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Dissociating learning and movement related signals within the striatum

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There are two main populations of striatal projection neurons (SPNs), defined by their expression of either D1 or D2-type dopamine receptors, which are evenly distributed throughout the structure. The traditional model of how the striatum organises behaviour is through the facilitation (D1-neurons) or suppression (D2-neurons) of complex motor programs which depend on corticostriatal transmission. Our previous research revealed that beyond their role in controlling movement, D2-neurons are essential for encoding and updating goal-directed learning (Matamales et al. 2020). In a dopamine-dependent process we termed D2-to-D1 transmodulation, D2-neurons were shown to prevent molecular activation in neighbouring D1-neurons. We hypothesised that this learning-related plasticity depends on local neuromodulatory signals amongst SPNs and that this is distinct from the canonical corticostriatal circuit controlling animal movement.

The availability of fluorescent biosensors to measure neuronal excitation (GCaMP6m) and dopamine (dLight1.1) allowed us to test this hypothesis in freely behaving animals using the technique of fibre photometry. Under isoflurane anaesthesia, mice (Drd1a-Cre, Adora2A-Cre or C57Bl6/J) were unilaterally microinjected with adeno-associated virus containing one of these biosensors into the dorsomedial striatum, followed by the implantation of an optic fibre. Three weeks later, they were placed in an open field and administered pharmacological agents known to produce robust intracellular signalling in D1- or D2-neurons, in combinations which would put these striatal systems in competition. We then monitored behavioural activity and fluorescence signals over time, followed by the mapping of molecular changes.

We found that dopamine signals increased in the striatum in response to pharmacological stimulation, with increases in both basal fluorescence and amplitudes of dLight transients. We also saw summation when D1- and D2-neuron stimulating drugs were combined, confirming strong dopaminergic activation was present under all conditions. Functioning as a proxy for neuronal excitation, the measured GCaMP transients were correlated with locomotion in both D1-and D2-neurons as expected. However, these signals and the animal's movement did not correlate with the underlying molecular state of striatal neurons: D1-neuron plasticity was blocked whenever D2-neurons were strongly transcriptionally active, regardless of how excitable those neuronal populations were while the animals were moving in the open field.

By combining optical monitoring of specific neuronal populations with a post-hoc analysis of molecular activity, we provide evidence of a dissociation in SPNs between the neuronal activity encoding movement and an underlying molecular plasticity associated with learning. This is an important finding as it suggests that sensors which are proxies of neuronal firing will be of limited use in understanding learning-related signals in real time and that utilising new fluorescent biosensors which report downstream signalling activity will be required.

Matamales, M., McGovern, A. E., Mi, J. D., Mazzone, S. B., Balleine, B. W., & Bertran-Gonzalez, J. (2020). Local D2-to D1-neuron transmodulation updates goal-directed learning in the striatum. *Science*, ***367***(6477), 549-555.