Should I buy this book? How we construct prospective value

Jamil P Bhanji & Mauricio R Delgado

People are able to form preferences for unfamiliar items, such as new books or foods, before experiencing them. A study in this issue of *Nature Neuroscience* finds that prospective evaluations of unfamiliar items can be based on stored neural representations of relevant, familiar items.

In 2009, a novel entitled *Pride and Prejudice and Zombies*[1] was released, and readers browsing in bookstores faced the intriguing, but simple, problem of deciding whether to buy the book. The problem is intriguing because it encapsulates a question of great interest to scientists studying the neural bases of decision-making: how do people evaluate a new item when they have no past experience with it? At the same time, this example is simple because there are telling clues for the reader in the title. Anyone familiar with classic literature and popular culture can instantly imagine the book as a mix of Jane Austen's classic novel and the undead characters from zombie films. The imagined picture is somewhere between exciting and repulsive and allows potential readers to gauge what they could expect without knowing the details. That is, they can prospectively evaluate the book before reading it. This seems simple enough, but how do our brains actually solve this problem of prospective evaluation? Barron *et al.*[2] address this question in this issue of *Nature Neuroscience* by showing that the human brain calls up memories of familiar items to form a prospective evaluation of a new, unfamiliar item.

Progress toward understanding neural systems that evaluate goods has been made by linking activity levels in a brain region (for example, the striatum) to variables, such as expected value, that might be computed in the decision process[3,4]. Barron *et al.*[2] took an entirely different approach. Rather than examining a relation between a decision variable and activity of a neural region, they investigated the information content of a neural response. That is, when people evaluate an unfamiliar item that can be broken down into familiar components, do neural responses include representations from memory of each component (for example, evaluating *Pride and Prejudice and Zombies* by concurrently recalling separate memories of Jane Austen's novel and zombie films)? Barron *et al.*[2] took on the challenge of probing the content of a neural response by the creative use of a phenomenon known as functional magnetic resonance imaging (fMRI) repetition suppression.

fMRI repetition suppression refers to the decreased response observed in the blood oxygen level–dependent (BOLD) signal for information that is repeated[5] (**Fig. 1a**). Although there is ongoing debate concerning its underlying mechanism, the phenomenon has traditionally been used in vision research[5,6] to probe the characteristics of information represented in a neural response to a stimulus. Barron *et al.*[2] gave the method a novel twist to examine neural representations during prospective evaluation. Whereas previous studies manipulated the repeated characteristics of visual stimuli (for example, the size of a raspberry) to test whether a neural representation is sensitive to those characteristics[5,6], Barron *et al.*[2] instead presented different stimuli one after another. They reasoned that a suppressed BOLD response to the second stimulus would indicate that neural representations of the two contained information in common. Specifically, participants imagined a familiar food (for example, raspberries or avocados) and then imagined an unfamiliar combination involving the familiar food (for example, a raspberry avocado smoothie). A suppressed BOLD response during the unfamiliar combination meant that a neural representation of the familiar component (for example, raspberries) was repeated when they imagined the unfamiliar combination (**Fig. 1b**).

The authors observed that using the knowledge of familiar foods to evaluate an unfamiliar combination of such foods involved two brain regions, the hippocampus and the medial prefrontal cortex (mPFC), that have been implicated in memory[7] and evaluative[3] processes, respectively. When participants imagined an unfamiliar food (for example, raspberry avocado smoothie) soon after imagining one of its familiar components (raspberries), regions of hippocampus and mPFC showed a decreased BOLD response. This pattern of BOLD response was measured in comparison to a trial in which the response of the unfamiliar food followed an unrelated familiar food (for example, popcorn). The only difference between the two instances of the unfamiliar food presentation was what preceded each (raspberry or popcorn). Thus, the authors reasoned that the suppressed response in hippocampus and mPFC resulted from repeating the representation of the familiar component (raspberries) when participants imagined the unfamiliar combination (raspberry avocado smoothie) soon after the component.

