Socioeconomic Disadvantage, Chronic Stress, and Hippocampal Subfield Development in Children

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ABSTRACT: Recent findings indicate that hair cortisol concentrations significantly mediate associations between socioeconomic disadvantage and reduced hippocampal CA3 and dentate gyrus volumes in children. In this commentary, we discuss these results and highlight important future research directions, including focusing on hippocampal subfield structural development in relation to episodic memory and mental health; the mechanistic role of excitatory amino acids, such as glutamate; and how chronic stress and cognitive stimulation may make unique proximal contributions to socioeconomic differences in hippocampal subfield volume. Building on the findings in these ways will contribute to advances in strategies aimed at reducing socioeconomic disparities in academic achievement and mental health.

KEYWORDS: Dentate gyrus, hippocampus, childhood adversity, cortisol, memory

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Socioeconomic inequality is currently at an extremely high level in the United States, with an increasing number of children living in families below the poverty threshold. Children exposed to socioeconomic disadvantage demonstrate lower academic achievement and are at increased risk for emotional and behavioral problems that persist over time.[1] Socioeconomic disadvantage is a distal contextual factor thought to exert its effects through more proximal factors, including exposure to chronic stressors (eg, neighborhood violence, noise/crowding, household chaos, and family turmoil).[2] Early interventions have shown promise as powerful strategies for reducing socioeconomic disparities in academic achievement and mental health. Understanding the proximal and neurobiological mechanisms underlying the effects of socioeconomic disadvantage is a key step toward the design of more targeted and effective prevention and intervention strategies.

Socioeconomic disadvantage has been consistently associated with smaller volume in the hippocampus,[3] a subcortical structure crucial to learning and memory[4] and strongly implicated in psychiatric disorders including depression.[5] The hippocampus is particularly vulnerable to the effects of chronic stress. Animal models indicate that chronic stress early in life has powerful and lasting effects on hippocampal structure and function. Moreover, the hypothalamic-pituitary-adrenal (HPA) axis plays an important mechanistic role in these effects, which vary across hippocampal subfields, including the cornu ammonis 1-4 (CA 1-4) subfields, dentate gyrus, and subiculum. Chronic stress and high levels of glucocorticoids exert particularly pronounced effects on the structure of the CA3 and dentate gyrus subfields, causing dendritic remodeling in CA3 neurons and inhibiting neurogenesis in the dentate gyrus.[6,7] Many effects of chronic stress in the hippocampus are mediated by glucocorticoid receptors, which are densely expressed in the CA1 subfield and dentate gyrus.[8] Glucocorticoid hormones suppress neuronal excitability and impair long-term potentiation in CA1 and dentate gyrus, affecting the consolidation of emotionally salient information.[9] Ultimately, impaired hippocampal function may lead to further increases in glucocorticoids as the subiculum is critical for negative-feedback control over the HPA axis.[10] However, in humans, the role of chronic stress as a mechanism through which socioeconomic context may impact hippocampal volume is not well understood.

In this commentary, we summarize our recent findings indicating that hair cortisol mediates socioeconomic differences in hippocampal subfield volume in children.[11] We then discuss these results and highlight important directions for future research in 3 sections. First, we discuss the implications of these findings for understanding socioeconomic differences in cognition and mental health. Second, we focus on the possibility that socioeconomic background may impact glutamate in stress-susceptible neural networks. Third, we cover the potential for chronic stress and cognitive stimulation to play unique roles in the mechanisms underlying socioeconomic differences in hippocampal structure.

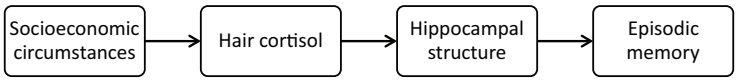

Figure 1. Model of the neurobiological mechanisms underlying the effects of socioeconomic context on episodic memory during childhood. Socioeconomic circumstances were hypothesized to affect hair cortisol, which would lead to altered hippocampal structure and in turn differences in episodic memory.

Hair Cortisol Mediates Socioeconomic Differences in Hippocampal Volume

In Merz et al,[11] we examined the associations among socioeconomic factors (family income-to-needs ratio, parental education), hair cortisol, the volume of the hippocampus and its subfields, and episodic memory in 5- to 9-year-old children from socioeconomically diverse families (see Figure 1). Thirty percent of the sample was living below the U.S. poverty threshold. Hair cortisol concentrations provide a measure of the accumulation of cortisol over a period of months. Hippocampal subfield volumes were measured using a reliable automated segmentation technique in FreeSurfer 6.0. Findings indicated that lower parental education was significantly associated with smaller total hippocampal volume, CA1 volume, and dentate gyrus volume. Higher hair cortisol concentrations were significantly associated with smaller volume in the CA3 and dentate gyrus hippocampal subfields, but were not significantly associated with CA1 or subiculum volume.[11] Furthermore, higher hair cortisol significantly mediated the association between lower parental education and smaller CA3 and dentate gyrus volumes. These results suggested that elevated hair cortisol levels were associated with the greatest volumetric reductions in hippocampal subfields previously identified as stress-sensitive in translational studies. Findings were consistent with the possibility that elevated cortisol may be part of the mechanism through which socioeconomic disadvantage influences hippocampal structure in children.

