healthy individuals and PTSD patients with a history of childhood maltreatment[31, 46]. The coincidence of multiple forms of abuse seems to predict more pronounced volume decreases[31], and the deficits are probably not apparent until early adulthood[31, 46], which is consistent with the delayed effects of early life stress on hippocampal development in rodents[47]. Outside the hippocampus, meta-analytic evidence from individuals without psychiatric comorbidities is lacking. However, an analysis that aggregated data from studies on unmedicated patients exposed to childhood abuse found widespread deficits in gray matter in the extended limbic circuitry, including in the amygdala, insula, parahippocampal gyrus and the middle temporal, orbitofrontal and inferior frontal cortices[48]. Interestingly, the human data suggest that the most detrimental effects on hippocampal[31], and possibly also amygdala[49], structure result from maltreatment in middle childhood, not early childhood or adolescence. Although this highlights preadolescence as a developmentally sensitive period for subcortical structures in humans, the role of other factors remains to be clarified, particularly the limited representation of specific developmental phases in self-report questionnaires and the restricted ability of humans to recall events from early childhood[31, 44].

The functional neuroimaging data in humans is consistent with the proposal that childhood maltreatment leads to lasting detrimental changes in circuits involved in the neural processing and regulation of threat and fear responses. Common reports include amygdala hyper-reactivity to emotional stimuli[44] and altered connectivity to limbic areas such as the hippocampus, ventromedial prefrontal cortex and subgenual ACC (sgACC)[44, 50]. Although the majority of work has been conducted in patients[44], a recent resting-state study in a community sample of young adults with childhood experiences of maltreatment confirmed the presence of deficits in hippocampus-sgACC connectivity (in both sexes) and amygdala-sgACC connectivity (in females). Structural equation modeling demonstrates that the severity of childhood maltreatment, the functional coupling of these regions and the extent of subclinical symptoms of anxiety and depression in early adulthood are related. These data suggest that connectivity impairments in fear-processing circuitry may represent a direct neural mechanism through which childhood maltreatment facilitates the risk for adult psychopathology[50].

Human imaging data on supportive caregiving are sparse, heterogeneous and focused on the neural correlates of plausible composite features such as mother-infant bonding. The findings reported most often in this area are enhanced amygdala, medial prefrontal and ventral striatal responses in mothers exposed to the view or cries of their own infants[51], which is consistent with a heightened emotional response to the well-being and needs of the child and the initiation of related caregiving motivations. In offspring, the duration of exclusive breastfeeding has been related to a greater neural sensitivity to positive emotional stimuli[52] and indirect measures of white matter development in later developing frontal and temporal white matter tracts[53]. However, the interpretation of these data is challenging, as differences in supportive caregiving, social factors correlated with caregiving (such as status) and even diet may have a role. Neuroimaging evidence on the quality of maternal behaviors is sparse, although one study related positive attributes such as caregiver nondirectedness, infant attentiveness and positive infant affect to a greater “own-infant response” of the mother's middle frontal gyrus[51].

Social support and exclusion in adulthood.

Human cooperation and other collective prosocial behaviors increase well-being[54] and have been crucial prerequisites for primate survival and brain development during evolution[55]. A large body of literature suggests that the extent and the quality of human social bonds influences various health-related factors, including positive affect, self-esteem, morbidity, longevity, recovery and risk for mental illness[56, 57]. In general, individuals who are more firmly embedded in their social surroundings are healthier than those with relatively thin social ties, an effect that is larger than that of other lifestyle factors such as exercise, diet or smoking status[58]. A plausible explanation is that social support modulates the cognitive and emotional appraisal of salient external stimuli, thereby decreasing the odds for frequent negative emotional states and exaggerated physiological stress responses[57]. Consistent with this, laboratory experiments show that social support from a spouse significantly attenuates HPA and cardiovascular stress responses to psychosocial stress, especially in males[57, 59, 60]. In contrast, hostile or lacking social relationships have been related to heightened neuroendocrine reactivity in individuals exposed to stressful experiences[57].

