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Early Variations in Amygdala Development May Signal Divergent Behavioral Outcomes

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The amygdala comprises only 0.3% of the brain, yet it is implicated in almost every neurodevelopmental and psychiatric disorder. It is a key part of a neural system that originally evolved to detect salient information, particularly danger, in the environment, to process cortical sensory input linking to previous knowledge, and to orchestrate other brain regions to produce an appropriate response. In primates, the amygdala plays a critical modulatory role in social cognition, including directing the individual to look at the eye region of the face to recognize emotions, judging trustworthiness, and encoding the degree of emotion in faces (1). If this system becomes dysfunctional, atypical social behavior or anxiety may arise, as is observed in many often debilitating psychiatric disorders. Indeed, altered amygdala structure and function has been identified in the pathophysiology of multiple psychiatric disorders, such as anxiety and obsessive-compulsive disorder, as well as neurodevelopmental disorders, such as autism spectrum disorder (ASD) and schizophrenia.

It is critical to map the developmental trajectory of the amygdala over the lifespan to better understand the etiology of these disorders. The amygdala clearly plays an important role in emotional learning; however, the specific function of the amygdala early in development is not well established, nor is the way deviation from the normative trajectory may impact later behavioral outcomes. Structural imaging and postmortem cellular studies of human and nonhuman primates demonstrate that the amygdala undergoes a prolonged developmental trajectory, increasing up to 40% from childhood to adulthood, that likely correlates with extensive functional maturation as the individual learns to handle an ever-changing environment. Although the primate amygdala is largely developed at birth, considerable cellular changes occur well into adulthood. In typical development, the number of mature neurons in the amygdala increases by approximately 30% from childhood to adulthood (2). The increase in the number of neurons coincides with a decrease in the number of immature neurons, a phenomenon that appears to be unique to the amygdala. With the increase in mature neurons, connections continue to be formed with increasing neuronal dendritic arborization into adulthood (3). Early perturbations in amygdala development could lead to a cascade of maladaptive neurodevelopmental events that affect the entire trajectory of maturation.

Little is known about amygdala cellular development during infancy, but neuroimaging studies have begun to shed light on early developmental trajectories. In this issue, Salzwedel *et al.* (4) describe a large longitudinal study of amygdala functional connectivity during the first 2 years of life and associations with emotion regulation, anxiety, and IQ at 4 years of age (4). The study consists of a large cohort of 223 infants, roughly balanced across sexes, with at least one scan at 3 weeks, 1 year, and 2 years of age. Salzwedel *et al.* (4) investigated right and left amygdala connectivity with whole-brain as well as with nine canonical resting-state functional networks at each cross-sectional time point and change in connectivity between 3 weeks and 1 year of age and between 1 year and 2 years of age. Salzwedel *et al.* (4) then evaluated associations between amygdala connectivity measures and several behavioral outcomes, including measures of anxiety, inhibitory self-control, and IQ at 4 years of age. Mapping out trajectories of amygdala development during the first years of life and identifying early predictors of later behavioral outcome could allow for earlier detection of altered trajectories in clinical populations, as well as the development of targeted interventions.

One interesting finding is the striking developmental change in functional connectivity between the amygdala and the medial prefrontal cortex in the first year of life. Existing evidence suggests that connectivity between the amygdala and the medial prefrontal cortex shifts from positive connectivity during childhood to negative connectivity (i.e., as medial prefrontal activity increases, amygdala activity decreases) during adulthood (5). This developmental shift is thought to reflect establishment of connectivity between the amygdala and the medial prefrontal cortex during childhood followed by emerging top-down regulation of amygdala reactivity in adolescence and adulthood. Positive amygdala–medial prefrontal cortex functional connectivity has been documented in children as young as 3 to 4 years of age (5). The current findings reveal an even earlier developmental shift in this circuitry. Salzwedel *et al.* (4) found that positive functional connectivity between the amygdala and the medial prefrontal cortex is not present in neonates but emerges by 1 year of age. Instead, neonates exhibit positive functional connectivity between the amygdala and primary auditory cortex and sensorimotor regions, a pattern that is not normally seen in older individuals. By 1 year of age, positive connectivity with the medial prefrontal cortex emerges and connectivity with primary sensory areas diminishes. Changes between 1 year and 2 years of age are subtler, with quantitative changes in the degree of connectivity but no large qualitative changes in the patterns of connectivity.

This early shift in the connectivity pattern of the amygdala from positive connectivity with sensorimotor areas to the medial prefrontal cortex could be useful in identifying early markers for neurodevelopmental disorders, such as ASD, for which there is some evidence of altered amygdala–medial

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prefrontal cortex connectivity (6). ASD is behaviorally diagnosed after symptoms emerge around 2 to 3 years of age, and there are currently efforts to identify early neural markers during infancy that could predict risk for ASD outcome. While there are several longitudinal studies indicating alterations in infants as young as 6 months of age who are later diagnosed with ASD, findings from the current study suggest that perhaps the field needs to expand to the neonatal period, when dramatic shifts in the development of connectivity patterns are more evident.

Another interesting set of findings from Salzwedel *et al.* (4) identifies associations between the change in amygdala functional connectivity from 1 year to 2 years of age with measures of anxiety and emotion regulation at 4 years of age. Specifically, growth from 1 year to 2 years of age in amygdala functional connectivity with regions within the default mode network and sensorimotor networks was associated with anxiety measures at 4 years of age. Relatedly, a recent functional connectivity study of nonhuman primates suggests that amygdala connectivity with the bed nucleus of the stria terminalis is both heritable and associated with early life anxious temperament (7). While the associations reported by Salzwedel *et al.* (4) need to be replicated and explored further, identification of early neural predictors of later outcome suggest the potential for development of targeted early interventions that could potentially alter the behavioral course and perhaps prevent disability later in life.

On a broader scale, imaging studies are a valuable tool to inform or guide cellular and molecular studies of psychiatric and neurodevelopmental disorders regarding when in development the amygdala deviates from the normative path (8). For example, structural alterations have been detected in children with ASD at 2 to 4 years of age, and these alterations were related to the severity of social and communication impairments (9). In a subset of children with ASD, the growth rate of the amygdala increases from 2 to 4 years of age (10). With guidance from imaging studies, studies of human postmortem brains find that the increased size of the amygdala may be related to alterations in cellular structure, specifically an increased number of neurons and spine density in children with ASD relative to typical development (2). Given the prolonged developmental trajectory of the amygdala and cellular alterations that occur in developmental disorders, it is not surprising that changes in connectivity of the amygdala with other brain regions could impact behavioral outcomes.

Functional connectivity studies not only shed light on the timing of amygdala development but also provide a guide of other potential neuroanatomical targets that are functionally integrated with the amygdala. For example, Salzwedel *et al.* (4) suggest that amygdala connectivity with primary auditory and sensorimotor regions may be transient yet critical during the first year of life and should be investigated further. It is possible that amygdala connectivity with primary sensory regions in the first few months of life may serve a more primitive role in sensing the environment. However, as the child matures, other neural circuitry with prefrontal regions becomes more evident as the role of the amygdala evolves into modulating more cognitive-driven social interactions. Understanding this shift in neural circuitry early in development may provide targets for pinpointing when and where these processes deviate in clinical disorders and perhaps lead to targeted interventions.

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Article Information

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