BRAINSTORMS
Clinical Neuroscience Update

Norepinephrine and Dopamine Regulate Signals and Noise in the Prefrontal Cortex

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Issue: *Norepinephrine and dopamine work in a cooperative yet reciprocal manner to regulate information processing at pyramidal neurons in the prefrontal cortex.*

The prefrontal cortex (PFC) is composed of a series of neuronal networks that establish the circuitry to process information in the brain.[1,2] Depending on which areas of PFC are involved, malfunctioning of different circuits can generate a wide range of psychiatric symptoms from problems of cognition and impulsivity to disorders of mood and anxiety.[1] Such malfunctioning PFC circuits can even be visualized and topographically localized with modern neuroimaging techniques.[1,2]

PFC neuronal networks are regulated by numerous neurotransmitters, including dopamine (DA) and norepinephrine (NE).[1–3] Hypothetically, abnormal regulation of PFC networks by DA and NE can cause various psychiatric symptoms.[1,3] Similarly, altering the actions of DA and NE at malfunctioning PFC circuits by administering various psychotropic drugs can hypothetically improve information processing and thereby reduce psychiatric symptoms (Figure 1).

Neurotransmitters such as DA and NE "tune" the PFC. Imbalance of neurotransmitters may be linked to the cause of various psychiatric symptoms, whereas psychotropic drugs acting on these networks can theoretically improve information processing in PFC circuits, and thereby reduce psychiatric symptoms (Figure 2).

References

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Take-Home Points

- Norepinephrine (NE) and dopamine (DA) regulate incoming glutamate signals at the level of dendritic spines on pyramidal neurons in the prefrontal cortex.
- Acting via α_{2A}-adrenergic receptors, NE *closes* cation channels located on the necks of dendritic spines. The specific channels involved here are called HCN (cAMP/hyperpolarization-activated cyclic nucleotide–gated cation) channels. This action of NE *strengthens* signals arriving at pyramidal neurons in the prefrontal cortex.
- On the other hand, DA *opens* HCN channels by its actions at dopamine D_1 receptors, which *weakens* signals, thus reducing the "noise" arriving at these same pyramidal neurons.

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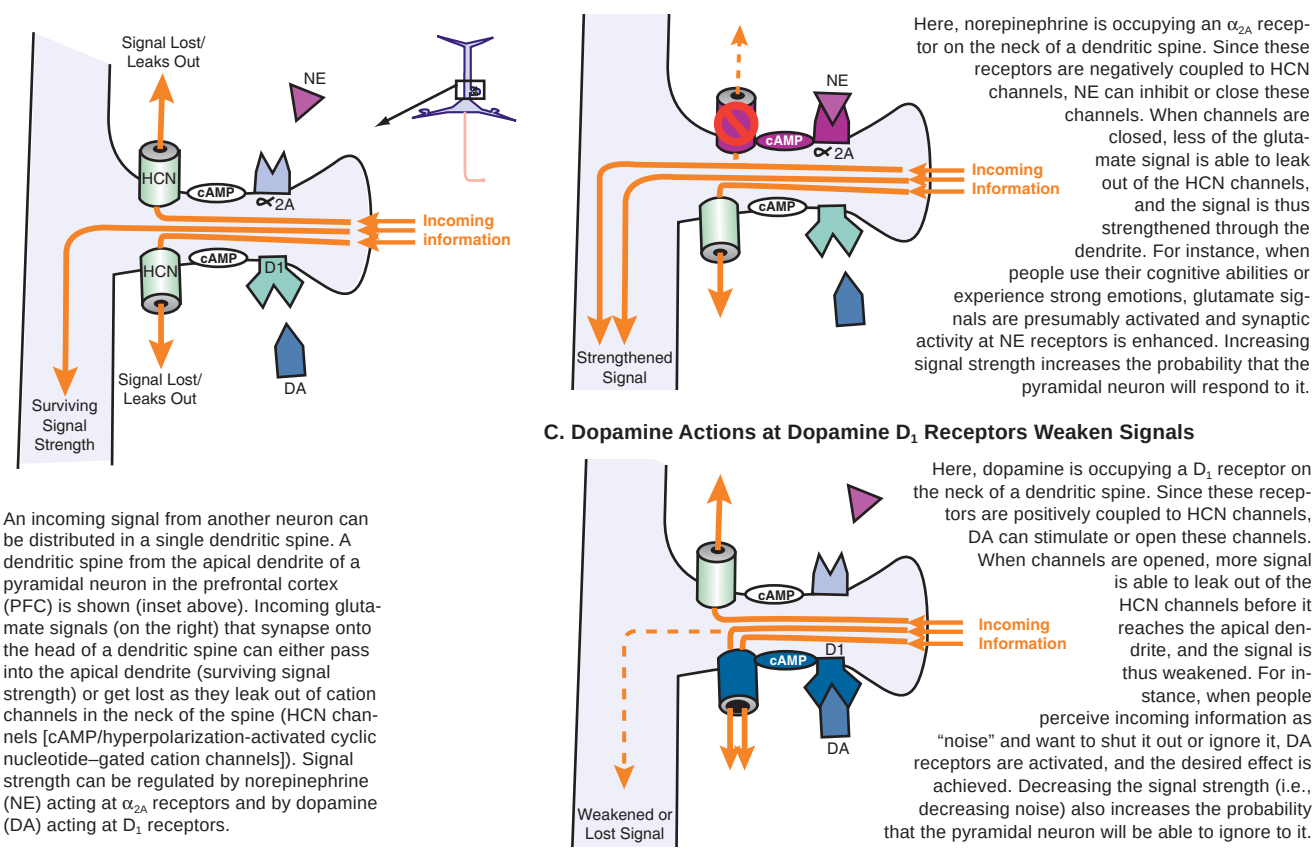
Figure 1. Signal Distribution in a Dendritic Spine

