the Li and DeVries paper seem well suited to support acuity information, and interestingly, these narrow-field bipolar cells skipped blue cones. When middle-wavelength light is in focus, short-wavelength light becomes blurred in the eye, a process known as chromatic aberration[5]. It is tempting to speculate that these blurred 'bluish' signals are skipped by the acuity pathway 'on purpose', to allow it to focus instead on the sharper, longer wavelengths.

Next, consider the issue of motion sensitivity. The ganglion cells that support a motion pathway are wide-field cells with high contrast sensitivity that collect signals from many bipolar cells[2]. Here, the goal seems to be a transient response to any stimulation within the receptive field, at the expense of acuity. The wide-field bipolar cells described by Li and DeVries collected from all cone types within their dendritic fields, suggesting that this pathway detects a luminance signal while ignoring wavelength information and accepting blur caused by chromatic aberrations (**Fig. 1**).

Finally, consider the issue of color opponency. All cones are 'color-blind' in the sense that a cone response, on its own, tells us nothing about wavelength. This is because a cone response reflects the number of photoisomerizations of the opsin molecule, and here wavelength can trade off with intensity to generate any given response level[6]. Therefore, wavelength discrimination depends on retinal circuitry to compare the relative output of two cone types in the same patch of the retina. Here, it would be optimal to have two types of bipolar cell that collected inputs exclusively from either blue or green cones, plus a way to compare the two bipolar signals. Li and DeVries recorded from a blue-cone bipolar cell, which was an ON-type cell (depolarized at light onset), plus a medium-field, green cone bipolar cell, which was an OFF-type cell (depolarized at light offset). A ganglion cell that combined the output of these two bipolar cell types would therefore compute a blue-ON, green-OFF signal, which is a proposed basis for color vision in the retina (**Fig. 1**). Indeed, just such a ganglion cell has been recorded in the primate retina[7,8], and this ganglion cell seems to integrate two types of bipolar cells that match the physiological types demonstrated in the ground squirrel[9].

This latest paper builds on previous work on cone circuitry in the ground squirrel retina. Ground squirrel green cones make electrical synapses with other green cones but not with blue cones. This selective coupling may help to increase the signal-to-noise ratio in the green cone mosaic, through averaging of voltage signals, while preserving the spectral sensitivity of each cone type[10]. Another study showed that OFF-type bipolar cells express distinct glutamate receptors of the AMPA or kainate type[11]. Such diversity of glutamate receptors endows each bipolar pathway with a unique temporal sensitivity.

One important question is how the present results in ground squirrel will generalize to other species, in particular primates. There is a controversy regarding the magnocellular (M) pathway in the primate retina. M cells represent the presumed luminance pathway in the primate retina[2,7], and, based on the ground squirrel data, we might expect the M ganglion cell to receive input from a bipolar pathway that collects both from blue cones and from red and green cones. (Old World primates have both red and green cones rather than just green cones[2].) However, two sets of recordings of the primate M-pathway yielded conflicting results regarding the presence of blue-cone signals[7,12]. A second controversy comes from the anatomical analysis of primate blue cone synaptic terminals. For ON-type bipolar dendrites, these blue cone terminals appeared to contact only the blue cone bipolar cell, leaving no evidence for a contact with a wide-field bipolar cell in the luminance pathway[13]. The Li and DeVries paper should motivate further work on these issues in primates.

Dual patch-clamp recordings, combined with cell type identification, yield invaluable information regarding connectivity in a neural circuit. A further challenge in regard to the retina is to determine how bipolar cells connect with amacrine and ganglion cells at the second synaptic layer. A similar strategy of paired recordings, combined with cell type identification, could be used to understand the selectively of connections in the cerebral cortex[14,15].

