machinery is downregulated in differentiated neurons, whereas the machinery for repairing transcribed sequences is maintained or upregulated. Second, perturbations in DNA repair more subtle than those caused by genetic mutations may contribute to the demise of neurons in age-related disorders such as Alzheimer's disease [20]. It will be of particular importance now to determine the influence of both dramatic and subtle variation in the different DNA-damage responses, particularly the SSB repair processing enzymes (Figure 1), as well as environmental factors, such as diet and lifestyle, on the susceptibility of neurons during aging.

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Decision Making: Don't Risk a Delay

Decisions under risk and choices between delayed outcomes are usually treated as two separate problems. A new study suggests that these two classes of decision making are more related than previously thought, and that delay discounting may tune an animal's attitude towards risky choices.

Tobias Kalenscher

Delay not; swift the flight of fortune's greatest favours
    Seneca

What you risk reveals what you value
    Jeanette Winterson

Have you ever lost money playing the lottery? And you still haven't arranged your private retirement provision? If you said yes to the first question, you are in good company, as approximately 40% of my German countrymen occasionally try their luck with the lottery, and even 11% do this on a regular basis [1]. If you answered the latter question with yes, too, you are likewise not alone: in 2001, only one third of all adult German citizens had a voluntarily provided private retirement provision [2]. When playing lotto, you show a certain risk-proneness, as you prefer to invest money into a gamble whose actual outcome is uncertain, instead of using that money to buy a commodity that you could obtain with certainty. On the other hand, when hesitating to contract a retirement plan, you prefer using your budget to afford things that you fancy today, instead of investing it to obtain benefits that are yet to come.

These scenarios exemplify two classes of decision making that are extensively discussed in the choice literature: decisions under risk, and inter-temporal decisions. The first class, decisions under risk, involve choosing between an option with
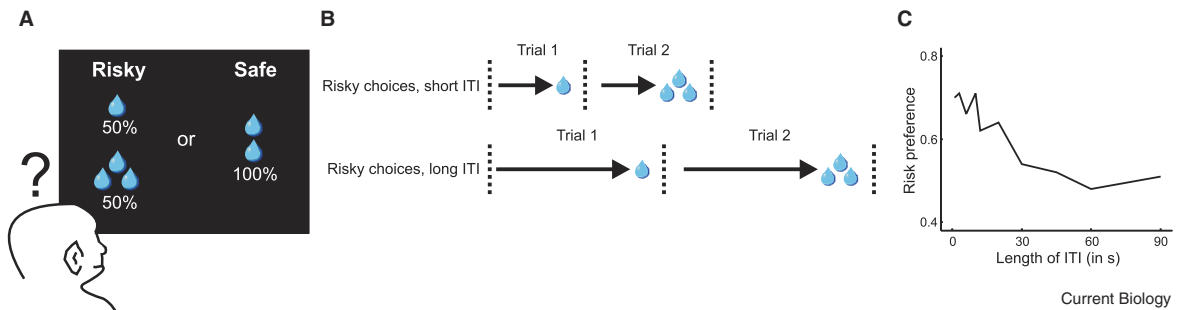
Figure 1. Summary of the new work by Hayden and Platt [13].
(A) In the task the monkeys chose between a safe option yielding a certain, medium-sized reward, and a risky option yielding a large and a small reward with equal probability. The average payoff was identical in both options. (B) In many of the risky choices, the monkeys did not receive the large reward immediately, but had to wait until one of the next trials. This panel illustrates a case where the animals received the large reward after the second risky choice (for simplicity, only risky choices are displayed). The length of the waiting period for the large reward depended on the duration of the intertrial-interval (ITI; duration indicated by the length of the arrows in the figure). With short intertrial-intervals, monkeys did not have to wait a long time for the large reward, but with longer intertrial-intervals, the total waiting time increased, and the monkeys, hence, discounted the large reward stronger. (See [13] for more details.) (C) Although the monkeys were risk-seeking at short intertrial-intervals, the probability of choosing the risky option decreased as the length of the intertrial-interval increased.

a sure outcome (obtaining a commodity with certainty) and another option with a probabilistic outcome (either winning the lottery or not). The second class, inter-temporal decisions, involve choosing between outcomes that will occur at different timepoints in the future (for example to invest in a pension for the far future or buy things now). An extensive body of evidence suggests that animals are risk-sensitive when choosing between certain and uncertain options: they are generally risk-averse, but occasionally risk-seeking [3]. Furthermore, animals discount (devalue) future rewards, and hence prefer immediate over delayed rewards [4–7].

Usually, most researchers treat risky and inter-temporal decisions as separate problems, and only few attempts have been made to theoretically or empirically link them [3,8–12]. A frequent assumption in these attempts is that delays in inter-temporal decisions affect choices in a similar way as uncertainty does in decision making under risk. In other words, animals may equate temporal distance with collection risk: a temporally proximal reward may be preferred over a temporally distant reward in the same way as a certain reward is preferred over a less certain reward, since delayed benefits may be lost during waiting time, and are hence realised with less confidence.

