Contextualizing adolescent structural brain development: environmental determinants and mental health outcomes

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Review

Contextualizing adolescent structural brain development: Environmental determinants and mental health outcomes

Lia Ferschmann[1], Marieke G. N. Bos[2,3], Megan M. Herting[4], Kathryn L. Mills[1,5] and Christian K. Tamnes[1,6,7]

Abstract

The spatiotemporal group-level patterns of brain macrostructural development are relatively well-documented. Current research emphasizes individual variability in brain development, including its causes and consequences. Although genetic factors and prenatal and perinatal events play critical roles, calls are now made to also study brain development in transactional interplay with the different aspects of an individual's physical and social environment. Such focus is highly relevant for research on adolescence, a period involving a multitude of contextual changes paralleled by continued refinement of complex cognitive and affective neural systems. Here, we discuss associations between selected aspects of an individual's physical and social environment and adolescent brain structural development and possible links to mental health. We also touch on methodological considerations for future research.

Addresses

[1] PROMENTA Research Center, Department of Psychology, University of Oslo, Norway
[2] Institute of Psychology, Leiden University, the Netherlands
[3] Leiden Institute for Brain and Cognition, Leiden University, the Netherlands
[4] Department of Population and Public Health Sciences, University of Southern California, USA
[5] Department of Psychology, University of Oregon, USA
[6] NORMENT, Institute of Clinical Medicine, University of Oslo, Norway
[7] Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway

Corresponding author: Ferschmann, Lia (lia.ferschmann@psykologi.uio.no)

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Brain structural development, Adolescence, Individual differences, Environmental factors, Mental health.

Introduction

From the pioneer quantitative structural magnetic resonance studies in the 1990s [1–4] to more recent large-scale and longitudinal work [5–9], our knowledge of how the human brain continues to develop across adolescence has gradually increased. This progress has been propelled by improvements in both image acquisition and analysis and by the curiosity and ingenuity of researchers asking new questions and applying new approaches. We now have detailed models of the spatiotemporal group-level patterns of typical changes in brain structure from childhood to adulthood [10,11].

Through multisite collaboration including longitudinal data sets from different countries, our research has shown consistent patterns of brain structural development. In the second decade of life, these developmental patterns are characterized by steadily decreasing cortical gray matter volume and a decelerating increase in white matter volume [12]. The dominant contributor to the adolescent cortical volume reductions is widespread thinning which is most pronounced in the parietal lobe, rather than the comparably smaller decreases in surface area [13]. Subcortical gray matter volumes, in contrast, show less consistent developmental patterns across structures, samples, and sex [14]. Studies using longitudinal data and modeling approaches that go beyond group-level patterns and probe the heterogeneity of structural brain development in adolescence have been called for [15,16], and recent work has begun to characterize how the substantial interindividual variability in adolescent structural brain development changes over age [17]. Here, we argue that what is now additionally needed is to contextualize individual differences in brain development within a broader developmental science that emphasizes the interconnectedness of the individual and their environment [18]. In this article, we focus on the following questions: what external factors shape an individual's brain development? and how does the dynamic unfolding of individual differences in brain development relate to adolescents' current well-being and lifelong patterns of mental health?

Search for influential environmental factors must consider the fact that twin and family studies have

established that brain structure is highly heritable [19]. A recent genome-wide association meta-analysis found that common genetic variants explained 34% of the variation in cortical surface area and 26% in cortical thickness. The authors also suggest that surface area is influenced by variants that change gene regulatory activity in neural progenitor cells in fetal development, whereas thickness is influenced by active regulatory elements that may reflect processes observed later during development; myelination; pruning; and branching [20]. As documented for cognition [21], genetic and environmental influences on brain structure likely interact through transactional processes in different ways across time and space, see Figure 1. New theoretical models suggest pathways in which the environment may alter neurodevelopment. For example, a recent model by Tooley et al. [22] proposes that environmental factors can affect the *pace* of brain maturation, that is, with negative contextual factors (particularly when these factors are long-lasting) resulting in accelerated brain development, reduced plasticity, and subsequently less efficient cortical networks.