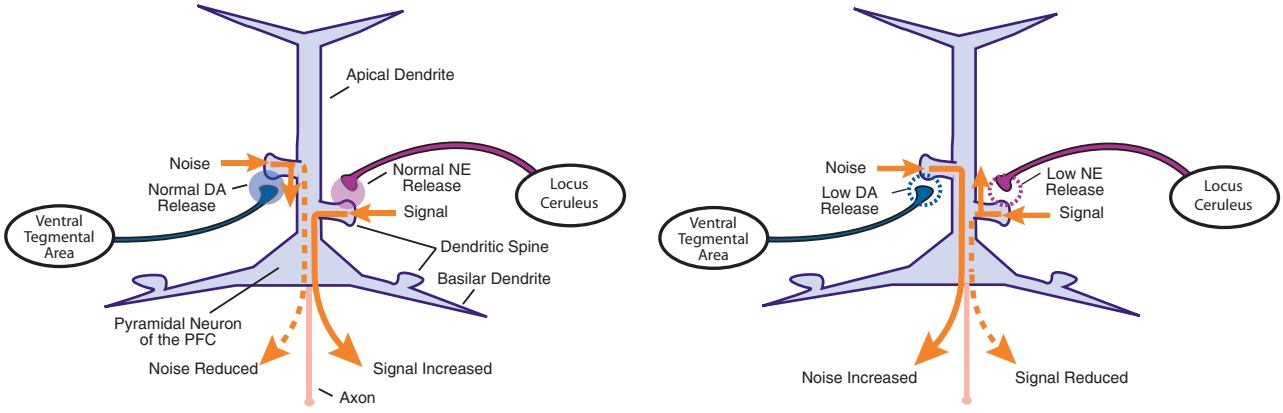


An incoming signal from another neuron can be distributed in a single dendritic spine. A dendritic spine from the apical dendrite of a pyramidal neuron in the prefrontal cortex (PFC) is shown (inset above). Incoming glutamate signals (on the right) that synapse onto the head of a dendritic spine can either pass into the apical dendrite (surviving signal strength) or get lost as they leak out of cation channels in the neck of the spine (HCN channels [cAMP/hyperpolarization-activated cyclic nucleotide–gated cation channels]). Signal strength can be regulated by norepinephrine (NE) acting at α_{2A} receptors and by dopamine (DA) acting at D_1 receptors.

Here, norepinephrine is occupying an α_{2A} receptor on the neck of a dendritic spine. Since these receptors are negatively coupled to HCN channels, NE can inhibit or close these channels. When channels are closed, less of the glutamate signal is able to leak out of the HCN channels, and the signal is thus strengthened through the dendrite. For instance, when people use their cognitive abilities or experience strong emotions, glutamate signals are presumably activated and synaptic activity at NE receptors is enhanced. Increasing signal strength increases the probability that the pyramidal neuron will respond to it.

Here, dopamine is occupying a D_1 receptor on the neck of a dendritic spine. Since these receptors are positively coupled to HCN channels, DA can stimulate or open these channels. When channels are opened, more signal is able to leak out of the HCN channels before it reaches the apical dendrite, and the signal is thus weakened. For instance, when people perceive incoming information as "noise" and want to shut it out or ignore it, DA receptors are activated, and the desired effect is achieved. Decreasing the signal strength (i.e., decreasing noise) also increases the probability that the pyramidal neuron will be able to ignore to it.

Figure 2. How Dopamine (DA) and Norepinephrine (NE) Hypothetically "Tune" the Prefrontal Cortex (PFC)



A. Baseline Information Processing With Signals Increased and Noise Reduced. Neuronal networks are regulated in part by a reciprocal and balanced relationship between DA and NE inputs. Ideally, signals detected as desirable cause NE to be released in order to strengthen them. By contrast, undesirable inputs are ideally detected as noise, and DA is released at these sites to weaken them. As time goes on, the brain may shift what it considers a signal and a noise, and presumably does so by altering where and how much DA and NE it releases, but this scenario illustrates a hypothetically well-tuned neuron with efficient information processing.

B. Low DA and Low NE: Inefficient Information Processing With Signals Reduced and Noise Increased. In the event that DA and NE are out of balance, the PFC neuronal networks do not function to process information efficiently. In the scenario shown here, which is hypothetically associated with various psychiatric symptoms from cognitive dysfunction to mood disorder, both DA and NE are low, and thus the PFC is "out of tune." Specifically, this pyramidal neuron is responding to noise and not to the signal—opposite to what is shown in Figure 2A. This displays what might happen in patients who are experiencing various psychiatric symptoms. The specific symptom depends on the specific neuronal network of microcircuits involved and their topographical localization with the PFC.

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