PERSPECTIVES

A new tool for your novelty centre

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Why did you start reading this text? Well, as a scientist you might have simply followed your well-developed novelty-seeking trait. Was this not the same reason why you have started scanning this new issue of *The Journal of Physiology*? Functional imaging experiments have shown that when humans are exposed to novel, unpredicted sensory stimuli, one of the most strongly activated brain areas is the ventral midbrain, where dopamine (DA) neurons are clustered in two overlapping nuclei, the substantia nigra (SN) and its medial neighbour, the ventral tegmental area (VTA) (Bunzeck & Düzel, 2006). These DA neurons release dopamine in various target regions, mainly within the basal ganglia but also in cortical areas not only in reaction to novelty, but also strongly in response to unexpected rewards and less vigorously to unexpected punishments.

One attractive and simple concept of the dopamine midbrain system is that its concerted global action, as monitored by functional imaging (D'Ardenne *et al.* 2008), and the firing responses of individual dopamine neurons, recorded *in vivo* (Fiorillo *et al.* 2003), essentially communicate the same message. Both the large network of up to 500,000 DA midbrain neurons as well as the single DA neuron appear to quantitatively code for a prediction error that serves as a teaching signal for the basal ganglia learning machine (driven by dopamine-induced changes in cortico-striatal synaptic plasticity).

This view that dopamine midbrain neurons speak *unisono* with a powerful single voice leaves little room for functional diversity and dynamic interactions among distinct types of SN and VTA DA neurons. However, several studies have provided strong evidence for a more complex picture of the dopamine midbrain system. For example, systematic *in vitro* analysis of electrophysiological properties and gene expression patterns of individual DA midbrain neurons with identified axonal projections has defined the presence of at least two highly distinct phenotypes of DA neurons that are likely to possess different functional roles *in vivo* (Lammel *et al.* 2008). In addition, the distinct functions of striatal subregions in the context of a spiral striatal–midbrain–striatal connectivity, as well as the discrete temporal–spatial profiles of dopamine release detected in different behavioural contexts, further support the notion of complexity within the DA midbrain system. However, the need for laborious cell-by-cell analysis has delayed our progress in defining and topographically mapping the functional diversity of the DA midbrain system. In this context, the contribution of Berretta, Bernadi and Mercuri in a recent issue of *The Journal of Physiology* (Berretta *et al.* 2010) is a very welcome and timely methodological advancement that promises to speed up our understanding of the DA midbrain system. The authors provide the first systematic *in vitro* brain-slice multi-electrode-array (MEA) study of the dopamine midbrain system in rodents, focusing on the apparently most homogeneous subpopulation of DA neurons in the SN. They have recorded the firing properties, as well as the responses to dopamine applications of an unprecedented large population of over 1000 SN neurons. Also, they studied the degree of functional connectivity between DA SN neurons by means of cross-correlation analysis. Even for the basic SN DA neuronal firing pattern that has already been intensively studied *in vitro* and *in vivo*, their novel MEA approach revealed new levels of complexity. Only about 50% of the analysed, putative DA SN neurons displayed the classical clock-like low-frequency pacemaker discharge, while the other half of recorded neurons showed more irregular firing with a similar frequency range. This result alone might point to significant differences in the control of intrinsic excitability and pacemaker stability between subpopulations of DA SN neurons. Future applications of the MEA technique in combination with ion channel blockers will help to define those ion channels that mediate the functional differences in intrinsic excitability reported in their current study.

Also, Berretta and colleagues report that the response to dopamine, which is known to activate somatodendritic dopamine autoreceptors of the D2 type in many DA neurons, was unexpectedly also far from homogeneous. In addition to the classical inhibition of spontaneous activity, a significant number of SN DA neurons did not respond at all or in contrast were even excited by dopamine. While, the underlying mechanism remains unclear, the MEA-approach again promises to facilitate future studies. Finally, the authors demonstrated that more than 10% of the analysed SN DA neurons appear to be functionally coupled and that the degree of their connectivity was modulated by dopamine itself. However, the MEA study did not immediately reveal a clear topographical pattern for the functionally distinct SN DA subpopulations that emerged. In the future, the MEA approach promises to dramatically speed up our understanding of the DA midbrain system – as an interacting and dynamic ensemble of distinct players. The new tool will help to better define the population changes of DA midbrain neurons occurring during ageing and in disorders such as Parkinson's disease, schizophrenia or drug addiction. *In vivo* multi-electrode arrays, suitable for the dopamine system, would nicely complement the achievement by Berretta, Bernardi and Mercuri described in this issue – and even further stimulate our novelty centre.

References

Berretta N, Bernardi G & Mercuri NB (2010). *J Physiol* **588**, 1719–1735.
Bunzeck N & Düzel E (2006). *Neuron* **51**, 369–379.
D'Ardenne K, McClure SM, Nystrom LE & Cohen JD (2008). *Science* **319**, 1264–1267.
Fiorillo CD, Tobler PN & Schultz W (2003). *Science* **299**, 1898–1902.
Lammel S, Hetzel A, Häckel O, Jones I, Liss B & Roeper J (2008). *Neuron* **57**, 760–773.

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