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NEUROSCIENCE

Making risk-takers settle

In rats, individual differences in risk preference and in sensitivity to gains compared with losses are controlled by a specific neuronal population, stimulation of which neutralizes risk-seeking behaviour.

NICK G. HOLLON & PAUL E. M. PHILLIPS

The world is rife with uncertainty, affecting everything from financial investments to animals' foraging decisions. Many individuals find uncertainty intrinsically aversive, choosing to settle for a sure thing even if it means forgoing the possibility of a better outcome. But some seek out the chance of a big win, even if it comes with the risk of getting next to nothing in return. In a paper online in *Nature*, Zalocusky *et al.*[1] report that driving the activity of a specific population of neurons can sway risk-seeking animals to make more risk-neutral decisions.

Although the term risk is often used colloquially to imply impending danger, in several subdisciplines of economics the formal definition simply describes the variance in the value or desirability of possible outcomes. Zalocusky *et al.* characterized rats' behaviour in a decision-making task that involved two options, each of which paid out the same sugar reward on average, but which differed in risk. The risky choice yielded either a large or a small reward, whereas the safe option yielded a guaranteed intermediate-sized reward. When choosing the risky option, a rat that received a large reward had made a relative gain, whereas a small reward was a relative loss compared with both the average value of that risky gamble and the certain reward of the safe option.

As a group, the rats' decisions were influenced by recent gains and losses. Like humans, however, not all individuals made the same pattern of choices (Fig. 1). Many rats selected the safe option for most trials, but a subset selected the risky option more than half the time, and these individual differences were stable across days of repeated testing. The likelihood of a rat taking another risk immediately after a winning gamble did not differ between these subgroups. However, there were marked differences in behaviour following a loss — risk-averse rats were more likely to switch to the sure bet, whereas risk-seeking rats were just as likely to gamble again as they were to opt for the certain intermediate reward.

What neural mechanisms account for these differences? A human study[2] implies that how well individuals learn to avoid losses is modulated by diversity in genes that encode D2-subtype receptor proteins for the neurotransmitter molecule dopamine. Moreover, clinical observations[3] indicate that pathological gambling can be a side effect of dopamine-related medications — particularly drugs such as pramipexole (used to treat Parkinson's disease) that directly activate D2 and D3 dopamine-receptor subtypes, which suppresses neural activity.

Previous studies in rodents have used various decision-making tasks to assess risky choices, but pharmacological manipulations of dopamine receptors have produced inconsistent effects[4]. Nonetheless, Zalocusky *et al.* found that treating rats with pramipexole caused a dose-dependent increase in risk-seeking decisions, in agreement with the human clinical data. The authors replicated this effect by infusing the drug directly into the rats' nucleus accumbens, a brain region in the ventral striatum that receives dense input from dopamine-producing neurons and is linked to risky choices[5].

Next, the authors selectively targeted D2-expressing neurons in the nucleus accumbens, engineering these neurons to express either a genetically encoded calcium indicator to monitor neuronal activity or a light-sensitive ion channel that can be used to promote activity. This is in itself a technical feat, improving our ability to analyse these cells in wild-type animals. Zalocusky *et al.* found that, at the time when rats were presumably deciding which reward option to select, activity in the D2-expressing cell population was higher when the previous outcome was a loss than after either gain or safe-choice outcomes. The magnitude of this difference predicted an animal's risk preference — those with greater relative D2-cell activity during decisions that followed losses exhibited risk aversion, whereas those in which D2-cell activity showed little difference following

