reporters and endogenous targets in a neuronal cell line, whereas AR knockdown reduced the expression of TFEB reporters and native targets. Perhaps the best evidence supporting a normal function of AR in TFEB regulation is the finding that a synthetic androgen was able to drive nuclear translocation of TFEB in an AR-dependent manner. However, in the disease context, mutant polyQ-AR retained its ability to interact with TFEB, yet apparently lost its capability to function as a TFEB coactivator and drive its androgen-dependent nuclear translocation. Together, these findings are consistent with an emerging theme in polyQ diseases that the mutant proteins can assemble into a macromolecular complex, but fail to mediate its function[10,11].

On the therapeutic front, the study provides tantalizing evidence that raising TFEB levels could benefit cells carrying the SBMA mutation. In mutant AR–transfected cells, overexpressing TFEB restores reporter activity for the CLEAR network and significantly enhances autophagic function. To further validate the findings in disease-relevant models, Cortes *et al.*[1] created induced pluripotent stem cell lines from three SBMA patients and three unaffected controls. Using neuronal precursor cells derived from these cells, they were able to replicate several disease-specific phenotypes originally observed in the overexpression system, including polyQ length–dependent aggregation, increased autophagy flux, reduced CLEAR target gene expression and a new cytotoxicity phenotype: depolarization of mitochondria. Overexpression of TFEB normalized both the autophagy flux and the mitochondria membrane potential in this genetically accurate SBMA cell model.

Given the consistent benefit of TFEB overexpression in counteracting autophagy deficits and proteotoxicity in SBMA cells, is it a foregone conclusion that raising TFEB expression or function should be beneficial in SBMA? The current standard for validating a molecular therapeutic target for polyQ disorders would require genetic and/or pharmacological manipulation of the molecular target in intact animal models to evaluate the overall effect on the disease-related phenotypes, as well as any potential harmful effects. In the case of TFEB in SBMA, this is particularly important to pursue, as evidence has already emerged from a previous study[12], as well as from the current one[1], that TFEB function is upregulated in muscle in two different SBMA mouse models—the opposite of the findings in neurons. Apart from the need to resolve the mechanistic differences behind such dichotomous effects of polyQ-AR on the CLEAR pathway in two distinct tissues, there is also the pressing translational need to understand whether TFEB upregulation in muscle contributes to skeletal muscle atrophy in the disease, as previously suggested[12]. Given that recent studies have revealed that mutant AR in muscle may have a more primary role in SBMA pathogenesis, at least in mice[13,14], it is essential to determine whether systemic increase of TFEB levels or function in animal models would lead to net benefit in both motor neuron and muscle disease in SBMA. In addition, a more targeted strategy to selectively normalize the interaction between TFEB and mutant AR may be optimal to ameliorate the clearance deficits in SBMA cells while minimizing any possible side effects of systemic TFEB activation.

Cortes *et al.*[1] offer another elegant case in which knowing the mechanism of the function of an affected protein provides fresh insight into pathogenesis as well as therapeutics for a neurodegenerative disorder. In the case of SBMA, Cortes *et al.*[1] have discovered a fascinating tale in the CLEARance Wars that has a CLEAR side, a dark side, a master (TFEB) and a character who switches from one side to the other. As we look forward to the next episode, we already have a hunch on which side the Force will be with.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Cortes, C.J. *et al. Nat. Neurosci.* **17**, 1180–1189 (2014).
2. Katsuno, M. *et al. Prog. Neurobiol.* **99**, 246–256 (2012).
3. Orr, H.T. & Zoghbi, H.Y. *Annu. Rev. Neurosci.* **30**, 575–621 (2007).
4. Katsuno, M. *et al. Neuron* **35**, 843–854 (2002).
5. Takeyama, K. *Neuron* **35**, 855–864 (2002).
6. Sardiello, M. *et al. Science* **325**, 473–477 (2009).
7. Settembre, C. *et al. Science* **332**, 1429–1433 (2011).
8. Tsunemi, T. *et al. Sci Transl. Med.* **4**, 142ra97 (2012).
9. Decressac, M. *et al. Proc. Natl. Acad. Sci. USA* **110**, E1817–E1826 (2013).
10. Lim, J. *et al. Nature* **452**, 713–718 (2008).
11. Nedelsky, N.B. *et al. Neuron* **67**, 936–952 (2010).
12. Chua, J.P. *et al. Hum. Mol. Genet.* **23**, 1376–1386 (2014).
13. Cortes, C.J. *et al. Neuron* **82**, 295–307 (2014).
14. Lieberman, A.P. *et al. Cell Reports* **7**, 774–784 (2014).

