requires endonucleolytic cleavage of crosslinks to initiate DSB responses. This difference and the requirement for different protein complexes during the initial recognition of each lesion could potentially account for the specific requirement for BRCA1 E3 ligase activity in the context of topoisomerase inhibitor-induced DSBs. It is interesting to note that differential requirements for BRCA1 are observed in response to poly(ADP) ribose polymerase inhibitors and ICL agents in mouse cells [17], thus invoking different BRCA1-dependent mechanisms to each response.

While the findings from this study await further investigation in additional cell lines and *in vivo* systems, they have several potential clinical implications. For example, BRCA1 mutant tumors may respond differently to topisomerase inhibitors in comparison to ICL agents in a manner that depends on where the BRCA1 mutation is located. Additionally, resistance mechanisms to each agent in tumors may not be equivalent. Finally, the studies by Sato *et al.* [12] emphasize the power of genetic systems to uncover additional complexity within cellular DNA damage responses and our ever-evolving understanding of how BRCA1 contributes to this process.

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Decision Making: How the Brain Weighs the Evidence

The brain has to weigh incoming sensory evidence against prior beliefs, the relative weight given to each depending on the relative uncertainties. Neuroscience now shows how the human brain accomplishes this.

Mathieu d'Acremont and Peter Bossaerts

Decisions are based on a combination of prior beliefs and evidence: the latter should be weighted to a greater extent if one is more uncertain about the former, and *vice versa*. In this issue of *Current Biology*, Vilares *et al*. [1] report experiments involving a task where perceptual evidence had to be evaluated appropriately against prior beliefs. These experiments have provided fascinating new insight into the neural processing behind sophisticated human reasoning. They show how the human brain encodes the signals that are needed to optimally merge available evidence with prior beliefs in order to reach a well-informed decision.

Vilares *et al.* [1] studied a situation like the following. Imagine you are playing a guessing game with your friends Bill and Betty. Bill will throw a gold coin in the middle of a murky pond. Betty sees where it landed, but you do not. You are to guess where the gold coin is. Betty will help you by tossing three silver coins in the direction of Bill's coin. She will show you where her coins landed (Figure 1).

To be good at this guessing game, you primarily need to track how good Bill and Betty are at coin tossing. If Bill isn't good and his coin could land anywhere despite his aiming for the middle, while Betty is likely to match Bill's toss, then you should rely more on the evidence Betty shows. Conversely, if Betty is lousy at coin tossing, while

Bill is good, you would want to bias your guess towards what you know Bill aimed at: the middle of the pond.

In all cases, you weigh your *prior belief* about the true coin location after Bill's coin throw with the *evidence* based on Betty's tosses. Weights depend on how uncertain you are about Betty's ability to match the true location of Bill's coin *relative to* Bill's skill in throwing his coin to the middle of the pond. That is, optimal guesses depend on the combination of prior beliefs (about Bill) with the evidence (that Betty generates) based on the relative uncertainty.

In a stylized version of this guessing game, Vilares *et al.* [1] show that humans indeed let their decisions be informed by the relative uncertainty of Bill's and Betty's coin throwing abilities. Little is known, however, about the neural mechanisms that lead to the observed choices in this perceptual decision game: specifically, *how is relative uncertainty encoded?*

There are a number of ways one can imagine that the brain encodes uncertainties. This includes a popular idea, which posits that uncertainty need not be encoded explicitly. According to this *co-localization hypothesis* [2,3], uncertainty is implicitly encoded through the precision of the signal generated by the collective activation of an ensemble of neurons. Diametrically opposed is the idea that uncertainty is encoded separately, and activation of neurons specialized in tracking uncertainty inhibits or excites output from neurons elsewhere that express the prior belief or the observed evidence. This hypothesis is inspired by tasks requiring choices among different gambles, where uncertainty has been found to be encoded separately from expected reward [4,5]. Finally, uncertainties about prior beliefs and about evidence may be tracked separately too, rather than merged into one neural weighting signal.

Using functional magnetic resonance imaging (fMRI), Vilares *et al.* [1] discovered that uncertainty about perceptual evidence is located in the same brain regions that process the perceptual evidence in the first place (the visuomotor regions), while uncertainty about prior beliefs is encoded in a range of frontal cortical regions (insula, orbito-frontal cortex) and sub-cortical (putamen, amygdala) regions.

