

Mother nurture and the social definition of neurodevelopment

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The quality of family life in childhood predicts the risk for multiple mental disorders, implying sustained effects on relevant brain circuits. Indeed, there is evidence for the idea that the social environment shapes individual differences in brain development and function. A limitation of this evidence is that most studies focus on extreme social adversity, such as parental deprivation (i.e., institutional rearing) or childhood maltreatment. Whether variations in parental care within the normal range are similarly relevant for human neurodevelopment remains unclear. Studies with rodents suggest so, but human brain development occurs within a more complex environmental context and over a longer period. In PNAS, Luby et al. (1) report the results of a prospective, longitudinal study that examined the association of maternal support at preschool and school ages, with hippocampal volume using MRI at three time points. A strength of the study is the laboratory-based assessment of maternal support during mildly stressful conditions, which very nicely mimics the challenges parents regularly face in child rearing. Maternal support at neither preschool nor school age emerged as a significant predictor of hippocampal volume, a finding consistent with cross-sectional studies showing that variations in maternal influences do not necessarily emerge as main effects in studies of neurodevelopment (2, 3). However, the unique, longitudinal approach of Luby et al. (1) reveals a compelling association between maternal support and hippocampal growth trajectories: hippocampal volume increased faster with age among subjects with higher levels of maternal support. In addition, hippocampal growth trajectories predicted emotional regulation, an important endophenotype for virtually all common mental disorders.

Sensitive Periods

Luby et al. (1) compared the association of maternal support at preschool or school ages with hippocampal growth and found a significant association only for maternal support at the younger age, leading the authors to suggest “an early childhood sensitive period for these effects” (see also ref. 4). Although there are well-defined sensitive periods for sensory systems and language

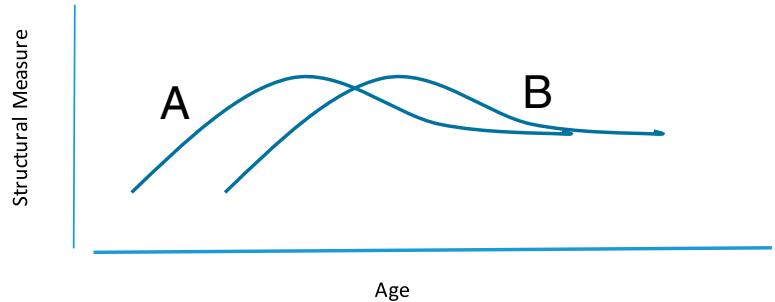


Fig. 1. Hypothetical curves intended to reflect accelerated (A) compared with later (B) developmental trajectories. Environmental conditions that shift the timing of a specific trajectory would be expected to have an age-dependent relation to the structural measure of interest at younger, but not older ages.

development, few studies examine whether comparable periods exist for neural systems that underlie socioemotional development. An effect of maternal support unique to early childhood is consistent with the reported efficacy of parent training programs in modifying developmental outcomes in younger children (e.g., ref. 5). These studies underscore the importance of early prevention programs that target parenting.

It is nevertheless important to place studies of sensitive periods into context. Early childhood appears to be a sensitive period for the influence of maternal support on hippocampal growth rates (1, 4). However, hippocampal plasticity endures throughout life in response to factors such as stress and physical exercise, as well as tasks that engage hippocampal activity (6). The evidence for the sensitive period in the Luby et al. report (1) should not imply that hippocampal structure is no longer plastic beyond the preschool period, but simply that it no longer appears to reflect the influence of maternal support. Indeed, there is evidence for greater effects of childhood maltreatment on a hippocampal structure in later compared with earlier childhood (7, 8), and perhaps even later for effects on the prefrontal cortex (7). A sensitive period for an environmental influence on neurodevelopment must thus be

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framed in terms of both the relevant environmental condition and the specific developmental outcome.

Sensitive periods for environmental signals are also regionally specific, which may explain the discrepancies noted by Luby et al. (1) between their findings and those of others groups. For example, the authors note that Lupien et al. (3) reported MRI findings with similarly aged subjects (mid-childhood), showing an association between postnatal maternal depression and the volume of the amygdala, but not the hippocampus. However, there are prenatal maternal influences, including maternal mood on the amygdala but not hippocampal volume, which are sustained into late childhood (9, 10). Because maternal mood generally remains stable across the peripartum period, the Lupien et al. (3) findings might reflect a prenatal maternal mood, thus resolving the apparent contradiction. In support of this idea, postnatal maternal mood, controlling for prenatal mood, predicts hippocampal growth trajectories (11). Similarly, prenatal maternal cortisol levels associate with the amygdala but not hippocampus volume in middle childhood (10). The reasons for regional specificity are not obvious and unlikely to map readily onto normal developmental profiles. The hippocampus and amygdala show considerable structural variation across fetal development and comparable rates of postnatal growth (12, 13).