All that glitters is not reward signal

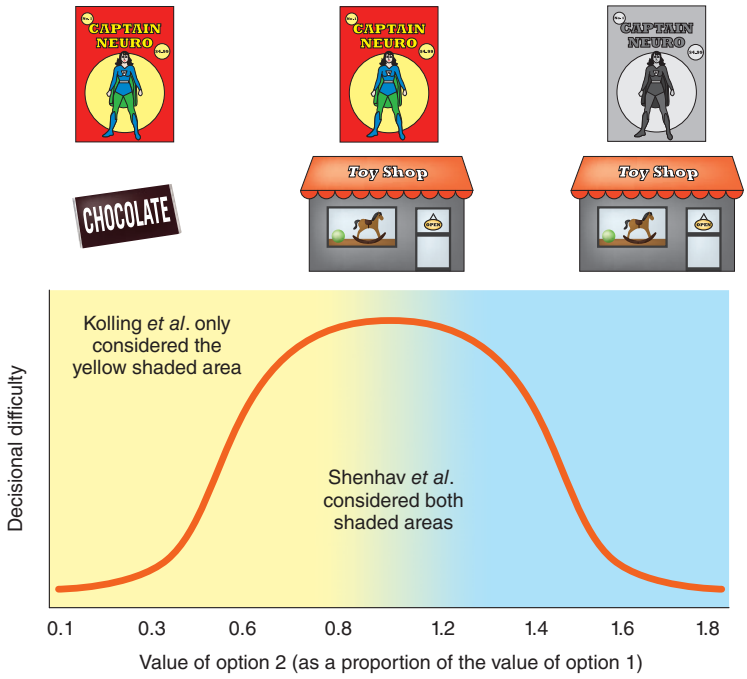
Benjamin Y Hayden & Sarah R Heilbronner

In this issue, Shenhav *et al.* critically evaluate the idea that neural correlates of value actually represent value. They describe how, in many situations, value correlates can reflect other cognitive factors, such as decisional difficulty.

Imagine you are an 8-year-old child who is given a $5 allowance every Saturday morning. This Saturday, allowance in hand, you encounter a new issue of your favorite superhero comic, *Captain Neuro*, at the drugstore. It costs $4.99. If you purchase it, you forgo the opportunity to buy anything else (including things you might like more) all week. What do you do? And, more importantly, how does your brain make that choice? The study of how our brains implement reward-based choices, also called economic choices, typically involves assessing where in the brain specific economic variables correlate with neural activity. These variables can be relatively straightforward, such as amount of money, or can represent hypothesized internal quantities, such as the value of searching the environment. In the aggregate, such variables combine to form decision-making models that, on the surface, seem to accurately represent the internal calculations subjects use to guide behavior.