1. Li, W. & DeVries, S.H. *Nat. Neurosci.* **9**, 669–675 (2006).
2. Wässle, H. *Nat. Rev. Neurosci.* **5**, 747–757 (2004).
3. Kouyama, N. & Marshak, D.W. *J. Neurosci.* **12**, 1233–1252 (1992).
4. Haverkamp, S. *et al. J. Neurosci.* **25**, 5438–5445 (2005).
5. Marimont, D.H. & Wandell, B.A. *J. Opt. Soc. Am. A* **11**, 3113–3122 (1994).
6. Baylor, D.A. *et al. J. Physiol. (Lond.)* **390**, 145–160 (1987).
7. Dacey, D. & Lee, B. *Nature* **367**, 731–735 (1994).
8. Chichilnisky, E.J. & Baylor, D.A. *Nat. Neurosci.* **2**, 889–893 (1999).
9. Calkins, D.J. *et al. J. Neurosci.* **18**, 3373–3385 (1998).
10. Li, W. & DeVries, S.H. *Nat. Neurosci.* **7**, 751–756 (2004).
11. DeVries, S.H. *Neuron* **28**, 847–856 (2000).
12. Chatterjee, S. & Callaway, E.M. *Neuron* **35**, 1135–1146 (2002).
13. Herr, S. *et al. J. Comp. Neurol.* **457**, 185–201 (2003).
14. Yoshimura, Y., Dantzker, J.L. & Callaway, E.M. *Nature* **433**, 868–873 (2005).
15. Song, S. *et al. PLoS Biol.* **3**, e68 (2005).

Evaluating apples and oranges

Jonathan D Wallis

Orbitofrontal cortex damage impairs decision making. A recent article in *Nature* shows that this brain region is critical for computing the subjective value of an outcome and using this value signal to make choices

"You cannot compare apples and oranges." So we are told, but of course, we can certainly make choices when it comes to lunch. The orbitofrontal cortex (OFC) is a region of the brain that is critical for this ability (**Fig. 1**). Damage to the OFC in monkeys, for example, causes them to choose foods at random rather than to show clear food preferences like normal monkeys[1]. However, we do not use our OFC just for choosing lunch. This is perhaps best illustrated by a case study, in which a successful, happily married young man with a well-paid job was diagnosed with a brain tumor. Although the operation to remove the tumor was successful, surgeons inadvertently damaged Elliot's OFC in the process[2]. Superficially, Elliot seemed unchanged by the damage: his language, memory, intelligence and sensorimotor abilities were unaffected. However, within months of the operation, he had quit his work, lost a large sum of money

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to a scam artist, divorced his wife, lost contact with family and friends, and been remarried to a woman he had known only a short while. In summary, after making a series of excellent life choices, within months of OFC damage he had made a series of catastrophic ones.

How can a single brain region contribute to decisions ranging from what to have for lunch to the choice of a spouse? Padoa-Schioppa and Assad, in a recent issue of *Nature*, have gone a long way toward addressing this question[3]. They trained two monkeys to make simple choices between different drinks while they recorded the electrical activity of neurons in the monkeys' OFC. The neurons encoded the choice outcomes, but not in a way that simply mapped onto the sensory properties of the drinks. Instead, the activity reflected the monkeys' individual valuations of the drinks that were available. These results suggest that an important function of the OFC is deriving a value signal that can guide behavior. They may help explain why patients with damage to this area have difficulty with everyday decisions, and shed light on some of the neuronal mechanisms underlying neuropsychiatric illnesses in which OFC dysfunction occurs.

Determining the value of something is a complex process often requiring us to consider many variables. For example, deciding whether you want coffee or a cold soft drink requires considering a whole range of factors, not just taste. You might consider their relative price, your energy level and even the weather. Similarly, in the Padoa-Schioppa and Assad experiment, the monkeys had to choose between different drinks, but this was not a simple decision. The monkeys saw two sets of squares on either side of a computer screen and had to choose one set by making an eye movement to them. The monkey made its choice based on the color of the squares, which indicated the type of drink the monkey would receive, and the number of squares, which indicated the drink's volume. To make its choice effectively, the monkey needed to consider both variables.