People may do well to rely on familiar memories to imagine an unfamiliar combination, but do we continue to do so once the combination has become more familiar? Barron *et al.*[2] found that experience changes the process of prospective evaluation, whether that experience comes from practice imagining an unfamiliar food combination or from the direct experience of tasting it. Specifically, participants formed a neural representation of

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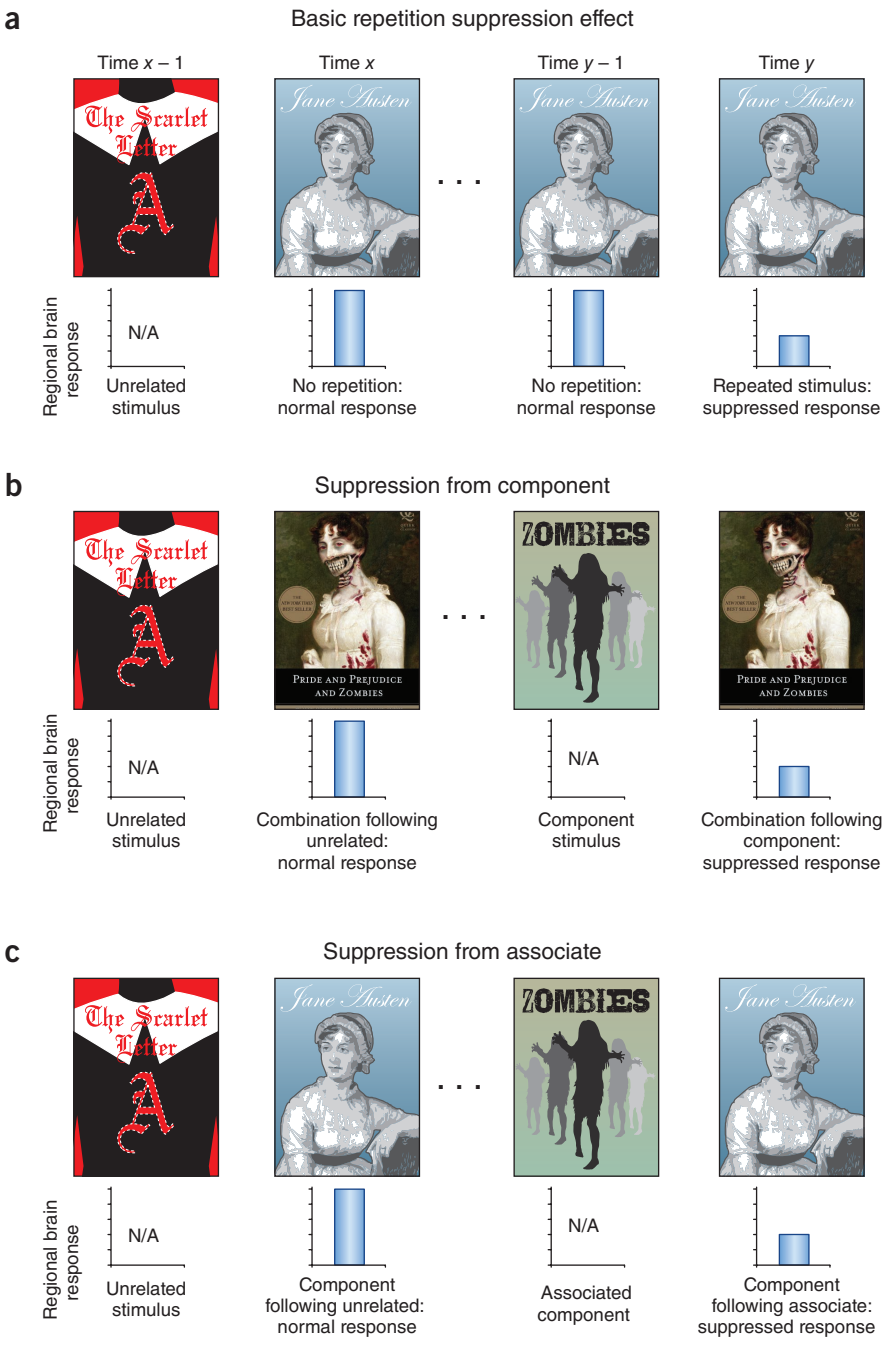