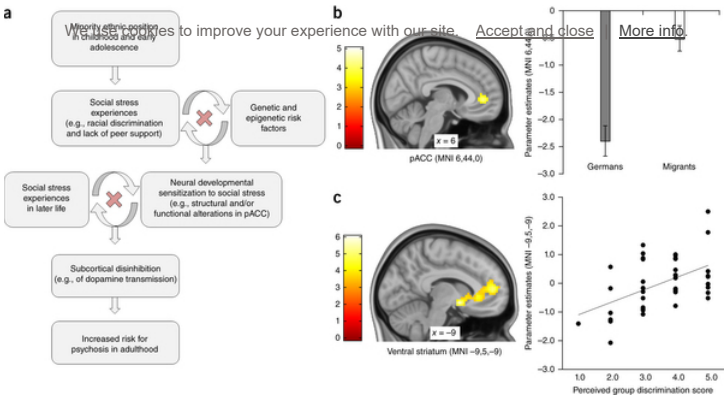
The oxytocin system seems to have a key role in the mediation of the stress-buffering effects of social support in the recipients[18]. Neurogenetic studies in humans have demonstrated that common single nucleotide polymorphisms in *OXTR* modulate prosocial temperament[61, 62], relate to the size of individual social networks[61], influence the seeking of emotional social support[63] and dampen cortisol responses to stress[60], possibly by influencing the efficacy of oxytocin in the regulation of hypothalamic-limbic circuits[62, 64]. Drug challenge studies in humans point to a complex interaction between oxytocin and the social context of support provided, with dampened stress responses in the context of a supportive friend but heightened stress responses in the context of a supportive stranger, which is consistent with an enhanced sensitivity to the embedding of social stimuli with increased oxytocin signaling[65]. Interestingly, these effects may extend across species; data show that oxytocin has a bidirectional role in mediating the affiliation between humans and domesticated dogs[66], a likely outcome of social coevolution.

At the neural system level, neuroimaging data point to modulatory effects of social support in brain areas involved in the affective processing of stress, pain and safety signals. People who view pictures of a romantic partner during the experimental induction of physical pain perceive less pain and show increased responses in the ventromedial prefrontal cortex (VMPFC)[67, 68] and posterior cingulate cortex[67] and decreased activity in superordinate areas of the pain-processing network, such as the dorsal ACC (dACC) and anterior insula (AI). Higher perceived social support and greater perceived analgesia were related to higher activity in the VMPFC, a region encoding the hedonic value of stimuli. It has been proposed that under conditions of threat and stress, the VMPFC encodes the subjective value of attachment figures for safety and comfort[68].

For social exclusion, neuroimaging data highlight the role of the dACC and AI. Here, a popular neuroimaging paradigm is the Cyberball game, a simulated ball-tossing match with two virtual players that can be used to induce experiences of social inclusion or exclusion, depending on whether the virtual players pass the ball to the study participant[69]. Increased neural activity in the dACC and/or AI has been linked repeatedly to social exclusion during Cyberball, in particular in individuals with a heightened sensitivity to social rejection[69]. In contrast, individuals with high levels of social support show dampened cortisol reactivity to social stress and decreased neural activity in the dACC during Cyberball, with higher dACC activity relating to higher levels of perceived social stress[70]. These data suggest that the correlation of social support with lower neuroendocrine stress responses and health benefits is mediated, at least in part, by 'desensitization' of higher-order affective brain areas to threatening social stimuli.

