IN BRIEF

SENSORY SYSTEMS

Merkel cells touch a nerve

Epidermal Merkel cells sense touch, but how they activate sensory neurons is not clear. Now, Hoffman et al. demonstrate that Merkel cells manufacture presynaptic and catecholamine-synthesis machinery, and can package and release a neurotransmitter analogue into and from vesicles, respectively. Noradrenaline evoked action potentials in Merkel cell afferents, and a β_2-adrenergic antagonist blocked touch-evoked neural responses. Thus, Merkel cells release noradrenaline across synapses to activate sensory neurons.

ORIGINAL ARTICLE Hoffman, B. U. et al. Merkel cells activate sensory neural pathways through adrenergic synapses. *Neuron* https://doi.org/10.1016/j.neuron.2018.10.034 (2018)

NEURAL DEVELOPMENT

Model potential

Human induced pluripotent stem cell (iPSC)-derived neurons could be used to model CNS development. Real et al. transplanted cultures of green fluorescent protein-expressing neurons and neural progenitors derived from human iPSCs into the somatosensory cortex of adult mice, and used multiphoton imaging to longitudinally track the grafts over 4 months. Grafts showed changes similar to those in developing human cortex, including axon growth, synapse formation and turnover, and oscillatory activity. By contrast, grafts derived from individuals with Down syndrome showed a lower synapse turnover rate, indicating that iPSC-derived cells can also be used to model aspects of neurodevelopmental disorders.

ORIGINAL ARTICLE Real, R. et al. In vivo modeling of human neuron dynamics and Down syndrome. *Science* https://doi.org/10.1126/science.aau1810 (2018)

EMOTION

Imagine no fear

The neural mechanisms underlying the effects of imaginal exposure therapy, in which threat-associated situations are repeatedly imagined to reduce fear responses, are unknown. Here, participants learned to associate an auditory tone with a shock, and were then exposed to the tone alone (real extinction) or asked to imagine the tone (imagined extinction). Both types of extinction reduced fMRI-measured threat-related responses after threat reinstatement. Similar networks — including the ventromedial prefrontal cortex as a central hub — were recruited by real and imagined extinction. However, the success of real and imagined extinction was predicted by activity in the nucleus accumbens and CA1, respectively, suggesting that they reduce threat responses in distinct ways.

ORIGINAL ARTICLE Reddan, M. C., Wager, T. D. & Schiller, D. Attenuating neural threat expression with imagination. *Neuron* **100**, 994–1005 (2018)

CHEMICAL SENSES

Do flies like fizz?

Drosophila melanogaster feed on yeast cells, which produce CO_2; however, whether flies are attracted to CO_2 is unclear. By manipulating the temperature and wind speed in a wind tunnel, the authors altered the activity levels of flies while recording their flight trajectories in response to plumes of CO_2. More active flies were attracted to CO_2, whereas less active flies found it aversive. Unlike aversion, attraction to CO_2 depended on the olfactory ionotropic co-receptor IR25a. Thus, flies show state-dependent responses to CO_2 through distinct pathways.

ORIGINAL ARTICLE van Breugel, F., Huda, A. & Dickinson, M. H. Distinct activity-gated pathways mediate attraction and aversion to CO_2 in *Drosophila*. *Nature* https://doi.org/10.1038/s41586-018-0732-8 (2018)

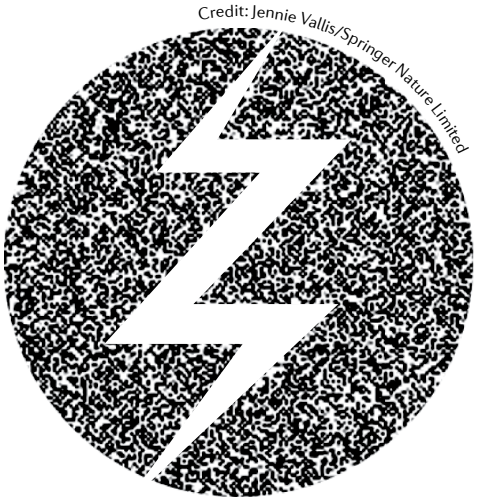
PREFRONTAL CORTEX

Boosting a bad signal

Dopamine (DA) has been suggested to increase the signal-to-noise ratio (SNR) of neural activity in the medial prefrontal cortex (mPFC); however, direct evidence of this model is lacking. Vander Weele et al. now show in rodents that DA released in the mPFC increases the SNR of aversive signals to the dorsal periaqueductal grey (dPAG).

The authors first investigated the activity of ventral tegmental area (VTA) neurons that release dopamine in the mPFC (VTA^{DA}→mPFC neurons), using fast-scan cyclic voltammetry and optogenetics. Photoinhibition of these neurons' terminals in layers 5 and 6 of the rat mPFC reduced their release of DA in response to an aversive stimulus (pinch). Photoactivation of VTA^{DA}→mPFC terminals was not aversive (as assessed in real time or conditioned place avoidance assays). However, in rats that were conditioned to associate auditory or visual cues with an aversive stimulus (a shock) or a reward (sucrose) and that were then presented with both cues simultaneously, photoactivation of VTA^{DA}→mPFC terminals induced more freezing and less reward-approaching behaviour. Thus, in the presence of conflicting cues, DA in the mPFC may bias responses towards aversion.

mPFC neurons are known to project to other structures in the brain, including the PAG. Selective activation of either the somata or terminals of mPFC→PAG neurons in rats led to avoidance in the place aversion assays and increased marble burying and time spent digging (behaviours that are thought to be defensive). Calcium imaging of mPFC→PAG neurons in mice revealed that a greater proportion of this cell population responded to shock than to sucrose, consistent with a role for these neurons in aversion signalling.



In mouse brain slices, optogenetic stimulation of VTA^{DA}→mPFC neurons did not affect the excitability of mPFC→dPAG neurons, and retrograde labelling showed that mPFC→dPAG neurons do not express DA receptors. Thus, the authors reasoned that the VTA^{DA}→mPFC projections may not directly excite mPFC→dPAG neurons but may instead increase the SNR of incoming sensory inputs relating to aversive stimuli. Consistent with this model, 10 minutes of VTA^{DA}→mPFC stimulation in mice in vivo reduced and increased the frequency and amplitude of calcium events in mPFC→dPAG neurons, respectively. Electrophysiological recordings revealed that although this VTA^{DA}→mPFC stimulation did not affect the firing rates of mPFC→dPAG neurons under basal conditions or in response to sucrose, it did increase mPFC→dPAG firing frequency in response to an aversive airpuff.

Together, these results imply that DA released in the mPFC increases the SNR of information transmitted to the dPAG.

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ORIGINAL ARTICLE Vander Weele, C. M. et al. Dopamine enhances sign-to-noise ratio in cortical–brainstem encoding of aversive stimuli. *Nature* https://doi.org/10.1038/s41586-018-0682-1 (2018)