

# This Week in The Journal

## Cocaine Reduces Afterhyperpolarization in Dopamine Neurons

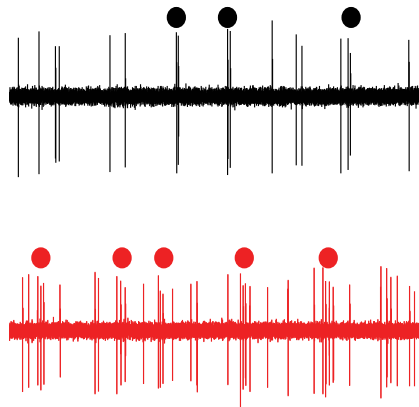
Meaghan Creed, Jennifer Kaufling, Giulia R. Fois, Marion Jalabert, Tifei Yuan, et al.

(see pages 10759–10768)

Addictive drugs enhance dopaminergic signaling in mesocorticolimbic circuits involving the ventral tegmental area (VTA), nucleus accumbens, and prefrontal cortex. Repeated drug use induces long-lasting plasticity in these circuits, which contributes to the development of addiction. But even a single dose of an addictive drug induces changes in glutamate signaling in the VTA that persist up to a week and set the stage for later plasticity. Specifically, drug-induced increases in extracellular dopamine levels lead to potentiation of excitatory synapses between laterodorsal tegmentum afferents and dopaminergic neurons in the VTA. This potentiation results from the insertion of calcium-impermeable GluN3-subunit-containing NMDA receptors (NMDARs) and subsequent insertion of GluA2-lacking calcium-permeable AMPA receptors (Lüscher 2016 *Ann Rev Neurosci* 39:257). How these changes affect the activity of VTA dopaminergic neurons has been unclear, however.

Creed et al. now report that a single dose of cocaine increased the firing rate and bursting activity of dopamine neurons within 3 h; activity remained elevated for up to 5 d. The increase in activity was associated with a decrease in the spike afterhyperpolarization (AHP) current carried by calcium-activated small-conductance potassium (SK) channels, which normally restrains spike rate and bursting. Consistent with this, an SK channel antagonist increased spike rate in control VTA neurons, but this effect was occluded by prior cocaine treatment. Importantly, cocaine failed to reduce AHP current and increase spiking in GluN3A-deficient mice. Moreover, an agonist of Group I metabotropic glutamate receptors, which causes GluN3A-containing NMDARs to be replaced with canonical GluN2A-containing NMDARs in VTA dopaminergic neurons, restored the AHP current and reduced the firing rate in cocaine-treated mice.

These results suggest that the cocaine-induced replacement of canonical calcium-permeable NMDARs with GluN3A-containing calcium-impermeable NMDARs results in reduced opening of calcium-activated SK channels, which in turn leads to increased spike rate and bursting. This would likely result in increased dopamine release in the nucleus accumbens and prefrontal cortex. This may enable subsequent drug exposure to induce plasticity in these areas.



The frequency of spikes and bursts (dots) in VTA dopaminergic neurons was higher 24 h after a single dose of cocaine (red trace) than in controls (black). See Creed et al. for details.

## Language-Circuit Function Is Lateralized After First Year

Robert W. Emerson, Wei Gao, and Weili Lin

(see pages 10883–10892)

Language comprehension skills develop over several years. During the first few months of life, infants begin to discriminate human voices from other sounds. Within a few months, they learn to recognize their names and the names of other objects. Toddlers can comprehend sentences, but learning to process complex syntax rules continues for several years. The development of these language skills depends on maturation of neural circuits involving several brain regions, including the left superior temporal gyrus (STG, also known as Wernicke's area), which contributes to the representation of word meaning, the left inferior frontal gyrus (IFG or Broca's area),

which helps represent the meaning of phrases, and the right STG and IFG, which process intonation, rhythm, and other prosodic information.

The development of language circuits can be investigated by using functional magnetic resonance imaging (fMRI) to detect the degree of synchronous activation (functional connectivity) between areas. Cross-sectional studies have indicated that communication between language-associated areas in each hemisphere predominates at birth, with adult patterns of communication predominantly within the left hemisphere emerging later (Skeide and Friederici 2016 *Nat Rev Neurosci* 17:323). To investigate the development of these circuits more precisely, Emerson et al. used fMRI to measure brain activity during sleep in 71 infants, repeating these measures multiple times over the first 2 years of life.

Over the first year, activity became more bilaterally symmetric in all cortical areas examined, including IFG, STG, sensory cortical areas, and regions of prefrontal cortex. While symmetrical activation persisted in most of these areas during the second year, it decreased in IFG and STG. At the same time, functional connectivity between ipsilateral IFG and STG increased, while correlated activation of ipsilateral somatosensory and visual cortex decreased. Notably, the amplitude and timing of the peak in symmetrical activation of IFG was correlated with language abilities in a subset of participants tested at 4 years of age. Specifically, earlier and higher peak synchrony between hemispheres was associated with better language performance.

These results suggest that language abilities benefit from early interhemispheric communication in language areas before lateralization occurs. Future studies should determine whether a similar increase in interhemispheric communication occurs in children at risk for autism, because abnormal lateralization of language function has been detected in children as young as 2 years who were later diagnosed with autism. Such studies could lead to earlier diagnosis of potential language deficits and to possible interventions.

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