A study in this month's issue of *Nature Neuroscience* demonstrates the pitfalls of this popular approach. Shenhav *et al.*[1] begin by reconsidering a particularly high-profile study on the neuroscience of foraging behavior[2]. In that study, human subjects made foraging decisions by comparing the values of two strategies: engaging versus searching. Returning to our example, engaging would be the equivalent of buying the comic book at the cost of waiting and searching the environment for better options. Kolling *et al.*[2] had found that brain activity in the anterior cingulate cortex (ACC) correlates with the value of searching. Once it computes this value, the ACC presumably

Benjamin Y. Hayden is in the Department of Brain and Cognitive Sciences and Center for Visual Science, and Sarah R. Heilbronner is in the Department of Pharmacology and Physiology, University of Rochester, Rochester, New York, USA.
e-mail: benhayden@gmail.com



Kim Caesar/Nature Publishing Group

Figure 1 The relationship between decision difficulty and value. Range of search:engage ratio values tested in both Kolling *et al.*[2] and Shenhav *et al.*[1] (yellow shading) versus exclusively by Shenhav *et al.*[1] (blue shading), plotted against choice difficulty. When the value of searching relative to the value of engaging is low, the choice to engage is easy: think of a choice between an amazing issue of a comic book and the possibility of a mediocre candy bar. When the value of searching relative to the value of engaging is high, the choice to search is also easy: think of a choice between a dull issue of *Captain Neuro* and a possible trip to a toy store. But when the values of searching and engaging are matched, choice difficulty is at its peak: think of a choice between an amazing comic and a possible trip to the toy store.

transmits it to a downstream area where it can be compared with the value of engaging; then, a choice can be made. Shenhav *et al.*[1] offer a different interpretation.

If this month's issue of *Captain Neuro* looks particularly dull, your choice may be easy: search for other alternatives. In that case, the value of searching relative to engaging is high. But if the scenario changes slightly—say, the issue looks only somewhat compelling, and you also think you are likely to visit a new toy store later in the week—the value of searching and engaging can become closely matched, and your choice is difficult. Shenhav *et al.*[1] noticed that, because of the design of the task, trials in the original foraging experiment were most difficult when the value of searching was highest (**Fig. 1**). Thus, search value was perfectly correlated with choice difficulty.

That confound is important because difficult decisions are likely to recruit extra cognitive resources, including self-control, mental effort and conflict monitoring—all of which tend to activate ACC[3,4]. Shenhav *et al.*[1] replicated the original Kolling *et al.*[2] results, then proceeded to test a broader range of foraging conditions. Notably, they found new conditions in which search value was decoupled from choice difficulty. ACC activation more closely reflected the executive control elicited by difficult decisions than the value of searching.

To be sure, the debate over the interpretation of these signals has not yet been resolved. Both sides have extensive literatures backing their own theories, and these will need to be addressed. In moving forward, we expect that the precise implementations of choice difficulty and search value as they relate to observable preferences and reaction times will be critically important for interpreting the ACC signal. One possibility is that both the searching and the choice difficulty signals are reliably present, but in slightly different locations in the frontal cortex.

Nevertheless, the importance of the study by Shenhav *et al.*[1] is not really about any one paper in the literature, but instead lies with the larger issues that they raise. Their study suggests that many correlates of specific economic variables may be spurious ones that, when tested under a broader range of conditions, will be shown to reflect variables related to executive control instead. Their arguments apply to any condition in which economic variables are confounded with elements of executive control, and this is likely to be common. Indeed, their results seem relevant in any study in which there is a tradeoff between economic variables, including benefit and cost, reward and delay, and reward and risk. Although their results do not immediately invalidate all previous neuroeconomic findings, they strongly suggest taking a second look.

Economic decision variables are difficult to study because it is so easy to find correlates for such values in the brain, but devilishly hard to disentangle them from other things. A decision-making model that seems to match human behavior may not reflect internal neural and psychological processes. A difficult choice demands more attention, and an easy decision can be made quickly and (relatively) effortlessly. The problem is that, in many cases, executive control and other cognitive processes are closely correlated with specific choice variables. Shenhav *et al.*[1] were able to decouple the two, but doing so is not always trivial.