A special case of social exclusion is ethnic discrimination, which may, in discriminating people, relate to automatic affective responses of the fusiform gyrus and amygdala to salient stimuli signaling outgroup status in others[71]. Epidemiological studies suggest that for those exposed, perceived discrimination is a likely psychological mechanism linking ethnic minority status to increased mental health risks[72]. Specifically, ethnic minority status is one of the best-established social-environmental risk factors for schizophrenia, with a doubling of the relative risk for the disorder across generations[73, 74]. Although the evidence base across diagnostic entities is sparse, the existing epidemiological data point to a degree of specificity of ethnic minority status as a risk factor for schizophrenia[75, 76]. The relative risk is modulated by social and perceptual factors, particularly the extent to which an individual stands out from the majority population in extrinsic features such as skin tone (darker skin tone is associated with risk) and the relative density of other people of the same or similar ethnic background in the neighborhood (higher density is protective). Consequently, current pathophysiological models highlight in the social environment adverse influences that may facilitate social stress experiences, thereby increasing schizophrenia risk through lasting changes in neural stress-regulatory circuits[77] (Fig. 1a). A recent neuroimaging study[78] in healthy adults examined this hypothesis by comparing the neural activity of second-generation immigrants in Germany to that of a demographically matched sample of the German majority population. The ethnic minority group reported a significant increase in chronic stress and showed diminished deactivation of the perigenual ACC (pACC) during social-evaluative stress, a key neural region for the regulation of negative emotion and stress[79] (Fig. 1b). In addition, increased neural activity in the pACC and the ventral striatum related to higher levels of perceived discrimination against members of one's own ethnic group in German society (Fig. 1c). These findings support current pathophysiological models by showing that the processing of social-evaluative stress is altered in higher-order stress regulatory areas in ethnic minorities and that the changes observed relate to perceived discrimination, a plausible facet of adverse social experience in ethnic minorities. Although functional abnormalities in the ACC and ventral striatum are also well established in individuals at increased risk for psychosis[80, 81, 82], more research on the neurobiological correlates of ethnic minority status is needed before conclusions on the relative diagnostic specificity or generality of these risk-associated findings can be reached.

Figure 1: Neural correlates of ethnic minority status.



(**a**) Theoretical framework adapting the vulnerability-stress model of psychosis to the special case of ethnic minority status as a complex social-environmental risk factor. Image adapted from ref. 141 (Springer). (**b**) Activity in the pACC during social stress processing is higher in people with ethnic minority status than in those in the German majority population. (**c**) Activity in the pACC and ventral striatum that correlated positively with self-perceived discrimination against one's own ethnic group in response to social stress in migrants. Images (**b**,**c**) adapted from ref. 78 (American Medical Association). Error bars, mean ± s.e.m.

These neuroimaging findings related to social support and exclusion are complemented by studies in laboratory rodents that examine the impact of social 'enrichment', social isolation and social defeat. Physical activity, exploration and social interaction with peers (environmental enrichment) during juvenile development can mitigate the deleterious effects of genetic abnormality and maternal deprivation[83, 84]. These experiences enhance dendritic branching and long-term potentiation and alter gene activity in multiple brain regions[84, 85]. Conversely, the experience of social isolation during juvenile development can reduce levels of oxytocin receptors within the hypothalamus and amygdala and increase hippocampal corticotropin-releasing hormone receptor levels[86, 87]. Enhancements in glutamatergic transmission in the mesolimbic dopamine system in response to social isolation during this sensitive period may account for enhanced learning of drug cues and resistance to extinction, which may contribute to addiction risk[88]. The experience of aggressive social encounters (social defeat) can result in an increase of depressive and anxious behaviors and is associated with genome-wide transcriptional remodeling within the striatum[89, 90]. This experience can also induce social avoidance, thereby exposing individuals to further social isolation.

Urban exposure and its components

In humans, one of the best-established area-level influences on mental health is city life. On average, urban dwellers tend to be healthier than their rural counterparts, owing mainly to the superior educational, economic and healthcare opportunities that large cities provide[91]. However, the opposite is true for mental health—psychiatric disorders are 34% more frequent in urban areas after adjustment for confounders[92]. The best-examined link is that between urban life and schizophrenia[73], with incidence rate ratios of 1.92 for male and 1.34 for female city dwellers as compared to their rural counterparts, even in high-income countries[93]. Evidence suggests a dose-dependent relationship between psychosis risk and the duration and magnitude of the exposure to urban environments during development, with a 2.75-fold increase in risk for people who live in highly urbanized areas throughout the first 15 years of life[94]. People at high genetic risk for the illness are particularly affected[95], and changes in urban exposure during childhood go hand in hand with changes in schizophrenia incidence later in life[94]. Given these observations, 'social drift' of vulnerable individuals to the city is unlikely to be the sole explanation. Instead, or in addition, it is believed that adverse qualities of the urban environment interact with genetic factors during upbringing to alter neural developmental trajectories and increase the odds of psychotic symptoms in adulthood[73, 96].