Corticolimbic regions do not uniformly reflect environmental influences. Luby et al. (1) note that their study did not distinguish between the anterior and posterior hippocampus, which differ in developmental profiles and function (14) and respond differently to the same environmental conditions. Variations in maternal care in rodents exert opposing effects on synaptic plasticity in the dorsal and ventral hippocampus (15). Future studies will need to couple the admirable longitudinal approach of Luby et al. (1) with MRI analyses of multiple brain regions, comparing growth trajectories and connectivity.

Why Are Effects of Maternal Support Age-Dependent?

Maternal influences on phenotypic development occur across an amazing range of phyla, including plants and insects. An important question in each instance refers to the nature of the relevant maternal signal, which is challenging when considering the complexity of human development. The relevant literature suggests two alternatives. First, maternal care “buffers” children from stressful conditions, moderating the impact of adversity (16). Second, maternal care is a form of “environmental enrichment” that regulates the expression of neurotrophic factors, such as brain-derived neurotrophic factor, that regulate synaptogenesis (17). These are not mutually exclusive options and both are broadly consistent with the idea that maternal care in mammals promotes anabolic processes while suppressing catabolic signals. Tactile stimulation derived from maternal licking in rodents stimulates growth hormone release and suppresses that of the highly catabolic glucocorticoids.

Studies of the ontogeny of fear behaviors provide a remarkable example of maternal regulation of developmental trajectories. Rat pups deprived of maternal care show a precocious onset of fear behavior mediated by an accelerated maturation of the amygdala and the capacity to activate stress responses (16). Maternal deprivation activates glucocorticoid release, which triggers amygdala maturation. A remarkably similar effect occurs in humans where institutional rearing, an obvious instance of parental deprivation, accelerates functional coupling of the amygdala to the prefrontal cortex (18). This effect is likewise mediated by glucocorticoids, which are inhibited by active maternal care in both rodents and humans (16). Accelerated maturation of amygdala-dependent fear

behaviors might occur as an adaptation to the absence of effective maternal buffering.

Timing Matters

Environmental regulation of growth trajectories may result in conflicting findings when comparing datasets from cross-sectional studies. The finding of an association between maternal support in early, but not later childhood, and hippocampal growth trajectories (1) is strikingly similar to that of an earlier report (4) linking parental care at 4, but not 8 y of age to hippocampal volume in later adolescence. However, this latter study found that increased parental

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nurturance predicted smaller hippocampal volume in adolescence, a finding seemingly at odds with that of Luby et al. (1) and an earlier paper from this group (19) reporting that maternal support positively associated with hippocampal volume. However, children in this earlier study (19) were imaged earlier in development than those in the Rao et al. study (4). Multiple subregions of the hippocampus, including those that were the focus of the Rao et al. study, show increasing volume through to early adolescence, followed by a decrease in volume (14). Thus, an inverse correlation between parental nurturance in early childhood and smaller hippocampal volume in adolescence might reflect an accelerated maturation that is actually consistent with the findings of Luby et al. (1, 19), as well as the increased hippocampal volume at earlier periods in development (Fig. 1).

Studies of environmental influences on human brain development are thus complicated by the fact that data must be interpreted within the context of dynamic variation in structure, connectivity, and function. However, this form of this dynamic variation, reflected in growth trajectories, may be absolutely critical for understanding of individual differences in mental health. Although most studies examining the neural correlates of common mental disorders are performed in adults, attention-deficit disorder, addictions, anxiety disorders, and depression all peak in onset in late childhood and adolescence, a time of dynamic variation in structure and connectivity. An understanding of the pathophysiology of common mental disorders should focus on dynamic patterns of neurodevelopment and the link to mental health in children and adolescents. By adulthood, the horse has left the barn.

The Ultimate Challenge

Figure 1 of the Luby et al. (1) paper shows greater variability in hippocampal growth trajectories among children with lower levels of maternal support. Several children of less supportive mothers show hippocampal trajectories well within the range of those with high maternal support. Parenting clearly matters, but more for some than others. Such differential susceptibility (20, 21) appears linked, in part at least, to genotypic variation, including polymorphisms in genes coding for neurotrophic factors. The moderating effect of genetic variation on environment–phenotype relations is clear from neuroimaging studies (22), as well as those examining socioemotional

outcomes (21). This is not surprising. The structure and function of neural circuits is shaped by interactions between gene networks and environmental conditions over time. A clear understanding of the forces that shape individual differences in neurodevelopment and thus vulnerability for psychopathology will thus require extensive longitudinal studies that incorporate measures of pre- and postnatal environmental conditions, repeated neuroimaging, genotyping, and measures of neural function over development. Samples sizes must also be adequate to account for variation as a function of gender,

socioeconomic status, and ethnicity. This is a daunting challenge, but one that must be embraced if we are to provide an empirical foundation for evidence-based public policy.

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