Recent literature is full of these would-be reward signals. For example, larger rewards are more attentionally salient than smaller ones, so reward frequently correlates with salience, which may drive executive control[5]. Often, close studies of the issue have claimed that salience, and not value, more closely matches the neuronal data. Relevant observations come from regions as diverse as the parietal cortex[6], posterior cingulate cortex[7], anterior cingulate cortex[8] and the dopamine system[9]. Of course, salience is nearly perfectly correlated with attention, and the difficulty of disambiguating attention from motor plans is well known[10]. Other factors that often correlate with reward size are mental effort, the need for learning, surprisingness, motor planning, the vigor of the response and even the stimulus features that make something more rewarding[11,12]. These elements are all potential confounds for value. Indeed, it may not just be value: other hypothesized variables, such as metacognitive signals, may also correlate with choice difficulty[13,14]. The results from Shenhav *et al.*[1] therefore highlight the danger of drawing jejune conclusions from simple correlates of brain activity in a broad range of possible contexts[11].

Ultimately, these results highlight the importance of psychology to economists. Economic theory deliberately ignores how the choice gets made, and often for good reason[15]. But when the time comes for a deeper mechanistic understanding, we need to consider the constraints that our brains give us. We are organisms that are well designed to produce efficient economic decisions in a wide variety of circumstances. But our decision-making repertoires are built on spandrels, evolved pieces, clumsy combinations and kludges, and these will be represented in our neural functioning. Knowing the psychological mechanisms at play during a choice is necessary to understanding the neural basis of decision-making.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Shenhav, A., Straccia, M.A., Cohen, J.D. & Botvinick, M.M. *Nat. Neurosci.* **17**, 1249–1254 (2014).
2. Kolling, N., Behrens, T.E., Mars, R.B. & Rushworth, M.F. *Science* **336**, 95–98 (2012).
3. Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S. & Cohen, J.D. *Psychol. Rev.* **108**, 624–652 (2001).
4. Shenhav, A., Botvinick, M.M. & Cohen, J.D. *Neuron* **79**, 217–240 (2013).
5. Maunsell, J.H. *Trends Cogn. Sci.* **8**, 261–265 (2004).
6. Leathers, M.L. & Olson, C.R. *Science* **338**, 132–135 (2012).
7. Heilbronner, S.R., Hayden, B.Y., & Platt, M.L. *Front. Neurosci.* **5**, 55 (2011).
8. Hayden, B.Y., Heilbronner, S.R., Pearson, J.M. & Platt, M.L. *J. Neurosci.* **31**, 4178–4187 (2011).
9. Redgrave, P. & Gurney, K. *Nat. Rev. Neurosci.* **7**, 967–975 (2006).
10. Bisley, J.W. & Goldberg, M.E. *Annu. Rev. Neurosci.* **33**, 1–21 (2010).
11. O'Doherty, J.P. *Neurosci. Biobehav. Rev.* **43**, 259–268 (2014).
12. Pearson, J.M., Watson, K.K. & Platt, M.L. *Neuron* **82**, 950–965 (2014).
13. Kepecs, A., Uchida, N., Zariwala, H.A. & Mainen, Z.F. *Nature* **455**, 227–231 (2008).
14. Kiani, R. & Shadlen, M.N. *Science* **324**, 759–764 (2009).
15. Samuelson, P.A. *Maximum Principles in Analytical Economics: Nobel Memorial Lecture* (Nobel Foundation, 1971).

Scenting Waldo: analyzing olfactory scenes

Timothy E Holy

Olfaction has often been described as a 'synthetic' sense. A study now reveals a surprising capacity to resolve individual odorants in complex mixtures, with implications for how the nervous system recognizes objects.

Glance at a busy street scene or chat with a few friends at a noisy party and you'll quickly appreciate your brain's ability to separate complex stimuli into their component parts. Efforts to understand this capacity for scene segmentation have been a mainstay of neuroscience research in the visual and auditory systems. In contrast, the sense of smell seems different: for many people, complex scents such as coffee or roses do not obviously trigger the olfactory equivalent of viewing a crowd. For this reason, olfaction has long been touted as a synthetic sense, fusing the independent components to make a new whole. Now a study by Rokni *et al.*[1] demonstrates that olfaction, like vision and audition, can also be analytic: mice have an extraordinary ability to pick out the presence or absence of a particular odorant amid complex, variable backgrounds. Because of the relative brevity of olfactory processing[2], this discovery opens up exciting new frontiers for understanding the neural mechanisms underlying scene segmentation.