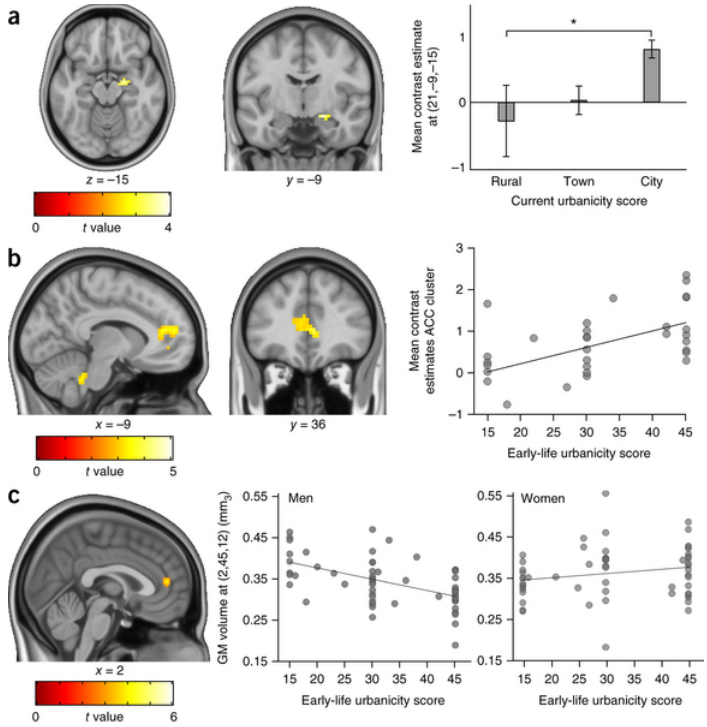
Psychosocial stressors.

The urban landscape is highly complex and heterogeneous, and 'urbanicity' serves as a proxy for a set of as yet poorly understood environmental influences that aggregate and interact in the city. Many researchers believe that the fast-paced urban environment is enriched in adverse psychosocial influences that, in combination, may provide the “toxic social circumstances”[97] that facilitate chronic stress and abnormal neural development in vulnerable individuals[98]. Indeed, several of the social risk factors discussed above can be plausibly related to increased stress in cities. These include higher odds for fleeting social relationships, fragmentation of family structures and supportive social networks, technology-driven remote interactions (i.e., decreased social support and increased social isolation), wider socioeconomic disparities (i.e., perceptions of social defeat and external control in disadvantaged residents), higher crime rates (i.e., actual experiences of violence or fear of victimization) and increased social competition (i.e., reduced social cooperation). In addition, infringement of personal space converges on the same evolutionarily conserved neural threat system that responds to imminent physical attack, implying that repeated exposure to crowds of strangers in close proximity may facilitate recurrent engagement of the amygdala[99] and downstream sympathetic and HPA stress systems, which may trigger the emotional reactions and defensive behaviors[100] that may lead to social conflict. Thus, it is plausible to propose that a core component of city risk is the combination of close physical proximity with fragmented social support and greater experience of adversity.

