Jamais vu all over again

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Abstract (35 words, now 35)

What is the basis for the feeling that someplace or someone is familiar? Molas et al. have identified brain structures involved in signaling familiarity, a necessary element for the expression of preference for novelty.

Body (•1000–1500 words; good target: 10 paragraphs, 100–150 words each)

Most of us have had the experience of encountering a person who looks very familiar, yet we cannot recall having met. A related phenomenon is *déjà vu*, a vivid but inaccurate feeling that the current situation is familiar. This strong sense of familiarity occurs in the absence of any explicit evidence that the situation was previously encountered. *Déjà vu* is generally accepted to be a memory-based illusion resulting from a brief bout of anomolous activity in memory-related structures of the medial temporal lobe [1]. *Jamais vu,* sometimes regarded as the opposite of *déjà vu*, is the intense feeling that the current circumstances are novel and strange, while objectively realizing that they have, indeed, been previously experienced [2]. Both *déjà vu* and *jamais vu* occur in temporal lobe epilepsy [3] as well as in normal individuals under ordinary situations. Compared with déjà vu, *jamais vu* is less common in normal populations and much more prevalent in some neuropsychiatric conditions; this difference in prevalence suggests that novelty and familiarity may be signaled by different brain pathways.

Moles et al. provide new evidence explaining how we differentiate the new and strange from the old and familiar. They have identified a circuit in the midbrain that combines familiarity and novelty signals to allow the expression of novelty preference. a capacity exhibited by all mammals that have been tested (need citation). Novelty preference and preferential exploration of novelty have yielded a number of paradigms useful in the of study attention, perception, recognition, sociability, and cognitive development. The novelty paradigm, originally developed by Fantz [4], has been used to study cognition in nonverbal species including chicks, rodents, non-human primates, and infant humans.

Moles et al. employed two versions of the classic novelty paradigm. The first is a social interaction test in which a mouse is first allowed to explore an empty pen and a pen holding a nonfamiliar (or novel) juvenile demonstrator mouse (Figure 1a, left). In the test phase, the subject mouse is presented with the now familiar demonstrator mouse and a novel demonstrator mouse. Normal mice will explore the demonstrator mouse over the empty pen and the novel demonstrator mouse over the familiar mouse. The second version of the novelty paradigm is spontaneous object recognition (Figure 1a, right). Here, the mouse is presented with two identical objects in the study phase. In the test phase, the mouse is presented with a third copy of a familiar object along with a novel object. Normal mice will preferentially explore the novel object, demonstrating novelty preference.

Social and nonsocial recognition memory, as identified by the novelty paradigm, rely on medial temporal lobe structures [5-9], but processing information about novelty is also important for non-mnemonic cognitive functions. Dopaminergic areas in the midbrain, including the ventral tegmental area (VTA), are known to code novelty [10], but how novel items become familiar is not known. To address the issue of where familiarity signals emerge in the mammalian brain, the authors took a hint from zebrafish experiments in which social conflict resolution was found to rely on medial habenula (mHB) input to the interpeduncular nucleus (IPN) [11]. Molas et al. hypothesized that the IPN and its input from mHB might be involved in signaling familiarity (Fig 1c).

Molas et al. began by testing mice in a version of the novelty paradigm that involves social interaction (Fig 1a, left). A subject mouse actively investigated a novel demonstrator mouse, and investigation diminished as the demonstrator mouse became more familiar. When a second novel demonstrator mouse was presented, the subject mice showed rebound of social investigation. If the IPN is involved in signaling familiarity, then social familiarity should activate the IPN. Using the immediate early gene, c-Fos, as a proxy for neuronal activation, the authors

found that IPN activation was much higher following exposure to a familiar demonstrator mouse compared to that following a novel demonstrator mouse. The same results were observed with exposure to familiar objects (Fig 1a, right). The authors next asked whether IPN activity increased with the degree of familiarity. Subject mice were exposed to the same demonstrator mouse up to seven times (Fig 1b). c-Fos progressively increased with successive encounters, peaking on the fifth day of exposure.