Children's books such as the popular *Where's Waldo?* series challenge readers to find a particular figure amid many visual distractions. However, the brain's talent for this task is no game. From the standpoint of computer science, object recognition has been the focus of decades of gradual progress, with applications that range from organizing your photo collection to robotics and national security[3]. In psychology and neuroscience, the ability to parse complex sensory input into recognizable objects has been studied under many names, including figure-ground organization, scene segmentation, object recognition and the cocktail party problem (**Fig. 1**).

Timothy E. Holy is in the Department of Anatomy & Neurobiology, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA.
e-mail: holy@wustl.edu

As a window into some of our most impressive cognitive facilities, the quest to understand how our brains process sensory inputs to identify distinct objects has led to major discoveries and numerous hypotheses[4,5].

By comparison with scene segmentation in other senses, however, scene segmentation has received relatively little attention in olfaction. Humans appear to be relatively poor at this task[6], and it has been argued that analytic processing is not a central component of olfaction[7]. It has been shown that the presence and concentrations of mixture components can be successfully extracted from the recorded firing rates of sensory neurons[8,9]; however, no evidence that mice actually perform such computations has yet been presented.

Rokni *et al.*[1] reframe this subject with an incisive experiment (see also ref. 10). Constructing the olfactory analog of *Where's Waldo?*, they asked mice to pick out target odorants in complex backgrounds. Mice were trained to lick for a drink of water only when they detected either of two particular target odorants among a panel of 16 compounds. The backgrounds were constructed from the other 14 odorants, with each distractor odorant present or absent at random. Altogether, the mice were presented with randomly generated mixtures containing up to 14 different compounds with a 50% chance of having one of the target odorants present, corresponding to more than 49,000 possible stimuli. As with *Where's Waldo?*, the authors intended some of their distractors to be very similar, in some experiments, to one of the targets: half of the odorants were from a family of compounds known as tiglates (2-methylbut-2-enoates) containing a shared structural motif.

The first surprise was how well mice performed at this task. Stimuli that happened to have only a single component were recognized correctly with 94% accuracy, but even the most complex mixtures, with 14 components, were scored correctly 85% of the time. By itself, this result reveals a previously unappreciated ability of the rodent olfactory system for scene segmentation.

Although errors were surprisingly rare, the mice in this study performed tens of thousands of trials. This provided the opportunity to ask a deeper question: what factors contributed to mistakes? One important finding was that when the mice did make errors, structural overlap between targets and distractors was a major factor. For tiglate targets, the likelihood of an error increased when there were more tiglate distractors and was unaffected by the number of non-tiglates; for a non-tiglate target, the converse relationship applied. Because the perception of odor quality is not always related in an obvious way to chemical structure, the authors also explored all other ways of splitting their chemicals into two groups. They found that the tiglate/non-tiglate dichotomy was indeed among the very best ways to group the distractors in terms of their potential for confusion.

The last main finding was an intriguing neurophysiological correlate of the animals' behavioral errors. To set the stage for these results, first let's imagine that you are asked to decide whether a group photograph includes your college roommate anywhere in the frame of the picture, and that you'll be paid handsomely if you say "yes" correctly and punished only mildly for a wrong response. One reason you might say "yes" is because you see someone in the photograph who looks like your roommate: it might be her (in which case you'd be correct) or it might be someone else who looks a lot like her (in which case you'd be wrong), but the chance for a reward outweighs the risk. Another reason to say "yes" might be because you notice a portion of your roommate's favorite shirt, even though the rest of the person wearing it is blocked from view by someone standing