Although the causal composite features of urbanicity await verification, recent neuroscience work in healthy human adults used magnetic resonance imaging (MRI) to study neural alterations relating to exposure to urban environments[101, 102]. On the functional level, the size of the community of residence was found to correspond to the extent of amygdala activation in a social stress challenge[101] (Fig. 2a). This observation supports the idea that the degree of urbanization of the immediate social environment has implications for the alertness of the neural threat response system. In contrast, the degree of exposure to urban environments in the first 15 years of life was associated with increased pACC activation[101] (Fig. 2b) and decreased gray matter volume in the prefrontal cortex. In addition, urban upbringing related to decreases in pACC volume in males[102] (Fig. 2c), who also show disproportionately higher rates of schizophrenia incidence in the context of urban upbringing. Because the ACC and prefrontal cortex are

also prime neural regions for structural and functional alterations in first-episode schizophrenia[103], these data are consistent with the proposals that urban upbringing alters the development of higher-order stress regulatory areas and that these abnormalities converge in brain regions that plausibly relate to the pathophysiology of schizophrenia. Moreover, the association of urban upbringing and reduced pACC volume in males is consistent with the idea that sex differences in the development of stress-regulatory brain areas may relate to sex-related periods of vulnerability to disturbance by psychosocial stressors (see also the contribution of Bale *et al.*[104] in this issue).

Figure 2: Neural correlates of urban life.



(**a**) Amygdala activity during social stress processing is highest in individuals residing in cities, intermediate in those residing in towns and lowest in those residing in rural areas. *$P \leq 0.05$; error bars, mean ± s.e.m.(**b**) Activity in the perigenual anterior cingulate cortex (pACC) during social stress processing correlates positively with urban exposure during upbringing. Images (**a**,**b**) adapted from ref. 101 (Nature Publishing Group). (**c**) Gray matter volume in the pACC correlates negatively with urban exposure during upbringing, specifically in males (image adapted from Haddad, L. *et al*. Brain structure correlates of urban upbringing, an environmental risk factor for schizophrenia, *Schizophr. Bull.* 2015, **41**, 1, 115–122, by permission of Oxford University Press)[102].

Poverty.

Poverty is one of the strongest predictors of social disadvantage and shows clear relationships to urban living and ethnic minority status. About 16% of the Western population is at risk of poverty, with rates exceeding 30% among single parents[105, 106].Numerous studies have shown that poverty is associated with a range of environmental risk factors, such as exposure to life stress[107] and substances[107], poor social support[108] and lack of access to resources[109] such as nutrition or education. A recent study provided an example of how poverty affects mental health and neural markers of vulnerability. In an epidemiological cohort followed from birth[107], early life poverty, as assessed at 3 months, predicted higher levels of conduct disorder symptoms during adolescence. In neuroimaging, individuals exposed to early life poverty showed decreased volume in the orbitofrontal cortex, a key regulatory region involved in emotion and reward processing. Furthermore, the association between poverty and conduct disorder was mediated by orbitofrontal cortex volume, suggesting a neural trajectory encompassing early adversity, compromised motivational and affective regulation and risk for psychopathology[107]. A link to the neural systems critical for regulation of stress was suggested by the findings of Luby *et al.*[108], who found that smaller amygdala and hippocampal volumes in poor children were mediated by caregiver support and stressful life events. Functional neuroimaging data in adults who were poor as children show reduced prefrontal activity during emotion regulation mediated by chronic stress exposure[110] and less default-mode network connectivity, which was inversely related to stress reactivity[111].

Air pollutants.

Another trigger for the detrimental neural effects of urban environments receiving increased attention is exposure to ambient pollution[112]. The urban atmosphere, especially in many megacities, contains a complex mixture of air pollutants such as fine particulate matter, polycyclic aromatic hydrocarbons (PAHs), lead and ozone. In humans, long-term exposure to air pollutants relates to higher odds of stroke, covert infarctions and brain atrophy[113]. Similarly, there is a dose-response relationship between the extent of prenatal exposure to PAHs and reductions in brain white matter volume, cognitive impairment and increases in symptoms of attention-deficit–hyperactivity disorder[114]. Animal studies have provided critical insights into the mechanisms of the observed associations: air pollutants may translocate to the central nervous system through nasal epithelial and alveolar capillary dysfunction and blood-brain barrier breakdown, thereby eliciting adverse neuroinflammatory and autoimmune responses[115]. Reported outcomes include microvascular damage, decreased dendritic spine density and branching in the hippocampus[116] and high expression of neurodegenerative marker proteins such as α-synuclein and amyloid-β in the midbrain and frontal and temporal lobes[117]. Thus, although current

research on the effects of ambient pollution tends to be centered on respiratory syndromes, these data suggest a mechanism for the effects of urban life on neural development that seems to operate through different biological mediators than stress-related psychosocial factors but may affect overlapping neural systems, causing additive effects.