Interestingly, c-Fos was evident in IPN cells containing the neurotransmitter, γ-aminobutyric acid (GABA). This suggests that IPN cells involved in signaling familiarity are largely inhibitory GABAergic interneurons (Fig 1d). The authors hypothesized that the IPN inhibitory interneurons act as a brake for novelty-induced exploration. To test this, they used optogenetics. Halorhodopsin, a yellow light-activated chloride pump, was expressed in the GABAergic interneurons of the IPN in order to optically suppress the cells' activity. Suppression of inhibitory interneurons would be expected to increase overall IPN activity. Mice explored the demonstrator mouse for two consecutive days (Fig 1a, left, study phase). On the third day, mice were offered the choice between the familiar mouse and a novel mouse (Fig 1a, left, test phase). For half the mice, yellow light was delivered to halorhodopsin-expressing IPN interneurons in order to suppress their activity. The other half of the mice served as controls and received no light. As expected, control mice explored the novel mouse much more than the familiar one. In contrast, the experimental mice explored the familiar mouse just as much as the novel one (Fig 1e).

Next the authors expressed channelrhodopsin-2, a blue light-activated cation channel, in IPN inhibitory interneurons. Activation of interneurons should have had the effect of decreasing overall IPN activity. Photostimulation of the inhibitory IPN cells decreased subjects' exploration of novel mice without changing exploration of familiar mice. Experimental results with inanimate objects paralleled results with social stimuli in that photostimulation of the inhibitory IPN cells decreased subjects' exploration of novel objects. Thus, if IPN interneurons are suppressed, overall IPN activity increases and exploration of familiarity increases. If IPN interneurons are activated, overall activity decreases and permits exploration of novelty. The authors suggested that IPN interneurons act as a brake on exploration of familiarity, allowing the expression of novelty preference.

Finally, Molas et al. used optogenetic tools to modulate excitatory input to the IPN arising from the mHB and the VTA. These inputs were hypothesized to provide familiarity and novelty signaling to the IPN, respectively (Fig 1d). Photosuppression of the mHb terminals in the IPN increased exploration of familiar social and nonsocial stimuli without affecting exploration of novel stimuli (Fig 1e, center). Photostimulation of the mHb terminals in the IPN decreased exploration of novel social and nonsocial stimuli without affecting exploration of familiar stimuli (Fig 1f, center). Finally, the authors photostimulated the VTA dopaminergic terminals in the IPN. Similar to the phenomenon of *jamais vu*, this manipulation mimicked the novelty signal resulting in increased exploration of a familiar mouse (Fig 1e, right). Interestingly, the photostimulation of dopamine terminals did not affect exploration of inanimate objects.

It is tempting to conclude that novelty is simply the absence of memory-based familiarity. Yet a number of studies have provided evidence that the processing of novelty information and familiarity information can be functionally dissociated in the forebrain medial temporal lobe memory system. A study using c-Fos expression methods combined with structural equation modeling found evidence that in rats presented with familiar objects, caudal perirhinal cortex activated the entorhinal-to-hippocampal field CA1 pathway, also known as the temporo-ammonic pathway [12]. When rats were presented with novel objects, perirhinal cortex activated the entorhinal-to-dentate gyrus pathway, also known as the perforant pathway. Another c-Fos

study showed that exploration of a novel environment increased activation in the hippocampus, prelimbic prefrontal cortex, and the dopaminergic reward circuit [13]. Exploration of a familiar environment, however, increased activation in the amygdala. A better understanding of how the midbrain circuits interact with the forebrain circuits could help explain the human prevalence differences in *déjà vu* and *jamais vu*. Future work could elucidate other neural bases of neuropsychiatric disorders by explaining dysregulation of novelty and familiarity processing, depersonalization, derealization, and other symptoms that involve detachment from familiar surroundings.

In this elegant series of experiments, Molas et al. have elucidated the mechanisms and circuitry by which novelty transitions to familiarity. A primary contribution of their work is the demonstration that novelty and familiarity are signaled by different pathways, partially overlapping in the IPN, to support novelty preference. These findings may explain why *déjà vu* and *jamais vu* contribute differently to symptom profiles of neuropsychiatric disorders. More importantly, the findings of Molas et al. have profound implications for understanding and treating a number of neuropsychiatric disorders in which processing of novelty and familiarity are compromised.

Foot note: subtitle is quoted from [14].

