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Behavioral Problems After Early Life Stress: Contributions of the Hippocampus and Amygdala

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ABSTRACT

BACKGROUND: Early life stress (ELS) can compromise development, with higher amounts of adversity linked to behavioral problems. To understand this linkage, a growing body of research has examined two brain regions involved with socioemotional functioning—amygdala and hippocampus. Yet empirical studies have reported increases, decreases, and no differences within human and nonhuman animal samples exposed to different forms of ELS. This divergence in findings may stem from methodological factors, nonlinear effects of ELS, or both.

METHODS: We completed rigorous hand-tracing of the amygdala and hippocampus in three samples of children who experienced different forms of ELS (i.e., physical abuse, early neglect, or low socioeconomic status). Interviews were also conducted with children and their parents or guardians to collect data about cumulative life stress. The same data were also collected in a fourth sample of comparison children who had not experienced any of these forms of ELS.

RESULTS: Smaller amygdala volumes were found for children exposed to these different forms of ELS. Smaller hippocampal volumes were also noted for children who were physically abused or from low socioeconomic status households. Smaller amygdala and hippocampal volumes were also associated with greater cumulative stress exposure and behavioral problems. Hippocampal volumes partially mediated the relationship between ELS and greater behavioral problems.

CONCLUSIONS: This study suggests ELS may shape the development of brain areas involved with emotion processing and regulation in similar ways. Differences in the amygdala and hippocampus may be a shared diathesis for later negative outcomes related to ELS.

Keywords: Abuse, Amygdala, Chronic stress, Development, Early life stress, Emotion, Hippocampus, Limbic system, Medial temporal lobe, Neglect, Neural plasticity, Neuroimaging, Poverty, Stress

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It is increasingly clear that early life stress (ELS) can compromise development, with research linking experiences such as child maltreatment or chronic poverty with behavioral problems, such as aggressive and oppositional behavior (1). Such problems are associated with substantial financial costs and sow the seeds for later psychopathology (2–4). To make inroads in conceptualizing, studying, and treating these problem behaviors, more recent work has focused on neurobiological risks (5–8). However, this research has not strongly focused on ELS. This gap is a major limitation because these behaviors often emerge after exposure to varying forms of ELS (9–25). To date, there have been very few investigations on the neurobiology of ELS and behavioral problems. These limited investigations have focused on brain regions involved in emotion processing and regulation, such as the prefrontal cortex (PFC), hippocampus, and amygdala (26). Consensus has begun to materialize regarding ELS and the PFC, with many studies reporting differences in this brain region after ELS (27,28). However, similar agreement does not exist for the hippocampus and amygdala, with inconsistent results being reported even in meta-analyses on the neurobiological effects of trauma (29,30). Resolving these inconsistencies is essential to understanding neural alterations associated with ELS and behavioral problems.

Divergence in these findings is not surprising when one considers that past human studies of ELS often relied on "natural experiments" focused on samples exposed to stressful experiences. These retrospective designs, although informative, have many significant limitations including the lack of random assignment. Working with multiple groups of children exposed to different forms of adversity is one fruitful way to overcome these limitations and has important advantages over past studies. First, limitations related to unobserved or unmeasured characteristics of specific stressful experiences can be minimized. For example, physical abuse is associated with familial poverty throughout development, more so than

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early neglect during institutionalization (31,32). Finding brain differences in both samples may indicate common neurobiological diatheses. Second, the timing, chronicity, and scope of stress may differ greatly between groups; however, the behavioral end-state (behavioral problems) is similar across populations. For example, children who experience early neglect commonly experience unresponsive caregiving and an overall dearth of individualized care and attention (33). In contrast, children who have been victims of physical abuse may interact with parents often, but these experiences may involve excessive physical aggression directed at the children (34). Examining different groups exposed to different forms of ELS is a powerful way to understand whether similar or unique patterns of neurobiological alterations put individuals at risk for behavioral problems.

Past research implicates the amygdala and hippocampus in basic socioemotional functioning, making them candidate brain regions for understanding behavioral problems following ELS. The hippocampus is involved in learning, memory, and the neuroendocrine response to stress (35,36). The amygdala is central to emotional and social information processing, with damage to this area leading to problems in evaluating the significance of social stimuli (37,38). However, major inconsistencies have emerged in research examining these structures in human and nonhuman samples exposed to stress (39).