Nature experience.

One obvious difference between the city and the countryside is the amount of available green space. Natural environments are a source of relaxation and regeneration and enhance human well-being. A growing body of literature shows that exposure to natural landscapes or their composite features, such as plants and animals, has beneficial effects on a variety of outcomes, including child development, well-being, physical and mental health, mood, morbidity, recovery from illness and mortality[118, 119, 120]. Although the topic is still under-researched, meta-analytic data suggest that physical activity in nature improves perceived energy and attention and reduces negative feelings such as anxiety, fatigue, anger and sadness[121]. The psychological benefits of nature experiences seem to translate to urban green spaces, especially those with high biodiversity[122]. One large-scale epidemiological study[120] showed a dose-dependent relationship between the abundance of green space and human health, with larger percentages of accessible green space in a 3-km radius around residents' homes relating to higher rates of self-perceived good health, particularly for people with fewer prospects for roaming beyond this radius (such as minors, elderly people or people with low socioeconomic status). Not surprisingly, the study also suggests that the disparities in perceived health between urban and rural dwellers can be explained partly by the varying amounts of green space in their living environments[120].

But what gives rise to these benefits? Is it the relative absence of risk factors such as social stressors, noise and pollution, or are there genuinely salutary aspects to natural environments that promote well-being? The neuroscience data are sparse, but psychoevolutionary theories have posited that humans are drawn to sounds such as birdsong or breaking waves and to sights such as colorful foliage as a result of natural selection because such experiences have signaled the presence of prey and the opportunity for shelter, tranquility, comfort, recovery from stress and restoration of attentional resources across human evolution[118].

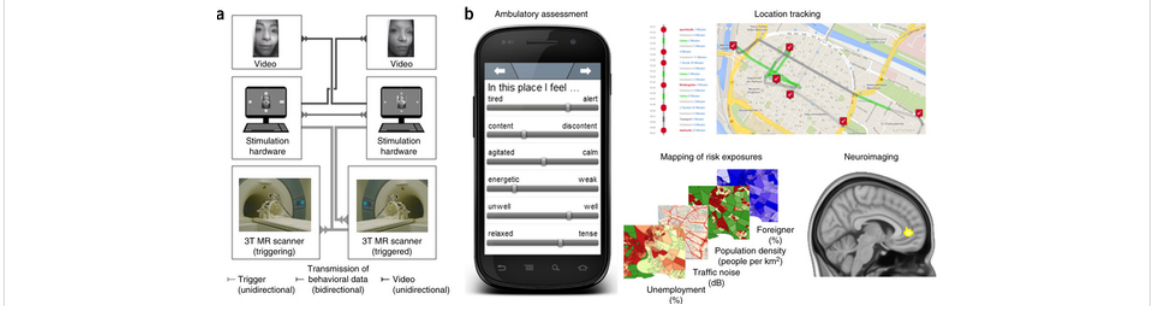
Research on and exposure to nature as a protective factor has a tradition in East Asian countries such as Japan. A particularly popular practice is Shinrin-yoku, a stress-management routine whose name translates to 'making contact with and taking in the atmosphere of the forest' or 'forest bathing'[123]. Although the empirical evidence base is small, both passive viewing of woody landscapes and active exploration of forest environments have been related to short-term beneficial effects on HPA and sympathetic stress markers, including salivary cortisol, systolic blood pressure and heart rate[123]. It is plausible that these effects could translate to other natural environments and that repeated nature exposures may foster resilience through effects on higher-order control areas of the human neural stress circuitry, but no corresponding empirical data are available to date. Current neurobiological evidence on the beneficial effects of nature experiences is restricted to reports of lower prefrontal hemoglobin concentrations during forest walking[124], an observation indicative of relaxation. Thus, although the salient composite features of nature experiences await identification and the physiological and neurobiological effects require further study, the existing data suggest that human contact with nature is more than an aesthetic luxury and could be used to mitigate health disparities and urban effects.

