This Week in The Journal

Gray Matter Density Increases during Adolescence

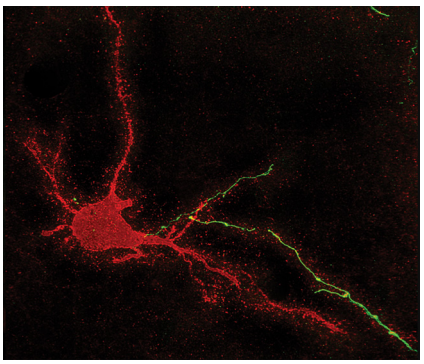
Efstathios D. Gennatas, Brian B. Avants, Daniel H. Wolf, Theodore D. Satterthwaite, Kosha Ruparel, et al.

(see pages 5065–5073)

Numerous studies have found that increases in cognitive abilities in human adults are associated with increases in cortical gray matter volume and/or thickness. During adolescent development, however, gray matter volume and cortical thickness decrease while cognitive abilities increase. Pruning of exuberant projections and synapses, which has been documented in other developing mammals, has been proposed to explain this apparent contradiction. But gray matter volume also tends to be higher in males than in females, despite similar intellectual abilities. This suggests that gray matter volume is not a reliable indicator of cognitive ability. Indeed, Gennatas et al. report that decreases in gray matter volume are accompanied by increases in gray matter density during adolescence and between males and females.

The authors analyzed magnetic resonance imaging (MRI) data from 1189 adolescents and compared cortical thickness, gray matter volume, and gray matter density across subjects. Consistent with previous work, total gray matter volume was greater in males than in females. Nonetheless, gray matter density was greater in females. Similarly, while total gray matter volume and cortical thickness were greater in the youngest than in the oldest subjects, gray matter density increased with age. Moreover, age-associated differences in gray matter density were found throughout the brain, whereas significant age-associated differences in gray matter volume were found in only 52–65% of gray-matter parcels. Finally, age explained more of the variance in mean gray matter density across subjects than it explained variance in gray matter volume.

Importantly, gray matter mass, defined as density × volume, decreased modestly during adolescence, suggesting gray matter loss does occur during this period. Nonetheless, the analyses suggest that gray matter loss during adolescence is much less than previously assumed. The authors suggest that increases in myelination during adolescent development may lead to compaction of gray matter. Alternatively, myelin development might affect the classification of gray and white matter in MRI scans, confounding interpretation of volume and density changes. Direct comparison of histological and imaging data in individual subjects will be required to determine how gray matter changes during development and to allow accurate interpretation of MRI data.



A pOFC axon terminal (green) closely apposes a dendrite of a DARPP-32-expressing neuron (red) in the intercalated masses of the amygdala. See Zikopoulos et al. for details.

Primate pOFC Projects Densely to Amygdala Intercalated Masses

Basilis Zikopoulos, Malin Hoistad, Yohan John, and Helen Barbas

(see pages 5051–5064)

To ensure survival, animals must respond appropriately to cues that predict rewards and threats. Because cues that are highly informative in some contexts may be uninformative in others, animals must learn to distinguish contexts and initiate or inhibit learned responses accordingly. This ability depends on the medial prefrontal cortex (mPFC). For example, the prelimbic region of rodent mPFC promotes expression of defensive responses, while the infralimbic region inhibits these responses after extinction training. These effects are mediated by projections from the mPFC to the amygdala. In particular, prelimbic cortex is thought to excite neurons in the basolateral nucleus, which elicit fear responses via projections to the central nucleus. In contrast, the infralimbic cortex is thought to inhibit communication between the basolateral and central nuclei, partly via projections to GABAergic neurons in the intercalated masses of the amygdala.

To gain further insight into how mPFC regulates amygdala circuitry, Zikopoulos et al. examined projections from primate posterior orbitofrontal cortex (pOFC) and anterior cingulate cortex (ACC) to amygdala nuclei. Both prefrontal areas innervated multiple nuclei in the amygdala, but the distribution of projections differed. For example, whereas ~70% of ACC projections targeted the basolateral nucleus, only ~28% of pOFC projections did. Moreover, a greater proportion of pOFC projections (30%) than ACC projections (8%) targeted the intercalated masses. Finally, only the pOFC innervated the lateral nucleus, a key site of fear learning.

The densest innervation by pOFC—and the largest, presumably strongest, synaptic terminals—occurred in the intercalated masses. Here, pOFC afferents formed synapses with the three main neuronal classes: spiny neurons that express the dopamine-responsive phosphoprotein DARPP-32, aspiny neurons that express calbindin, and aspiny neurons that express nitric oxide synthase. The largest of these classes comprises neurons expressing DARPP-32, and accordingly, most pOFC terminations apposed these neurons.

The authors suggest that primate pOFC is equivalent to rodent infralimbic cortex and that it inhibits fear responses by exciting neurons in the intercalated masses, which in turn inhibit neurons in the central nucleus that initiate defensive behaviors. Most pOFC targets in the intercalated masses are sensitive to dopamine, which inhibits these neurons in mice. Therefore, dopamine likely opposes the effects of pOFC. This might explain why stress, which elevates dopamine levels, interferes with extinction and allows inappropriate generation of fear responses in posttraumatic stress disorder.

This Week in The Journal was written by Teresa Esch, Ph.D.