For example, a thirsty monkey might prefer the taste of fruit juice to water. If this is the case, then if the choice is between equal volumes of both, he will obviously choose the juice. However, increasing the volume of water available can compensate for its less desirable taste. If the volume of water is sufficiently large relative to the volume of juice, then the monkey will pick the water. At some point, the volume of water will compensate for its less desirable taste exactly, and the monkey will be indifferent between the two choices. To determine this indifference point, the authors paired up different drinks and systematically varied their volumes. They measured the proportion of times the monkey chose one drink over another and calculated the indifference point. This was the point at which the monkey was equally likely to choose either drink. This effectively measures the monkey's value of one drink's taste relative to the other. For example, if the monkey is equally likely to choose four drops of water or one drop of fruit juice, we know that the monkey considers the taste of juice four times more valuable than water.

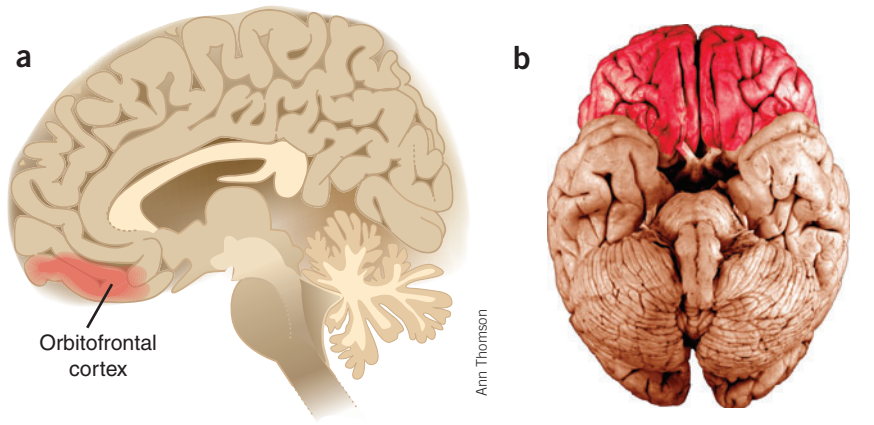


Figure 1 The location of human orbitofrontal cortex. (**a**) A schematic of a mid-sagittal section through the head, depicting the OFC (red shaded region). (**b**) A postmortem photograph of the ventral surface of the brain. The OFC is so named because of its position on top of the eye orbits.

By using this ingenious task, the authors were able to obtain a very sensitive behavioral measure of the monkey's subjective preferences as well as the objective physical properties of the rewards. The key question was what the activity of OFC neurons would look like when the monkey was making these choices. It turned out that the firing rates of OFC neurons varied systematically with the value of the drinks, rather than with the drinks' physical properties such as their taste or volume. In particular, they often encoded the value of the drink that the monkey would choose.

To see how the authors determined this, let us return to the juice and water example. A neuron that was encoding the subjective value of the chosen drink might show a higher firing rate when the monkey was choosing one drop of juice than when he was choosing one drop of water. However, the neuron's firing rate would be the same when the monkey was choosing one drop of juice as when he was choosing four drops of water. We cannot explain this pattern of neuronal activity based on the drinks' volume, because equal volumes of the drinks produce different neuronal firing rates. Nor can we explain it solely by the drinks' taste, because certain volumes of the drinks produce equal levels of neuronal firing. However, we can explain it in terms of the monkey's subjective preferences, because when his valuation of the two drinks is the same (such as when he is offered four drops of water or one drop of juice), the neuronal firing rate is also equivalent.

These results suggest that OFC neurons are important for deriving the value of an outcome and for using this value signal to guide choice behavior. The authors focused on gustatory stimuli, but these processes could easily apply to higher-level decision making. A common feature of decisions involves weighing one attribute of a choice outcome against another. As an example, let us return for a moment to Elliot. After his series of poor life choices, he returned to live with his parents. He found an accountancy job, but it involved a 200-mile round-trip commute. After a few weeks, the company fired him for lack of punctuality. Elliot had failed to determine the value of the job properly by not integrating all the factors relevant to the decision. Indeed, a systematic study of patients with OFC damage found that they had a specific difficulty in integrating multiple attributes pertaining to a decision[4].