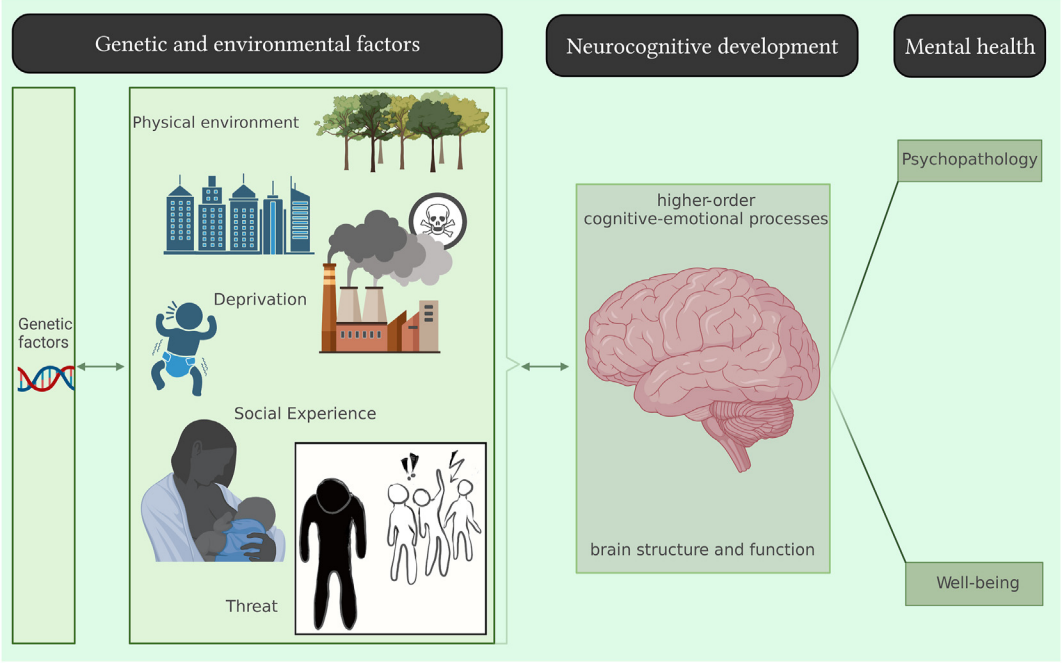
We note that although many recent studies have examined associations between aspects of socioeconomic inequality and child brain structure and functions [23,24], genetically informed studies involving causal modeling are ultimately needed to determine the relative importance of social causation and social selection (for further discussion see work by Farah [25]). Moreover, longitudinal studies of proximal factors in the physical and social environment are necessary to identify the specific mechanisms involved. Thus, although caution is warranted in the interpretation of the existing literature, we believe that identifying modifiable environmental effects that impact neurodevelopment in children and adolescents is an important endeavor because practical application of this knowledge may translate into long-lasting improvements in mental health. In the following paragraphs, we will discuss how aspects of an individual's physical and social environment are related to brain structural development, as well as possible links to mental health. Selected methodological issues and future directions will be discussed throughout the text.

Effects of the physical environment

Although genes together with prenatal influences and processes set the stage for an individual child's brain structure, postnatal environmental factors can also impact aspects of brain morphometry and the pattern of the brain's structural development [26,27]. The context of the child's development includes both the physical and the social environment.

Recent efforts have shown that local contexts, such as urbanicity and neighborhoods, can influence the health and well-being of individuals [28]. Yet, the role of the

Figure 1



Genetic and environmental influences on neurocognitive development and pathways to mental health. A developing brain conceptualized in dynamic transactional interplay with the different aspects of an individual's physical and social environment. These associations may have lasting impact on mental health and well-being. The figure was created with BioRender.com.

