*Nature Reviews Neuroscience* | AOP, published online 12 December 2012; doi:10.1038/nrn3419

LEARNING AND MEMORY

# Teaching the accumbens a valuable lesson

> Structural imaging of the NAc confirmed the selective targeting of CINs by GPNs — a remarkable and unexpected finding, given that only 1% of neurons in the NAc are CINs

In associative learning, the processing of environmental stimuli with motivational relevance predominantly involves dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Less often discussed are the GABAergic projection neurons (GPNs) of the VTA, which synapse locally but also project to the NAc and whose functional role is not well understood.

Using immunohistochemical localization and optogenetic projection targeting, Brown *et al.* found that GPNs selectively target cholinergic interneurons (CINs) in the NAc, forming multiple symmetrical GABAergic synapses, mostly in somatic regions and on proximal dendrites. Structural imaging of the NAc confirmed the selective targeting of CINs by GPNs — a remarkable and unexpected finding, given that only 1% of neurons in the NAc are CINs.

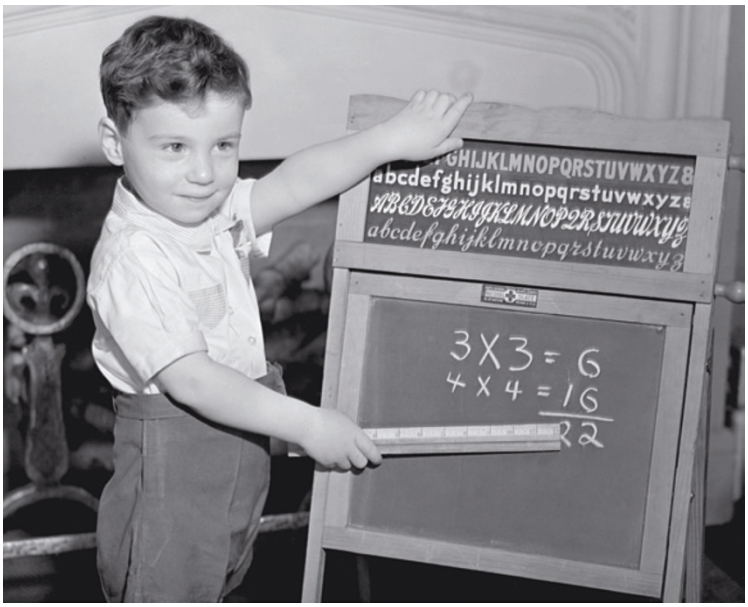
CINs fire tonically, but when rodents or primates are exposed to motivationally important stimuli (either rewarding or aversive), the spontaneous activity of CINs ceases temporarily. In mouse brain-slice preparations, optogenetic activation of VTA GPNs produced inhibitory postsynaptic currents in CINs, and artificial activation of GPNs *in vivo* (again using optogenetic stimulation) produced a similar pause in CIN activity. This activity was abolished by bicuculline, suggesting that it is mediated by type A GABA receptors.

In non-human primates, this pause in CIN activity has been shown to occur as the animal learns to associate a particular stimulus with a particular outcome (associative learning) and is known as the 'conditioned pause response'. Given the known role of the VTA in associative learning, the authors reasoned that the activity in the GPN–CIN projection is likely to be involved in this learning process. To test this hypothesis, the authors subjected mice to a discrete cue and contextual learning task in which mice were exposed to two different stimuli — one associated with an aversive outcome (footshock) and one with no associated outcome. Combining this paradigm with optogenetically forced pauses in CIN firing resulted in enhanced learning of the stimulus–outcome association with the motivationally important stimulus. Importantly, the net activity of VTA–NAc dopaminergic neurons did not differ significantly from baseline levels, ruling out an influence of dopamine in this effect.

Overall, these findings point to a key role of the GPN–CIN axis in associative learning.

*Sian Lewis*

**ORIGINAL RESEARCH PAPER** Brown, T. C. *et al.* Ventral tegmental area GABA projections pause accumbal cholinergic interneurons to enhance associative learning. *Nature* 25 Nov 2012 (doi:10.1038/nature11657)




PhotoDisc