Implications for Socioeconomic Differences in Cognition and Mental Health

Findings from this study may have important implications for socioeconomic differences in cognition and mental health. Altered hippocampal structural development may be part of the mechanism through which childhood socioeconomic disadvantage (1) alters learning and memory development and (2) increases risk for depression and anxiety across the lifespan.

Learning and memory

Although hippocampal volume has been associated with memory in children and adolescents,[4] in our study, total hippocampal volume and hippocampal subfield volume were not significantly associated with episodic memory task performance in children. These findings may be partially attributable to differences in these associations across development.[4] Indeed, structural hippocampal development continues through childhood and adolescence.[12,13] The hippocampus develops in an inverted U-shaped trajectory across childhood and adolescence, with volumetric increases during childhood and into early adolescence and plateauing then decreases during late adolescence. And, these developmental trajectories have recently been discovered to vary by hippocampal subfield.[13] Moreover, in a 4- to 8-year-old sample, associations between CA1 volume and memory were moderated by age.[12] Hippocampal subfield volumes were found to increase with age in our 5- to 9-year-old sample, especially in the CA3 and dentate gyrus subfields (see Figure 2), although there were no significant age × hippocampal subfield volume interactions for memory. Collectively, these findings point to longitudinal studies as an important next step in understanding these associations. Longitudinal research is needed that focuses on the effects of socioeconomic background on hippocampal structural development and memory during childhood.

Mental health

The impact of socioeconomic disadvantage on hippocampal subfield structure during childhood may contribute to an increased risk for depression and anxiety, with depression spiking in prevalence during adolescence. The hippocampus is heavily involved in the formation of memories in emotional contexts and emotional memory retrieval. Converging evidence from animal models and human studies has shown associations between hippocampal structure and function and contextual fear conditioning and extinction.[14,15] Indeed, connections among the hippocampus (especially the ventral hippocampus), amygdala, and vmPFC have been found to be involved in fear memory formation and extinction.[16] Future studies are needed that focus on socioeconomic background, hippocampal subregional development, and emotional memory processes during childhood, as a precursor to the onset of depression in adolescence.

Mechanistic Role of Glutamatergic Neurotransmission

Findings from Merz et al[11] suggest a role for elevated cortisol in the mechanisms through which socioeconomic disadvantage may lead to reduced hippocampal volume. Another important mechanism through which these effects may occur centers on excitatory amino acid neurotransmitters, such as glutamate. In animal studies, chronic stress has been found to impact both glucocorticoids and glutamatergic neurotransmission in the hippocampus and in turn impact hippocampal structure.[7,17] For example, excitatory amino acids have been found to be involved in the suppression of neurogenesis in the