Ecologically enhanced methods for social neuroscience

Many environmental exposures related to mental health outcomes involve multiple individuals interacting in contexts that are socioculturally complex as well as physically differentiated. Efforts to further define the neural substrate of social-environmental influences in humans face at least two critical methodological challenges. First, although the whole-brain neural circuit account of most pathophysiological models calls for neuroimaging as the method of choice, data acquisition during naturalistic social interactions is limited by the spatial and physical constraints of the MRI setting. Second, experiments that expose people to real-life social risk factors would be ethically problematic and often not feasible, given the time scale of the naturalistic exposures and their neural consequences[125].

Most neuroimaging studies on the processes underlying social interactions in humans to date have been of limited external validity. The experiments have typically focused on neural activity in one participant responding to experimental stimuli in scenarios that emulate social contact (through, for example, recorded videos or computer avatars). Recently, and building on earlier efforts[126], an enhanced version of a neuroimaging setup termed hyperscanning was developed, and this method overcomes some of these prior limitations[127]. A hardware setup is established in linked MRI scanners to allow the immersive audiovisual interaction of two individuals through live video stream and delay-free data transmission while the brains of both participants are scanned in a precisely synchronized fashion (Fig. 3a). The method was validated using a joint attention paradigm and a data-driven analysis approach that identified cross-brain connectivity components of dyadic interactions that were unique to real interacting (as opposed to randomly assigned) human pairs. Although the approach is costly, it could be extended to study social groups in the context of asymmetrical and asynchronous social interactions. This would provide a good entry point for a more naturalistic examination of health-related social processes such as social support, ostracism or the establishment of social hierarchies.

Figure 3: Ecologically enhanced methods for social neuroscience.



(**a**) Hardware environment for functional MRI hyperscanning enabling delay-free data transmission, synchronized data acquisition and live video streaming between scanner sites to study real-time human social interaction. Adapted from ref. 127 (NAS). (**b**) A multimodal approach for the study of the neural correlates of real-life environmental risk exposures through a combination of neuroimaging with the real-time acquisition of position data, multivariate geographical mapping of natural risk sources and EMA of stress-related psychological variables (MovisensXS platform, Movisens GmbH). Map sources: GeoBasis-DE/BKG, Google (location tracking); OpenStreetMap contributors and City of Mannheim Office of City Planning (traffic noise); Nexiga LOCAL (unemployment percentage, population density and foreigner percentage).

The second challenge can be partially addressed through the combination of neuroimaging with frequent and spatially tagged assessments of psychological measures that capture, for example, dynamic variations in stress-related event appraisal and mood in everyday life. The ecological momentary assessment (EMA)[128, 129] is a promising technique that uses a smartphone app to obtain psychological data in real-time and real-life contexts (Fig. 3b). A recent neuroimaging study highlighted the value of the method for neuroscience research[130]: EMA was used to quantify the duration of real-world positive affect to winning a game in naturalistic settings. The authors show that individuals with a prolonged positive affect show a more sustained engagement of the ventral striatum to rewards in the functional MRI environment, a finding that sheds light on the neural basis of emotional functioning and well-being in everyday life. Simultaneous acquisition of position data and geographical maps (for example, of land use or sociodemographic characteristics of the environment) can extend the approach by informing and triggering EMA acquisitions in locations where epidemiology has highlighted the presence or absence of natural risk exposures. Combined with a large-scale longitudinal study of different age cohorts, the approach is expected to provide novel insights into the neural substrate of social-environmental influences.