physical environment, or 'place,' has arguably been understudied in psychology [29] and neuroscience. More than half the world's population lives in cities [30], which are composed of diverse neighborhoods and communities. Whereas urban environments can provide access to important medical, cultural, and institutional resources, living conditions within urban areas vary by social strata, race, and ethnicity [31]. Recent studies suggest that characteristics of the child's neighborhood also matter for neurodevelopment. For example, neighborhoods characterized by poverty and unemployment have been associated with worse neurocognitive performance and smaller brain structure in children across the United States [32], even after accounting for the family's socioeconomic position. Interestingly, what mattered the most were the local differences in neighborhood disadvantage within each city, rather than how cities differed in neighborhood disadvantage from each other, suggesting an important role of relative poverty. Although emerging studies such as this indicate that the local context is important to consider in regard to brain development and mental health, questions still remain as to the mechanisms underlying why neighborhoods matter. For example, disadvantaged neighborhoods may have a lack of social and educational opportunities, access to quality health services, nutritional foods, and parks and recreation facilities, as well as result in greater exposure to pollutants, environmental toxins, or social stressors. Recent findings suggest these factors in and of themselves, including air pollution [33–35], greenspace [36,37], and noise pollution [38], are linked to brain development and mental health in children and adolescents. Given that many of these urban environmental factors are common but can also be reduced or mitigated, this emerging area of research may have the potential to impact environmental regulations and public policy to improve each child's neurodevelopment and long-term health.

Moving forward, large longitudinal studies are needed to assess long-term effects of the local environment and place-based disparities on neurodevelopmental outcomes and to determine whether developmental effects vary by sex, family-level socioeconomic status, and/or genetic factors with generalizable findings. To address these key questions about how our physical environment affects human brain health, we need large-scaled multicohort efforts, such as the new Environment working group within the enhancing neuroImaging genetics through meta-analysis ENIGMA consortium [39]. Specifically, the ENIGMA environment focuses on georeferenced environmental information based on an individual's residential address to begin to assess how the local environment may influence brain structure and function across the lifespan. The 44 participating cohorts span across 21 countries, with more than 43,000 individual participants, provide the ENIGMA environment an unparalleled reach of both geographical and sociodemographic diversity to examine the potential heterogeneity in the local context on brain health worldwide in a robust and rigorous way. Given that the local environmental context in urban cities and local communities can be modified, further individual or consortium-based studies aiming to elucidate what a healthy place means for brain development have the potential to identify preventable and modifiable behavioral and policy interventions that could help ensure all children reach their maximal potential.

Effects of social experiences

Developmental changes in human brain structure should also be considered in conjunction with social environmental factors. This might be especially crucial not only in the infancy period of attachment [40] but also during the adolescent period of social reorientation [41]. Social contexts ranging from immediate influences, such as the caregiving environment [42], to broader contexts such as socioeconomic status [43], have been found to relate to brain structure in adolescence. However, there are few longitudinal investigations characterizing how social contextual factors relate to patterns of structural brain development. We highlight a few below, as well as approaches to address key questions regarding how the social environment shapes brain development in adolescence.

Studies of broad social contexts such as poverty have shown that the pace of early brain development differs between children living in low and high resource contexts [44]. More proximal social influences, such as the experience of adverse early caregiving environments, have recently been shown to relate to the developmental patterns of amygdala volume across childhood and adolescence [45]. Structural development of cortical regions involved in mentalizing varies between adolescents who experience different levels of quality in close friendships [46]. Observed changes in structural brain development during adolescence reflect the continued brain plasticity of this period and opportunities in terms of adaptive fine-tuning of the organism's system [47]. Even though there are emerging investigations on how social experiences relate to brain development, future work would benefit from testing how the timing of these experiences relates to differences in brain developmental patterns.

One social contextual factor understudied in developmental cognitive neuroscience is the experience of racism. Race and ethnicity shape children's and adolescents' social experience with the world [48]. Recent meta-analyses have demonstrated that racial/ethnic discrimination is related to negative outcomes across multiple developmental domains, and these effects are particularly strong in adolescence [49]. As affiliation with some racial or ethnic groups may carry a risk of experiencing rejection and social marginalization, we

hypothesize that experiences of discrimination may represent a form of chronic social stress that may impact adolescent brain development.

With any examination of how a particular factor relates to differences in brain development, we encourage researchers to avoid a deficit model. Even if the social contextual factor is by definition a negative experience, this does not necessarily equate to a maladaptive pattern of brain development. When possible, including a functional outcome may help disentangle brain developmental processes reflecting positive adaptation to difficult contexts from those which might reflect brain mechanisms linking negative social experiences to negative outcomes.