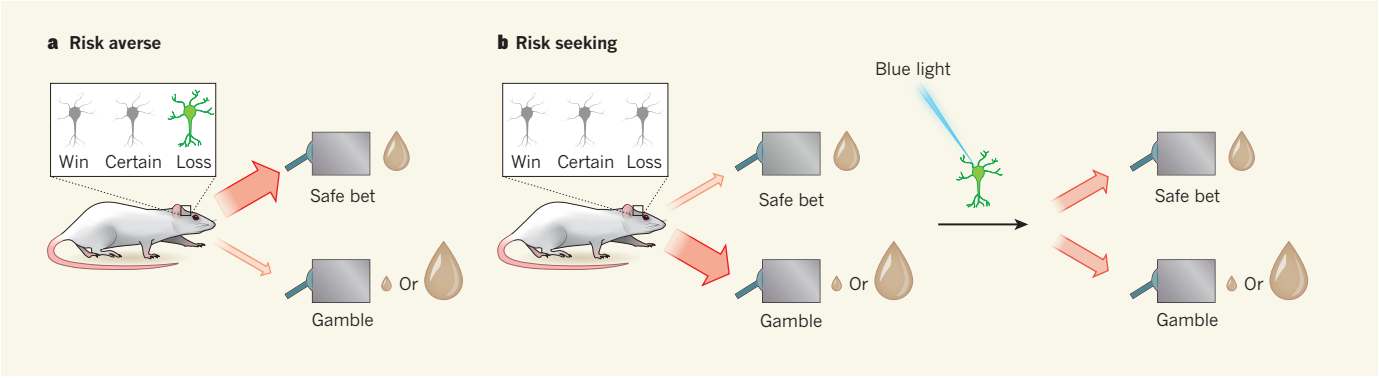

Figure 1 | Neutralizing risk seeking. Zalocusky and colleagues[1] tested rats on a decision-making task that involved a choice between two levers. Pressing one lever yielded a guaranteed, intermediate-sized sugar reward, whereas the other produced either a small or a large reward. **a**, Some rats were risk averse, choosing the safe bet more often than the gamble. When these animals made their choice, neurons in the brain's nucleus accumbens that expressed the D2 receptor protein were more active (blue) following a losing gamble than following a win or a certain outcome. **b**, By contrast, some rats sought out risk — they more often took the gamble, and showed blunted elevation in D2-expressing neuron activity following a loss. Artificially increasing the activity of the D2-expressing neurons using a protein activated by blue light caused risk-seeking rats to make fewer risky choices.

each of the various outcomes exhibited risk-seeking behaviour. Moreover, selectively and briefly activating the D2-expressing cells during the decision period reduced gambling in risk-preferring rats, but had no effect on risk-averse rats.

Behavioural economics has described many ways in which actual human behaviour deviates from the predictions made by long-dominant economic theories, ostensibly owing to emotional and cognitive biases that affect our judgement and decisions. For example, prospect theory[6], a pre-eminent behavioural economic framework, highlights the idea that losses loom larger than gains — a behavioural phenomenon known as loss aversion. Within this framework, Zalocusky and colleagues' behavioural analyses highlight that individual differences in loss sensitivity might underlie variations in risk preference, and the authors' neural recordings and manipulations suggest a plausible mechanism that links loss and risk aversion. Other components of prospect theory that should be considered when interpreting the current data include differences in how individuals subjectively weight probabilities, and in how they determine their basis for comparison when appraising a given outcome as a gain or a loss.

Caveats of the current study involve the neural circuitry of the nucleus accumbens. In other, closely related regions of the striatum, D2-expressing neurons are mostly distinct from D1-expressing neurons, and the neuronal subsets feed into relatively segregated output pathways[7]. This segregation makes interpreting the functions of discrete neuronal circuits fairly straightforward[8]. However, the output pathways of D1- and D2-expressing neurons in the nucleus accumbens might be less segregated[9]. The authors also acknowledge that analysing an entire population of D2-expressing cells obscures potential differences in the information conveyed by discrete ensembles within this population, as occurs in other neural populations[10].

Nevertheless, Zalocusky *et al.* have identified specific neural signatures that predict risk preferences, and demonstrated that the activity of these neurons at specific time points contributes to animals' decisions. These findings offer a potential biological substrate for loss aversion and its contribution to risk attitude. As such, the study represents a success for neuro-economics — a field that strives to link economic models to brain function. ■

Nick G. Hollon *is in the Molecular Neurobiology Laboratory, Salk Institute for Biological Studies, La Jolla, California 92037, USA.* **Paul E. M. Phillips** *is in the Department of Psychiatry & Behavioral Sciences and the Department of Pharmacology, University of Washington, Seattle, Washington 98195, USA. e-mails: nhollon@salk.edu; pemp@uw.edu*

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