In rodents, the importance of an enriched living environment for experience-dependent brain plasticity has been purported for decades[131] but is increasingly recognized in recent literature[132]. Environmental enrichment refers to housing conditions that provide more opportunities to interact with the environment than are found in standard conditions. Typical enrichments include the provision of running wheels or toys or rearing in large groups of conspecifics, which result in enhanced sensory, cognitive, social and motor stimulation. Histological studies have demonstrated that environmental enrichment influences the morphological features of neurons such as the number of dendritic spines and the branching and length of dendrites[133, 134, 135]. A recent neuroimaging experiment in adult rodents demonstrated that even short periods of environmental enrichment result in rapid volumetric changes in brain areas controlling spatial memory, navigation and sensorimotor functions (for example, the hippocampus and sensorimotor cortex)[136]. Because standard housing conditions lack key features of the natural habitat of rodents, an interesting question that arises from these data is whether the biological mechanisms inferred from experiments using animals kept in standard housing reflect 'normal' experience-dependent brain plasticity or brain plasticity under impoverished living conditions[137, 138, 139]. As it moves toward the broader implementation of enriched environments in rodent research, the neuroscience field faces at least two major challenges, namely the inconsistency of current enrichment protocols and the difficulty of assessing real-time data in complex environments. The first challenge is increasingly being addressed through detailed open-source information on specific enrichment protocols such as the Dynamic Maze for Environmental Enrichment of Rodents (http://www.mouseimaging.ca/technologies/maze.html). The second challenge is addressed in part by a technological solution that allows for real-time data acquisition in multiple animals in semi-naturalistic environments[140]. The method, which is based on video and radio frequency tracking data and automated phenotyping algorithms, enables detailed study of dyadic and collective social interactions in rodents under enriched environmental conditions. As with human neuroscience research, these efforts are expected to enhance the ecological validity of studies on the neural consequences of complex environmental exposures.

Conclusions

Though genetic influences on brain development and risk and resilience have occupied center stage in research, the study of environmental influences has recently gained traction. We have reviewed a variety of factors related to the social world that can have enduring (or at least discernible in adulthood) effects on the structure, connectivity and function of neural circuits. While the social-environmental factors vary in structure, duration, time of impact and, arguably, the degree to which they have been specified, the neural system they affect tends to include key structures for the regulation of the stress response, notably amygdala, hippocampus and prefrontal regions closely linked to these structures. In turn, convergent evidence shows that these circuits are the target of prosocial hormones such as oxytocin in animals and probably also in humans. Furthermore, genes that interact with the environment and can be linked to social influences, such as the common 5-HTTLPR polymorphism in *SLC6A4* (which encodes serotonin transporter) or near the promoter for *MAOA (*encoding monoamine oxidase A), also affect these circuits. This suggests a convergent, systems-level account of social risk that should be studied further.

One aspect we have highlighted here is that social experiences are embedded in the larger environment and interact with factors such as urbanicity and modern problems associated with it, such as air pollution, but also, potentially, with evolutionarily ancient representations and preferences for a natural habitat. Future work in this area should highlight aspects of the urban environment that further enhance resilience to stress and mental illness. Progress in this area will require cooperation among a variety of disciplines and the incorporation of new technological opportunities afforded by, for example, momentary environmental assessments with portable sensors in smartphones or other wearable devices. We expect that neuroscience will have a relevant role in these efforts to identify environmental targets for prevention, because methods such as neuroimaging under stress permit, in principle, the measurement of quantitative risk markers in subjects who do not (yet) show signs of illness.

Another challenge for future work will be the development of animal models reflecting the complexity of environmental challenges in the modern human environment. As we discuss here, many of the key neural circuits affected by social stressors show strong cross-species homologies and do not, as a rule, primarily concern brain regions thought to be part of the uniquely human social brain. It should therefore be possible to make progress in modeling (at least some components of) environmental social risk beyond conserved behaviors such as attachment.

Much more so than the genome, the environment is modifiable. A continued study of risk and resilience mechanisms thus offers the hope of preemptive approaches to psychiatric disorders and of furthering well-being in a species challenged by the rapid environmental change its own activities engender.

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