In a thought-stimulating new study, Hayden and Platt [13] turn this logic around, and, instead of assuming that delay is equivalent to risk, argue that the risk attitude of animals may be a function of delay discounting. This idea was triggered by the finding that macaque monkeys were risk-seeking when given the choice between a sure option, yielding a medium-sized reward with certainty, and a risky option offering either a small or a large reward, with a 50% chance each [13,14]. Their risk-proneness was puzzling, because the expected payoff of both options was identical, and monkeys should, therefore, be indifferent between the alternatives, at least in theory.

Why do monkeys prefer the risky choice even though it is not any better than the certain option? To address this question, Hayden and Platt [13] reasoned that, if an animal consistently sticks with the risky option offering a 50% chance of a large payoff, they will with certainty receive a large reward eventually: if not on the current trial, then on a future trial. Hence, the risky strategy gives a practically guaranteed, though potentially delayed large payoff, and monkeys may consequently construe the risky reward not as risky, but as large and delayed (compare [11]). If this were true, then increasing the delay between choices — prolonging the time to the next reward

opportunity — should result in stronger delay discounting, because the monkeys would have to tolerate longer waiting times for the large reward. This, in turn, should be reflected by a reduced tendency to choose the risky option (Figure 1B).

In the new work, Hayden and Platt [13] tested this hypothesis. By making saccades to one of two locations on a computer screen, monkeys could choose between a medium-sized, guaranteed fluid reward, and an even gamble between large and small rewards. The authors varied the intertrial-interval — the time between choices — and hypothesized that the preference for the risky option should decrease as the length of the intertrial-interval increased. This is precisely what they found (Figure 1C). Moreover, they modeled their animals' preference pattern by assuming that delay discounting accounted for the monkeys' risk sensitivity. Consistent with overwhelming evidence from the behavioural literature on temporal discounting, and in support of their hypothesis, a hyperbolic model described the monkeys' delay-dependent shift in risk attitude better than a linear or an exponential model. Just think about this: risk-preference as a function of patience and self-control? We may have to revise some of our stereotypes!
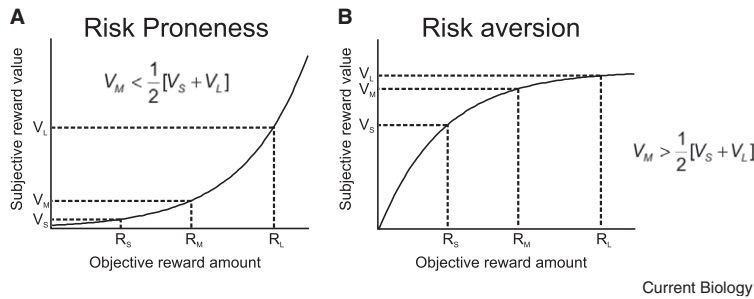
Figure 2. Risk-sensitivity as a function of non-linear value representation.

(A) Risk proneness would be expected if the representation of the subjective reward value were an accelerated function of the objective reward amount (on the x-axis: R_S, small reward; R_M, medium reward; R_L, large reward). Due to the acceleration of the curve, the subjective value of the large reward (V_L on the y-axis) would be disproportionally higher than the value of the medium (V_M) or small reward (V_S). It is assumed that the animal computes the overall expected utility (EU) of the safe and the risky options as the weighted sum of all sampled reward values gained by choosing the respective options. Due to the disproportionally high subjective value of the large reward, the EU of the risky option, consisting of large and small rewards, $EU_{risky} = \frac{1}{2}[V_S + V_L]$, would exceed the EU of the certain, medium-sized reward $EU_{certain} = V_M$. Animals should, hence, prefer the risky over the certain option [16,18–19]. (B) A concave value function would predict risk-aversion due to the disproportionally lower subjective value of the large reward [15–17].

This finding not only strengthens the postulation that risky and inter-temporal decisions share similar cognitive mechanisms, it also opens up entirely new and simple vistas on why animals are risk-sensitive, and not risk neutral, when the expected payoffs are identical. One of the most established accounts in economics and foraging theory is outlined in Figure 2. The theory goes that the utility of a reward [15–17], or its Darwinian fitness [18,19], is not linearly proportional to its objective amount, but increasingly accelerated, so that the value of a large reward is disproportionally higher than that of a small reward (Figure 2A). In such a scenario, the average subjective value of all risky outcomes would exceed the average value of all medium-sized certain outcomes, and animals should prefer the risky over the certain option.

Despite its wide acceptance, this theory fails to explain the current observation that variations in the intertrial-interval affected risk preference, as the length of the intertrial-interval should have only little, if any, effect on the experienced reward value [20]. Hayden and Platt's [13] suggestion that risk-sensitivity is due to interpreting the risky outcome as a large, delayed reward, is capable of explaining the

current data better than the traditional approach, and thus provides a new view on the old problem — a serious challenge to the established risk theories.