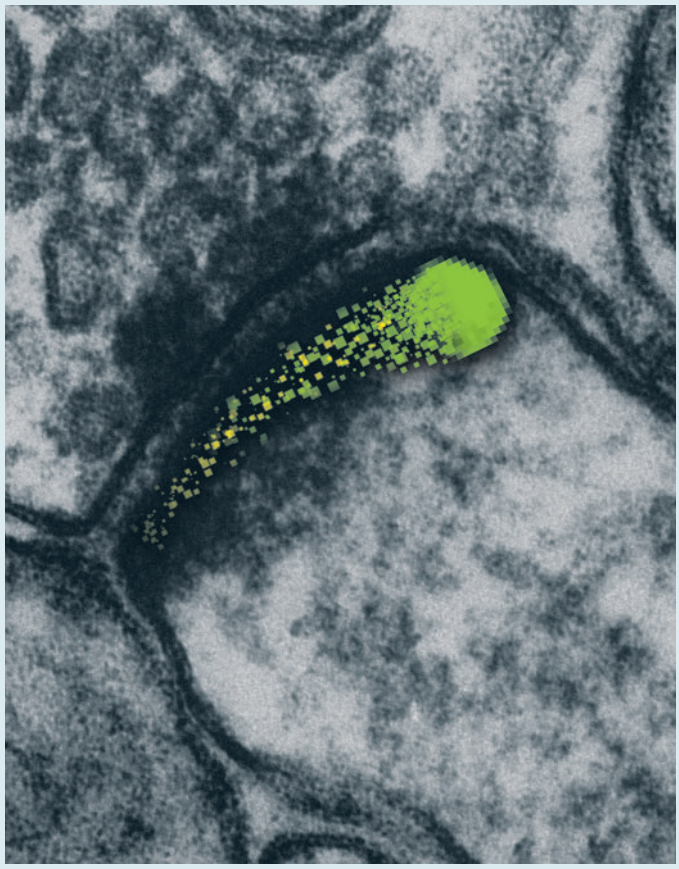
The authors also noted that OFC neurons encode a relatively 'pure' value signal that is unrelated to visuospatial or motor factors. Whether a choice appeared on the left or right of the screen (thereby requiring a left or right eye movement) rarely influenced neuronal firing rates. Encoding value and action separately in the brain makes sense from a computational perspective as it avoids the combinatorial explosion that would occur if they were encoded jointly. However, the final picture will undoubtedly be more complex, because the action itself can affect the value of the choice. Choice outcomes that involve minimal effort are more valuable than those that require us to exert ourselves. A question

for future research is how the value signal incorporates this aspect of a decision. Does it involve feedback from motor areas into the OFC, or does a different brain area encode this information? The latter seems more likely, as the OFC connects only weakly to motor areas[5]. Furthermore, the medial PFC in rats (which connects to both motor and reward areas) is critical for integrating effort and payoff information[6,7].

Further questions remain regarding choice behavior. Determining how much we value something is the first step, but despite our decision that a certain course of action is valuable, we often have trouble implementing our choice. After all, how many New Year's resolutions make it to February? For most of us, this is a minor inconvenience, but for some, such as the morbidly obese, drug addicts, compulsive gamblers or individuals with eating disorders or obsessive-compulsive disorder, the inability to control choice behavior is more serious. Furthermore, there is evidence that these disorders involve OFC dysfunction[8,9], although its precise role in these illnesses remains unclear. By specifying the processes that underlie the control of choice behavior in healthy individuals, as Padoa-Schioppa and Assad have done, we can begin to understand what goes awry in these neuropsychiatric populations.