Figure 1 Repetition suppression effects reveal elements in common between neural responses to distinct stimuli. (**a**) In a basic example of repetition suppression, a neural region that responds to properties of a stimulus exhibits a reduced response when those properties are repeated. The researcher then infers that the repeated properties are part of the neural region's representation of the stimulus[6]. (**b**) Barron *et al.*[2] observed suppressed neural responses (in hippocampus and mPFC) if participants imagined a novel, unfamiliar combination of two familiar items soon after imagining either familiar item individually (for example, imagining *Pride and Prejudice and Zombies* after imagining a zombie movie). The effect suggests that the neural representations of familiar components are invoked when imagining their unfamiliar combination. (**c**) Barron *et al.*[2] also found suppressed neural responses (in mPFC) to a familiar component if it followed its other half from the imagined combination (for example, imagining Jane Austen's *Pride and Prejudice* after imagining a zombie film). This suppression effect suggests that imagining a novel, unfamiliar combination of two familiar items leads to the incorporation of one familiar item into the neural representation of the other. N/A, not applicable. Cover from ref. 1 is by Doogie Horner, reproduced by permission of Quirk Books.

the unfamiliar combination that was independent of its components after 20 min of practice imagining the unfamiliar combination, which was the case from the outset for participants who tasted the food combinations at the beginning of the experiment. In other words, with practice, participants seemed able to imagine a raspberry avocado smoothie without needing to call upon representations of raspberries and avocados from memory. This finding suggests the possibility that, in a way, evaluations of an unfamiliar item can be trained as much by imagination as by direct experience. A question that might be asked next is whether this kind of practiced imagination makes people better able to predict what they will like. Or, more broadly, what characteristics of information processing lead to accurate prospective evaluations? One idea is that, to accurately use a memory to evaluate a new item, we must reinstate the same pattern of neural activity associated with the original encoding of the memory[8]. Further research inspired by these findings may lead to a more complete understanding of how prospective evaluation can lead to good or bad choices and influence people's happiness with those choices[9].

Beyond the neural response associated with evaluating a novel combination, Barron *et al.*[2] also uncovered an intriguing dynamic in associations between neural representations of the familiar components that they mentally combined. By virtue of having to recall two familiar items together to evaluate an unfamiliar item, the neural representations of the familiar items became linked. Specifically, Barron *et al.*[2] found that the mPFC (and the hippocampus for some participants) exhibited repetition suppression when one component of an unfamiliar combination (for example, raspberries) followed another (avocados). This finding suggests that, after having learned to associate two familiar foods by imagining them together, the neural representation of one includes the other (**Fig. 1c**). In other words, once one has thought about raspberry avocado smoothies, the neural representation of raspberries includes avocados, and vice versa. The strength of the effect was modulated by how much the participant valued the imagined combination of the two foods. If a person thought that raspberry avocado smoothies would taste good, then the mPFC and hippocampus representations of raspberries and avocados were more strongly linked, as evidenced by the repetition suppression effect. This finding touches on a fascinating way in which the end product of an evaluation can influence memories that formed the evaluation, as though someone

who likes the idea of *Pride and Prejudice and Zombies* (but not someone who dislikes the combination) will then remember Jane Austin and zombies together.