Connecting environmental influences, structural brain development, and mental health

Mental health problems, such as social anxiety, mood problems, and substance abuse, often have their onset during adolescence [50]. Adolescent-onset mental health problems set the stage for mental health and well-being across the lifespan and highlight the urgent need to understand why some adolescents are more vulnerable to develop problems. Central to understanding the onset and maintenance of mental health problems across adolescence and beyond is to take an ecological neuroscience perspective [51]. Linking the impact of physical and social environmental influences on neurocognitive development and examining how this complex interplay contributes to the risk of negative mental health outcomes may give us insights into the balance between mental well-being and ill-being and facilitate optimized prevention and intervention programs.

Longitudinal work has focused on understanding the relations between development of brain structure and the emergence of specific symptomatology, such as depression [52,53], aggressive behavior [54], or psychotic symptoms [55]. In a similar vein, studies focusing on the more general distinction between internalizing and externalizing problems show associations with distinct developmental trajectories of cortical and subcortical structures [56,57]. Yet, the specific brain regions involved and direction of the developmental effects (i.e. accelerated versus attenuated) differ between studies, and overlapping brain regions are also implicated in different mental health problems. These differences might be explained by differences in sample size characteristics (age, sex, pubertal timing, symptom severity, high comorbidity between disorders) or methodological differences, such as study design or statistical modeling. Nevertheless, although the specific patterns remain to be established, timing in brain maturation — whether accelerated or delayed — is assumed to be a risk factor for negative mental health outcomes [58].

An exciting task for future research is to quantify and describe which individual differences in brain structural development represent atypical brain development and determine the magnitude of the impact of environmental factors on the developing brain. It is essential to assess the observed effect of an environmental influence in relation to the magnitude of change expected, as well as the degree of variability present, in a given developmental stage. Another promising approach is to identify individual atypicality by using normative modeling [59]. This statistical technique allows for determining heterogeneity in, for example, mental health problems by providing mappings between quantitative biological measures (e.g. cortical development) and clinically relevant variables. This allows for identifying whether an individual can be seen as an extreme case (i.e. atypical) by comparing it to the full range of variability within a typically developing population. Normative modeling is a bottom-up approach and therefore has the opportunity to identify the variables that might be key to explain mental health problems but lacks the opportunity to test for its potential causal mechanism. In addition to this data-driven and big-data method, we need hypothesis-driven research to empirically test new theories on the complex interplay between environmental factors, brain development, and risk to mental health problems.

One such example of a conceptual model which proposes a testable framework based on an ecological neuroscience perspective attempts to conceptualize how environmental factors are associated with negative mental health outcomes while taking neurobiology and psychosocial processes into account [60]. More specifically, the authors argue that we should adopt complex analytic models that take into account the different aspects of poverty, bidirectional associations between self-regulatory behavior and the brain, and longitudinal links to psychopathology. Future work also needs to use methods that facilitate causal inference. Identifying causal sequences originating in an individual's physical and social environment that impact neurodevelopment and later psychopathology may inform policymaking because many of the environmental conditions under which children develop are modifiable. However, gene—environment correlations represent a major challenge in these efforts. As already stated, genetically informed studies involving causal modeling, including moving beyond observational studies and using natural and quasi-experimental studies, are needed to determine the relative importance of social causation and social selection. In addition, further studies of proximal factors in the physical and social environment are needed to identify the specific mechanisms linking broad contextual factors, adolescent brain development, and mental health. Finally, further examining the impact of different environmental influences as a function of when in

development they occur may be highly informative for policy and prevention efforts.

Conclusion

The past decades of *in vivo* neuroimaging of healthy developing samples have provided us with knowledge of how different brain structural metrics on average develop at different ages. Recent work has moved beyond studying group-level differences and started to characterize the individual differences in brain development. We propose that future research should focus on contextualizing these individual differences in brain development in relation to physical and social environmental factors and mental health outcomes. Key research challenges for future studies include identification of environmental factors with causal effects on neurodevelopment, whether and how the timing of these influences matter, and to distinguish when such neurocognitive changes represent a positive adaptation to a difficult environment or when they represent vulnerability to psychopathology.

Conflict of interest statement

Nothing declared.

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