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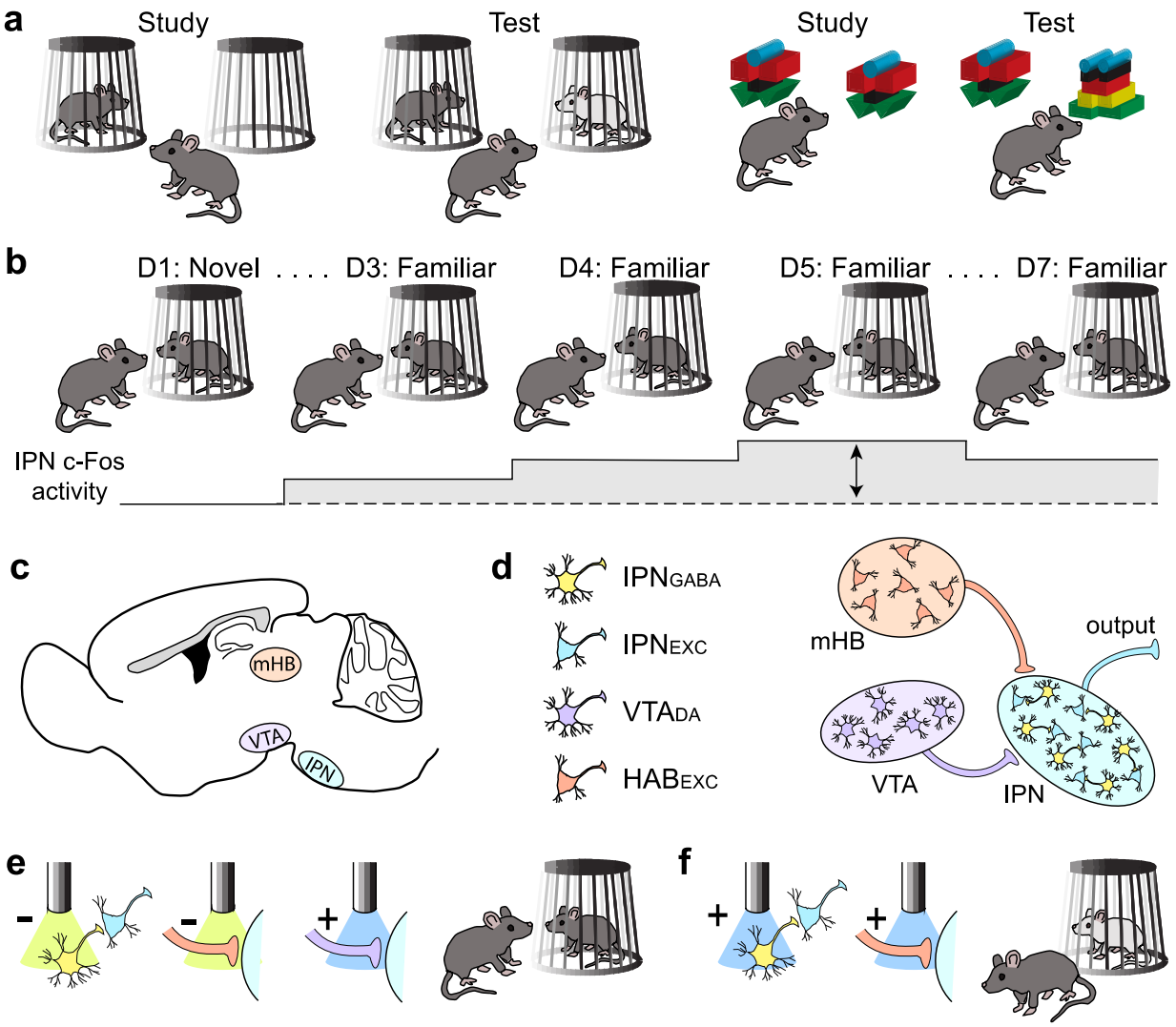

Figure 1. A circuit-based mechanism for familiarity signaling and novelty preference. (a) Mammals show a preference for novelty. A mouse will explore an unfamiliar mouse more than a familiar mouse (left) and a novel object more than a familiar object (right). (b) Following repeated exposures to the same mouse, shown left to right, c-Fos activity in the IPN increased compared to activity following exposure to a novel mouse, peaking at the fifth exposure to the same mouse. (c) This sagittal schematic of the mouse brain shows the location of the interpeduncular nucleus (IPN) together with two important input regions, the medial habenula (mHB), and the ventral tegmental area (VTA). (d) These regions form a circuit for familiarity signaling and expression of novelty preference in which the IPN is a critical node. Cholinergic/glutamatergic input from the mHB provides a familiarity signal and dopaminergic input from the VTA provides a novelty signal. (e) Optical suppression of IPN interneurons or mHB input to the IPN boosts the familiarity signal increasing familiarity exploration with no impact on novelty exploration. Optical activation of VTA input to IPN also increases familiarity exploration, presumably by mimicking novelty. (f) Optical activation of IPN interneurons or mHB input to IPN degrades the familiarity signal decreasing novelty exploration with no impact on familiarity exploration. Other abbreviations: D, day; DA, dopamine; EXC, excitatory; GABA, GABAergic.