Like every other innovative idea in science, this study raises a handful of new questions. First, in contrast to the monkey results, pigeons' risk preferences are not affected by variations in trial length, and hence intertrial-interval duration [10]. Future research needs to determine if this merely reflects a difference between species, or if the current results are a peculiar, non-generalizable effect of the specific task arrangement. Second, alternative accounts need to be ruled out. For example, the monkeys' mental representation of the probability distributions of the risky reward amounts may be asymmetrical [3,18]. If the length of the intertrial-interval has an impact on the skewness of an asymmetric representation, monkeys would make intertrial-interval-dependent and systematically distorted predictions of what to expect from the risky option. This, in turn, should influence their risk preference, and could thus explain the current data, too. Third, the precise cognitive process underlying the computation and representation of the discounted value of the risky/delayed option is unknown, and so is its

neurophysiology. The standard approach is to assume that an animal continuously samples the current subjective value of a reward every time it occurs, and calculates the gamble's overall utility as the weighted sum of all reward values [3,6,18,19]. In contrast, Hayden and Platt's [13] idea implies that the monkeys look forward only until the next large reward. This suggests that the animals do not sample the reward values continuously, but combine the sequence of small payoffs until the large reward into a single value representation. One thing is certain: the next big question to be tackled will be to address whether this assumption holds, and how this focus on large rewards is implemented in the brain. Do not risk missing out on upcoming new and exciting developments in this field.

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T-Cell Subsets: The More the Merrier

This year, IL-17-producing T cells were recognized as a distinct lineage and soon thereafter, the cytokines responsible for their induction were delineated. Now, a transcription factor driving their development has been identified.

Casey T. Weaver[1] and Kenneth M. Murphy[2]

CD4^{+} T cells have a talent for taking on multiple personalities in the face of different infections, each one of which is suited for coordinating the effector activities that best combat the invading pathogen. Early in infection, CD4^{+} T cells become activated and release cytokines that help to orchestrate the activities of other immune cells, such as helping to expand cytotoxic CD8^{+} T cells. During more prolonged infections, CD4^{+} T cells can become polarized towards distinct subsets that promote different types of effector activity. The first such subsets identified, the T_H1 and T_H2 cells [1], have been recognized to arise in response to conditions created by the interplay between pathogens and the innate immune system [2]. The tendency to oversimplify the classification of T-cell subsets into either T_H1 or T_H2 subsets [3] has gradually been tempered, and several different regulatory CD4^{+} T cell subsets are now recognized that act to maintain tolerance and limit immunopathology during infection [4,5].

A detailed picture has emerged to explain the development of these subsets at the transcriptional level. T_H1 development is triggered by pathogens that stimulate production of the cytokines IFN-γ and IL-12, which signal via the factors signal transducer and activator of transcription 1 (STAT1), T-bet (also known as Tbx21) and STAT4 [6]. T_H2 cells emerge when IL-4, through STAT6, induces expression of the transcription factor GATA-3 [7]. Regulatory T cells can develop in response to TGF-β signaling by inducing the transcription factor FoxP3 [8] (Figure 1).

Last year, a new CD4^{+} T-cell lineage was proposed, characterized by production of members of the IL-17 cytokine group, including IL-17A and F, whose development involved mechanisms that were independent of the STAT pathways required for T_H1 and T_H2 cells [9]. Relatively quickly, the development of this lineage, dubbed 'T_H17', was shown to be induced by the combined actions of the cytokines TGF-β and IL-6 [10–12], naturally sparking interest in the transcriptional basis of their development. Dan Littman's lab at New York University School of Medicine has now identified at least one transcriptional component of the T_H17 pathway. A recent report in *Cell* provides compelling evidence that the retinoic-acid-related orphan receptor RORγt is necessary and apparently sufficient for

T_H17 commitment and differentiation [13].

RORγt is an isoform of the widely expressed RORγ gene. The RORγt isoform is expressed during normal thymocyte development at the CD4^{+}CD8^{+} double-positive stage, and its expression is driven by an alternative upstream promoter, generating a transcript that differs slightly from RORγ by encoding a unique amino-terminal sequence. RORγt is also expressed by lymphoid tissue inducer (LTi) cells involved in the development of peripheral lymphoid tissues, such as cryptopatches and lymphoid follicles in the lamina propria [14].

Littman's laboratory had already generated 'GFP-knock in' mice — in which GFP is targeted to the first exon of the gene encoding RORγt to act as a reporter of RORγt expression — for studies of T-cell development and lymphoid organogenesis [15,16]. In examining intestinal cells from these RORγt GFP-knock in mice, this group identified lymphocytes that expressed the RORγt GFP reporter, but at levels that were lower than those expressed by LTi cells. When these reporter-positive lamina propria lymphocyte (LPL) cells were stimulated, a large fraction of TCR$\alpha\beta$ T cells were found to express IL-17, whereas the reporter-negative cells did not express IL-17. By examining differential gene expression in T_H1 and T_H17 cells using DNA microarrays, the authors found that RORγt mRNA was increased in T_H17 cells relative to T_H1 cells, suggesting a link between the RORγt^{+} T cells in the intestinal lamina propria and the T_H17 lineage. In mice homozygous for this GFP-reporter allele, which are