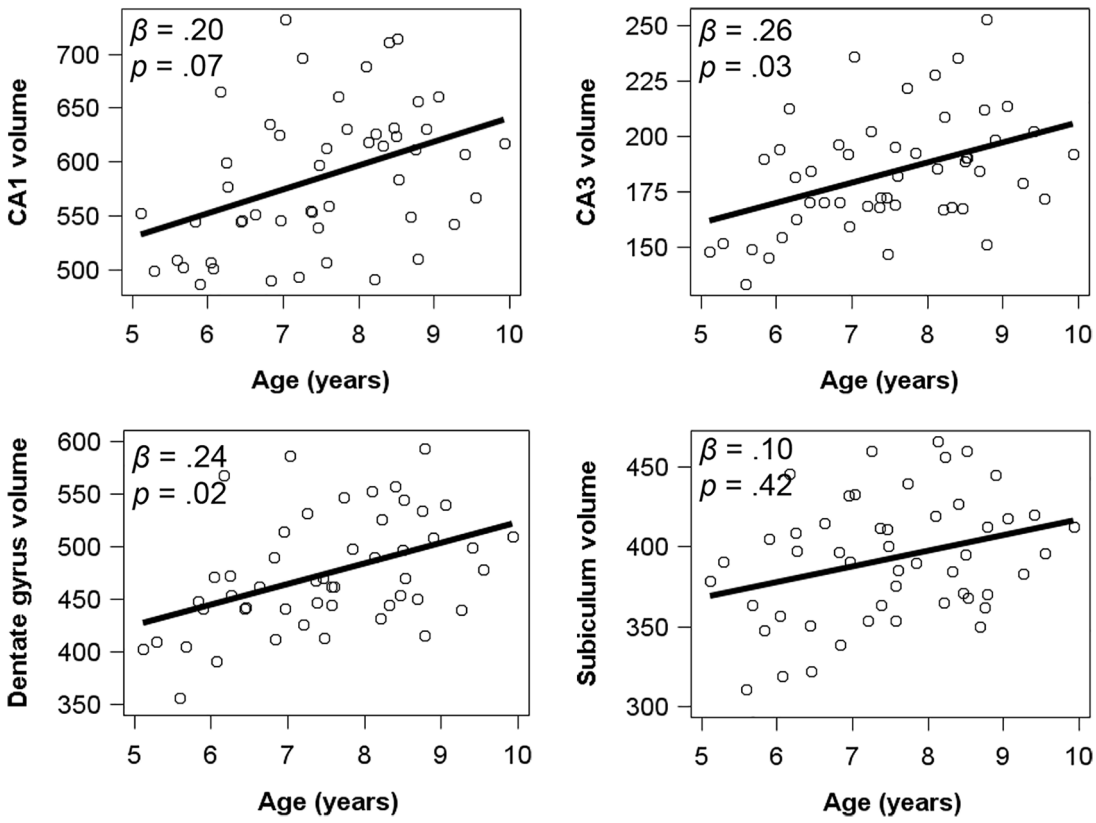

Figure 2. Hippocampal CA3 and dentate gyrus volume (mm^3) increased significantly with age in 5- to 9-year-old children. Regression analyses controlled for sex, parental education, and whole brain volume. Volumes were averaged across the right and left hemispheres.

dentate gyrus.[18] There is also evidence that elevated glucocorticoids impair glial clearance of synaptic glutamate, potentially causing spillover and increased extracellular glutamate levels. Prolonged glutamate exposure causes excitotoxicity, which then leads to neuronal atrophy and reduced neurogenesis in the hippocampus.[19,20]

Concentrations of brain metabolites, such as glutamate, can be measured in vivo in humans using proton magnetic resonance spectroscopy (^{1}H-MRS). Yet, the associations of socioeconomic disadvantage and chronic stress with glutamate concentrations in the hippocampus are not well understood. Beyond hippocampal volume, altered glutamatergic neurotransmission has also been implicated in other outcomes associated with exposure to socioeconomic disadvantage, including differences in PFC structure and depression. Indeed, studies using ^{1}H-MRS in humans have repeatedly implicated glutamatergic neurotransmission in the pathophysiology of psychiatric disorders, such as depression.[21] Taken together, future studies should examine the effects of socioeconomic disadvantage on glutamate concentrations in the hippocampus and address whether differences in glutamate concentrations may partially explain socioeconomic effects on hippocampal volume and in turn memory and mental health. Understanding these associations would shed light on the mechanisms underlying socioeconomic differences in hippocampal structure, cognition, and mental health.

Cognitive Stimulation as a Proximal Factor

In addition to chronic stress, cognitive stimulation is another proximal factor through which socioeconomic context may impact hippocampal structure. Socioeconomic disadvantage has been consistently associated with lower levels of cognitive stimulation in the home, including reduced toys, books, trips, and language input.[2] Animal models have shown that variability in cognitive stimulation influences hippocampal structure. For instance, environmental enrichment or complexity has been found to promote dendritic branching, synaptic density, and higher rates of neurogenesis in the hippocampus,[22,23] and in turn improve performance on tests of spatial learning and memory.[24] Together, these findings suggest that variability in cognitive stimulation may play a role in socioeconomic differences in hippocampal structure in humans. Thus, future research should study chronic stress and cognitive stimulation in conjunction with one another to disentangle their relative roles in socioeconomic differences in hippocampal structure and function. It is most important to test the effects of interventions that target these proximal factors (reduce chronic stress and/or increase cognitive stimulation) on hippocampal development in children. Such work would be poised to make causal inferences and shed light on the "active ingredients" needed for early interventions to be effective in reducing socioeconomic disparities in children's development.

Conclusions

In Merz et al,[11] we demonstrated for the first time that higher hair cortisol concentrations were associated with smaller hippocampal CA3 and dentate gyrus volumes in children, and hair cortisol partially mediated socioeconomic differences in the volumes of these hippocampal subfields. These findings extend our understanding of the stress-related mechanisms underlying the well-documented socioeconomic differences in hippocampal volume in children.[3] Based on these findings, important future research directions include focusing on developmental trajectories of hippocampal subregional structure in relation to episodic memory and mental health; the mechanistic role of excitatory amino acids, such as glutamate; and how chronic stress and cognitive stimulation may make unique contributions to socioeconomic differences in hippocampal volume. Set in motion by the current findings,[11] such research will inform the design of more effective strategies for reducing socioeconomic disparities in academic achievement and mental health.[25]

Author Contributions

EM, XH, BM, and KN contributed to the writing of this commentary.

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