1. Baylis, L.L. & Gaffan, D. *Exp. Brain Res.* **86**, 617–622 (1991).
2. Damasio, A.R. *Descartes' Error: Emotion, Reason, and the Human Brain* (Putman, New York, 1994).
3. Padoa-Schioppa, C. & Assad, J.A. *Nature* (in the press).
4. Fellows, L.K. & Farah, M.J. *Cereb. Cortex* **15**, 58–63 (2005).
5. Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R.J. & Reinoso-Suarez, F. *Cereb. Cortex* **10**, 220–242 (2000).
6. Walton, M.E., Bannerman, D.M. & Rushworth, M.F. *J. Neurosci.* **22**, 10996–11003 (2002).
7. Rushworth, M.F., Walton, M.E., Kennerley, S.W. & Bannerman, D.M. *Trends Cogn. Sci.* **8**, 410–417 (2004).
8. Volkow, N.D. & Fowler, J.S. *Cereb. Cortex* **10**, 318–325 (2000).
9. Everitt, B.J., Dickinson, A. & Robbins, T.W. *Brain Res. Brain Res. Rev.* **36**, 129–138 (2001).

Clearing obsolete NMDA receptors



The subunit composition of NMDA-type glutamate receptors at nascent synapses changes with synaptic maturation. Immature NMDA receptors that include NR3A subunits are distinguished by their low Ca^{2+} permeability and Mg^{2+} sensitivity. Mature NMDA receptors exclude NR3A subunits, are highly Ca^{2+} permeable upon stimulation, and are powerfully blocked by Mg^{2+}. Thus, the original juvenile receptor types need to be removed and exchanged for the mature types as development proceeds.

On page 611 of this issue, Pérez-Otaño and colleagues look into the mechanism by which NR3A-containing NMDA receptors are cleared from synapses in hippocampal cultures. Although it has been reported previously that the NR1 subunit (common to all NMDA receptors) coalesces at emerging synaptic sites in maturing cultures, the authors observed here that the NR3A subunit remained diffusely distributed along the dendritic membrane. Under baseline conditions, NR3A-containing receptors were internalized at much higher rates than receptors lacking NR3A. Inhibitors blocking either neural activity entirely, or NMDA receptor activity specifically, prevented the endocytosis of NR3A complexes.

How are NR3A-containing NMDA receptors targeted for preferential activity-dependent endocytosis? The authors found that the intracellular tail of NR3A, but not of other subunits, interacts with PACSIN1, a neuron-specific multivalent adaptor molecule that had already been implicated in regulation of endocytosis as well as the actin cytoskeleton. PACSIN1 linked NR3A to the clathrin-dependent endocytosis machinery, and expression of a fragment interfering with PACSIN1 inhibited NR3A internalization and increased NR3A localization at *bona fide* postsynaptic specializations. The figure is an artistic rendition of NR3A (green) 'escaping' the postsynaptic density, presumably aided by PACSIN1.

In vivo, the authors found that the onset of PACSIN1 expression correlates with the critical phase of postnatal synaptic maturation in juvenile rat forebrain. As PACSIN1 expression increases, NR3A expression decreases, consistent with the idea that PACSIN1 serves to clear NR3A-containing NMDA receptors from maturing active synapses. The data also suggest a hypothetical function for the NR3A subunit itself: its primary role may not be to confer specific channel characteristics to young NMDA receptors. Instead NR3A might target juvenile NMDA receptors for PACSIN1-mediated endocytosis at the appropriate time, allowing their replacement with mature NMDA receptors capable of sustaining Ca^{2+}-dependent synaptic plasticity such as long-term potentiation and long-term depression. NR3A knockout mice, which have been available for some years, show higher spine densities and greater NMDA currents as juveniles. Close inspection of these animals, as well as generation of PACSIN1-null mice, will reveal whether the intriguing mechanisms and hypotheses put forward by Pérez-Otaño and colleagues correctly describe *in vivo* maturation of glutamatergic synapses.

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