The results of Barron *et al.*[2] have far-reaching implications, not only for research on the neuroscience of decision-making, but also for research on the interplay between evaluation and memory processes in the brain. Studies examining how we evaluate all kinds of familiar items have associated mPFC activity (and other regions, such as the striatum) with the end product of an evaluation (that is, how much is this good worth?)[3,4], but Barron *et al.*[2] associate mPFC with the process of using memories to influence evaluations and even using evaluations to influence memories. Their findings raise fascinating questions. Does the value of an imagined combination not only affect associations between the components, but also influence their valuations (for example, liking Jane Austen more as a consequence of imagining *Pride and Prejudice and Zombies*)? Other research shows that a positive evaluation can transfer from a valuable stimulus to another non-valuable, but associated, stimulus through interactions involving hippocampus and striatum[10]. It could be that a similar mechanism is at work when imagining two items together. At a different level of analysis, could the mechanisms examined in Barron *et al.*[2] be involved when people reminisce over positive memories? Recalling memories can be a constructive process[11]. For example, reminiscing over a past vacation can involve putting details together and reconstructing the memory in a manner that might resemble constructing an evaluation of a novel item. Reconstructing memories in a positive way can improve mood and have other psychological benefits[12]; thus, the findings of Barron *et al.*[2] could inspire further understanding of factors that promote well-being.

With further research, the findings of Barron *et al.*[2] may even prove insightful for the study of other elusive mental operations, such as creative thought. Just as people can put together knowledge of existing items to evaluate something new, people can also synthesize existing ideas to create something new[13]. In other words, we might find something very close to what Barron *et al.*[2] found if we looked inside the brains of authors brainstorming new book titles. In this way, Barron *et al.*[2] provide a promising template for research on creativity and could eventually help us understand where ideas like *Pride and Prejudice and Zombies* come from.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Starvation favors glioma stem cells

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High-grade glioblastomas survive glucose-poor environments by becoming more stem cell–like. Increased glucose uptake by the transporter Glut3, a new biomarker of poor clinical outcome, drives this enhanced malignant progression.

Altered metabolism is a hallmark of cancer. Most cancer cells carry out aerobic glycolysis, associated with lactic acid fermentation in the cytoplasm, rather than oxidative phosphorylation in the mitochondria (**Fig. 1a**). This provides macromolecules needed for tumor growth, at the expense of energy production. Otto Warburg was the first to observe this phenomenon in cancer cells, which is now known as the Warburg effect[1]. Astrocytes and neurons in the brain have among the highest glucose and ATP requirements of any cell type in the body. These cells are highly dependent on glucose as a carbon source and should be unusually vulnerable to the reduced levels of ATP available through the Warburg effect. Because normal brain cells consume glucose so avidly, tumor cells from the most common primary brain tumors, namely glioblastomas (GBMs), upregulate glycolysis to more than three times that in normal brain tissue[2]. Brain tumor initiating cells (BTICs, also called glioma stem cells), the putative engine driving these tumors, have been shown to reside in hypoxic areas, also raising questions as to how BTICs manage to thrive in a relatively inhospitable microenvironment. In this issue of *Nature Neuroscience*, Flavahan *et al.*[3] show that BTICs are more successful in competing for nutrient resources than other cells of the tumor, providing insights into BTICs as drivers of tumor growth and survival.

Glioma represents the most common primary brain tumor in both adults and in children. Glioblastomas (GBMs), the highest grade tumors, are the most commonly arising and lethal type of glioma. Despite decades of clinical and basic research, the prognosis for most patients with malignant glioma remains poor[4]. Thus, it is crucial to learn what drives glioma progression. The identification of tumor cells with stem cell properties, termed cancer stem cells (CSCs), has enhanced our understanding of tumor initiation and growth. Gliomas were among the first solid tumors in which the CSC model was demonstrated experimentally[5]. BTICs have been shown to express stem cell markers, to self-renew and to differentiate into all three neural lineages. Furthermore, BTICs can give rise to tumors following xenotransplantation, and they display radio- and chemoresistance[6,7]. Most conventional therapies preferentially target the rapidly proliferating, but nontumorigenic, components of solid tumors, sparing the relatively quiescent CSCs and leaving a reservoir of cells to drive relapse.

To explore the effects of glucose restriction on the CSC phenotype, Flavahan *et al.*[3] exposed human GBM cells to low glucose. They found upregulated expression of stem

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