This Week in The Journal

Estrogen Rescues Interneurons in Preterm Infants

Sanjeet Panda, Preeti Dohare, Samhita Jain, Nirzar Parikh, Pranav Singla, et al.

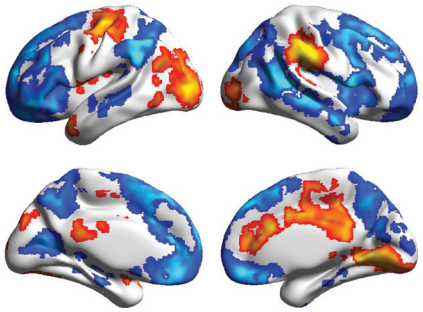
(see pages 7378–7391)

Medical advances have greatly increased survival of infants born before 37 weeks of gestation, but such children continue to face challenges. For example, up to half of preterm infants exhibit cognitive or behavioral impairments later in life. The etiology of these impairments is unclear, but disruption of developmental processes that are ongoing at the time of birth likely plays a role. These processes include axon growth and myelination, migration of cortical interneurons, and cortical folding. These might be disrupted by eliminating oxygen, nutrients, hormones, and/or growth factors normally provided through the placenta (Ortinau and Neil, 2014 Clin Anat 28:168).

Because some neurological problems associated with preterm birth have also been linked to an altered balance between excitation and inhibition in the brain, Panda et al. asked whether preterm birth alters the genesis and/or migration of inhibitory interneurons. They examined autopsy tissue from preterm infants and compared interneuron density in infants that were born at early gestational ages but survived several weeks with the density in infants that were born at later gestational age but died within days of birth; thus, infants were compared at similar times after conception. The density of parvalbumin-expressing interneurons in upper cortical layers was lower in infants born at 26–27 weeks gestation than in infants born at 32–33 weeks. In contrast, the density of somatostatin-expressing neurons was higher in the upper cortical layers of infants born more prematurely.

Previous work by this group showed that treatment with estrogen (the levels of which drop ~100-fold after birth) reversed changes in interneuron development in preterm rabbits. They now show that estrogen increased the density of parvalbumin-expressing interneurons and transiently reduced the density of somatostatin-expressing interneurons in these animals. Increased expression of Arx, a transcription factor involved in maturation and migration of cortical interneurons, may have contributed to these effects.

These results suggest that preterm birth disrupts the production and/or migration of cortical interneurons in humans, and that this effect might be reversed by estrogen treatment. Future work should investigate how long alterations in interneuron density persist, whether such changes contribute to cognitive or behavioral impairments, and if so, whether estrogen therapy reverses these impairments.



Increasing cortical levels of norepinephrine and dopamine increased correlated signal fluctuations in many brain areas, shown here. Correlations between other areas were suppressed. See van den Brink et al. for details.

Catecholamines Alter Brain-Wide Activity Patterns

Ruud L. van den Brink, Sander Nieuwenhuis, and Tobias H. Donner

(see pages 7476–7491)

Neuromodulators, including the catecholamines dopamine and norepinephrine, regulate numerous cognitive processes, such as arousal, attention, learning, and behavioral choices. Although brain nuclei that release catecholamines project throughout the brain, studies of their effects typically focus on the cellular or local-circuit level; little is known about their effects on brain-wide activity patterns. Yet functional magnetic resonance imaging (fMRI) studies in humans show that such large-scale changes in brain activity accompany the successful performance of cognitive tasks, and recent studies suggest that these changes are mediated by neuromodulators. Moreover, numerous studies in invertebrates have demonstrated that neuromodulators reconfigure neural circuits to allow a given set of neurons to participate in multiple functions. Therefore, understanding how neuromodulators reconfigure networks in humans will likely be important for understanding cognitive processes.

In previous work, van den Brink et al. investigated the effects of catecholamines on network activity by comparing correlations in resting-state activity fluctuations across pairs of brain regions in people before and after administering atomoxetine, a drug that increases synaptic norepinephrine and dopamine levels. These analyses showed that the number of strongly correlated regions and the formation of functional ensembles between resting-state networks decreased after atomoxetine treatment. By analyzing these data in a new way (generalized eigenvalue decomposition), the authors now present a more fine-grained, voxel-level map of the predominant atomoxetine-induced increases and decreases in correlated fMRI signal fluctuations across the brain. Notably, the pattern of increased correlations did not match that of any established resting-state networks and resembled the map of D2-dopamine-receptor expression, consistent with previously reported roles of these receptors in cortical disinhibition. In contrast, the map of reduced correlations included peaks in portions of the default-mode and attention networks and was most similar to the map of α1-norepinephrine-receptor expression, consistent with previous work showing that activation of these receptors weaken circuit interactions in the cortex.

These results demonstrate that catecholamines reconfigure network activity in the resting brain. Thus, neuromodulators can exert such changes independently of sensory input or task engagement. Of course, in these experiments, catecholamine levels were increased indiscriminately throughout the brain; future work should investigate the global effects of activating selected populations of these neurons to mimic neuromodulatory activity occurring under natural conditions.

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