Chronic stress causes reductions in dendritic spines and apoptosis of hippocampal neurons in adult nonhuman animals (40–42). In humans, one form of ELS, child maltreatment, is consistently related to smaller hippocampi in adults (30,43,44). Earlier in development while the hippocampus is still changing, these findings are less clear. Smaller hippocampi have been reported in children living in poverty (45–47) and children exposed to ELS such as parental separation or loss (48). However, no differences in hippocampi have been found in nonhuman primates separated from their parents (49), human children exposed to early neglect and later adopted into enriched environments (50–53), or human children who experienced abuse before being diagnosed with posttraumatic stress disorder (54–57).

For the amygdala, volumetric increases such as dendritic arborization in amygdala nuclei have been reported in adult rodents exposed to stress (58–61). However, structural neuroimaging studies examining amygdala volumes in humans have been inconclusive. In children exposed to early neglect, research reports have noted larger amygdalae (50,51) as well as no differences (52,53). Child poverty has been associated with larger (46) as well as smaller (47) amygdalae. Smaller amygdalae (62) as well as no differences (54–57) have been found in adolescents who experienced child maltreatment. Many previous investigations in humans (45,46,51,55,56) have had a large age range of participants (e.g., 5–15 years old); this is particularly important to note because amygdala development appears to be nonlinear in nature (63,64).

Divergence in results may also be due to methodological factors, such as magnetic resonance imaging (MRI) acquisition parameters or amygdala and hippocampal quantification procedures (65). For example, a review of amygdala quantification found the range of volumes was 1050–3880 mm^3, suggesting great variance in how researchers label these regions (66). Automated quantification of the hippocampus and amygdala also may be adding to inconsistencies in research findings. Methods such as FreeSurfer yield high variability and low validity for regions such as the amygdala (67,68), often changing study results (Supplement 1) (69). To resolve prior discrepancies, highly valid and reliable measures of the amygdala and hippocampus are needed across different groups exposed to different forms of ELS.

In addition to methodological factors, the effects of stress on the medial temporal lobe (MTL) may be nonlinear with different types of volumetric alterations depending on the timing and chronicity of stress (70–72). Understanding of the effects of ELS on the MTL has been primarily informed by nonhuman animal models employing chronic immobilization stress (CIS), although other nonhuman animal paradigms exist (73). Although informative, CIS models may be hard to translate to human samples, particularly in how to understand the long-term neurobiological sequelae of ELS. For example, research suggests the amygdala may adapt and function differently after increased dendritic arborization. Enlargement of amygdala volumes (58–61) and amygdala hyperactivity (74,75) result from CIS. McEwen (76) noted parallels between these findings and patterns of brain alterations in humans during initial episodes of major depression, where larger volumes and increased functional activity of the amygdala have been noted (77,78). McEwen further suggested that this hyperactivity might give way to eventual shrinkage, citing reports of smaller amygdalae after repeated depressive episodes (79). Similar ideas have been advanced and supported in research focusing on the amygdala and autism where volumetric overgrowths have been reported early in development, but smaller volumes have been noted later in life (72,80,81). In further support of this idea, more recent work employing CIS found a single, prolonged stressor caused apoptosis of amygdala cells (82).

Based on this body of evidence, ELS may result in an initial increase in amygdala volume along with increases in activity and excitatory neurochemistry. Such speculation fits with three research reports finding higher amygdala activity in children who experienced ELS (83–85). Over time, this excessive functional activity may lead to a loss of neurons (70,74). Individuals exposed to greater amounts of stress or exhibiting greater levels of impairments may have smaller volumes caused by this hypotrophy. In regard to the hippocampus, stress is theorized to be accompanied by a glucocorticoid cascade causing smaller hippocampi over time. Initial data suggest that hippocampal alterations may "reverse" over time, with previously detected differences not present after stress-free periods. However, differences in the amygdala are seen even after stress-free periods in nonhuman animals (86). Such models help in understanding nonlinear patterns seen in other trauma-exposed populations (87) along with inconsistencies seen in previous research. For example, work by Mehta *et al.* (50) found larger amygdalae in children exposed to early neglect (a type of ELS); however, these investigators found the amount of early neglect to which these same children were exposed was actually related to smaller amygdalae.

The present study examined different forms of ELS, employing the same quantification procedures for the MTL for children who experienced early neglect, experienced physical abuse, or were from low socioeconomic status