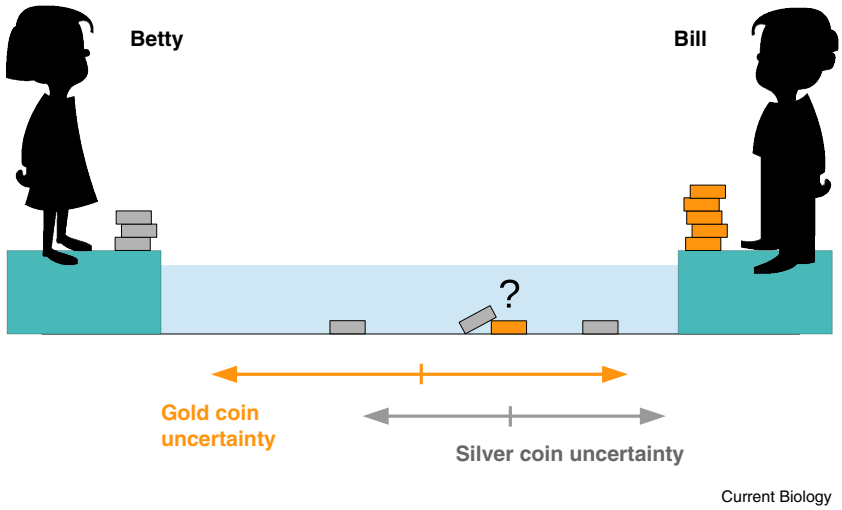

Figure 1. Coin tossing game.

Bill aims at the center of the pond and throws a gold coin first. Then Betty throws several silver coins, aiming for the gold coin. The game is to guess the position of the gold coin when one only observes Betty's silver coins.

Interestingly, the identification of an fMRI signal correlating with evidence uncertainty in the regions processing the perceptual evidence is compatible with the idea that uncertainty is co-localized. Uncertainty about prior beliefs is differentially localized in non-perceptual brain regions, generally known to be involved in executive control, and in particular, in tracking of reward and risk when choosing between gambles.

These findings constitute a significant step towards uncovering the neural mechanism behind human belief formation. Subsequent steps include studying the neural representation of beliefs themselves — of the *probabilities* that subjects assigned to all contingencies [6]. Where is the prior probability encoded that the gold coin has landed in a given area of the pool? Where are the probabilities based solely on the evidence from Betty's silver coins? Another important question for future research is how the probabilities (beliefs) are updated, one coin toss at a time. Is the updating optimal — does it conform to Bayes' law [7], and if so, how does the brain accomplish this?

Further research is also needed to determine to what extent the results of Vilares *et al.* [1] generalize to other settings. Very different brain activation may ensue when presentation of information is altered. For example, the authors told subjects only that Bill's ability to toss gold coins changed from one block of trials to another, but not by how much. As such, subjects needed experience to form correct prior beliefs. Alternatively, Vilares *et al.* [1] could have provided explicit, verbal information, for example: "Bill's gold coin on average lands 30 cm from the middle". Prior belief uncertainty may then be encoded in a different way because verbal information would engage the semantic memory system [8], while learning by experience recruits the episodic memory system [9].

The reader may be familiar with tasks on learning to predict uncertain rewards (or avoiding stochastic losses). Major progress has been made towards understanding the underlying neural processes [10–14]. One question is whether the coin tossing task in [1] is different in some important respect. It is, because the events about which subjects were asked to express beliefs had no value to the subject *per se.* Whether Bill's gold coin was more likely to land on the edge of the pond did not change subjects' rewards. As such, belief formation and valuation were dissociated. In reward learning tasks, instead, the two are confounded. The coin-tossing analog of a typical reward learning task would be to pay the subject depending on where Bill's gold coin landed. There, the events (Bill's coin throws) directly entail value.

Vilares *et al.* [1] have therefore started to discover the neural mechanisms of formation of beliefs about stimuli (in their case, coin tosses) that are devoid of value themselves. We would argue that this represents an important aspect of typical learning tasks humans are exposed to and that unfortunately has been neglected in the reward learning literature. Indeed, humans routinely have to predict events (for example, snow) before knowing what opportunities (skiing; driving), and hence, what value (fun; danger) these events will entail. Classical conditioning theories such as reinforcement learning cannot readily deal with such situations.

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