As with all pathways in biology, the sequence of events described by the authors is embedded in a complex cellular environment that interacts with and potentially alters the described course of pathogenesis. **Figure 1** attempts to capture the authors' main points, as well as this cellular context. The G_4C_2 expansion leads to R-loop formation and DNA damage, as well as to dipeptide RAN synthesis and inhibition of DNA repair. These two pathways, acting together, are sufficient to trigger neurodegeneration, but both can be worsened by other events taking place in the cell. Consider, for example, the creation of DNA damage by R-loops. Cells are constantly subjected to DNA damage and so have evolved overlapping layers of repair processes. Despite these restorative efforts, unrepaired DNA damage accumulates and likely serves as a master driver of the aging process in neurons[12] and other cells[13] of the brain. Indeed, neuronal activity itself has been proposed to contribute to DNA double-strand breaks[14]. We may be able to fix our breaks when we are young, but as DNA damage accumulates with age (at this locus and others), we are less and less able to correct the errors. This makes our brain cells increasingly vulnerable to the damage caused by the *C9orf72* expansions. This would lead to the prediction that we should be more vulnerable to ALS and FTD as we age, and this is indeed the case.

A second way in which context could work to enhance the R-loop and DPR story is in regard to DNA repair. Any somatic event that leads to a loss of ATM, for example, would increase the sensitivity of cells to downstream events requiring its activity. Compromised ATM activity has been shown to increase with age. Indeed, the loss of ATM activity can occur on a neuron-by-neuron basis during neurodegenerative disease[15]. If a neuron begins with a deficit of ATM activity, the effects of enhanced G_4C_2 production would be amplified and thus hasten the cell along the road to destruction.

The study by Walker *et al.*[2] thus answers many questions but raises many others, as any good paper should. The interdependent pathways described in detail by the authors offer a compelling model that accounts for many of the known features of *C9orf72*-repeat-driven disease. More importantly, in describing a molecular pathway at work in two uncommon diseases, they potentially pull back the curtains covering explanations for the loss of neurons in a wide range of more common neurodegenerative conditions, including Parkinson's, Huntington's and Alzheimer's diseases.

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Jamais vu all over again

Rebecca D Burwell & Victoria L Templer

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.

Most of us have had the experience of encountering a person who looks 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 anomalous 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, despite the objective realization 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.

Molas *et al.*[4] provide 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 virtually all mammals that have been tested. Novelty preference and preferential exploration of novelty have yielded a number of tasks useful in the study of attention, perception, recognition, sociability and cognitive development. The novelty task, originally developed by Fantz[5], has been used to study cognition in nonverbal subjects including chicks, rodents, nonhuman primates and infant humans.

Molas *et al.* employed two versions of the classic novelty task. The first is a social interaction test in which a mouse is first allowed to explore an empty pen and a pen holding an unfamiliar (or novel) juvenile demonstrator mouse (**Fig. 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 in preference to the empty pen and the novel demonstrator mouse in preference to the familiar demonstrator mouse. The second version of the novelty task is spontaneous object recognition (**Fig. 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 the familiar object along with a novel object. Normal mice

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will preferentially explore the novel object, demonstrating novelty preference.

Social and nonsocial recognition memory, as identified by the novelty task, rely on medial temporal lobe structures[6–10], 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 encode novelty[11], 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)[12]. Molas *et al.* thought that the IPN and its input from mHB might be involved in signaling familiarity.

The authors began by testing mice in a version of the novelty task that involves social interaction (**Fig. 1a**, left). A subject mouse would actively investigate 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 expression of the immediate-early gene c-Fos as a proxy for neuronal activation, the authors found that IPN activation was much higher upon exposure to a familiar demonstrator mouse than upon exposure to 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 once a day for up to 7 days. c-Fos increased progressively with successive encounters, peaking on the fifth day of exposure (**Fig. 1b**).

Interestingly, c-Fos was evident in IPN cells containing the neurotransmitter GABA. This suggests that IPN cells involved in signaling familiarity are largely inhibitory GABAergic interneurons (**Fig. 1c**,**d**). The authors hypothesized that the IPN inhibitory interneurons act as a brake for novelty-induced exploration. To test this, they used optogenetics, expressing a yellow-light-activated chloride pump, halorhodopsin, in the GABAergic interneurons of the IPN to enable optical suppression of the cells' activity. Suppression of interneurons would be expected to increase overall IPN activity. Mice explored the demonstrator mouse for two consecutive days. On the third day, they were offered the choice between the familiar mouse and a novel mouse. For half the mice, yellow light was delivered to halorhodopsin-expressing IPN interneurons to suppress their activity (**Fig. 1e**, left). 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 light-exposed mice explored the familiar mouse just as much as the novel one (**Fig. 1e**, right).

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 (**Fig. 1f**, left). Photostimulation of the inhibitory IPN cells decreased subjects' exploration of novel mice without changing exploration of familiar mice (**Fig. 1f**, right). Tests with inanimate objects paralleled results with social stimuli: photostimulation of the inhibitory IPN cells decreased subjects' exploration of novel objects. Thus, when IPN interneurons are suppressed, overall IPN activity increases and exploration of familiarity increases. When IPN interneurons are activated, overall activity decreases and permits exploration of novel stimuli. The authors suggest that IPN interneurons act as a brake on the exploration of familiar stimuli, 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 signals to the IPN, respectively (**Fig. 1d**). Photosuppression of the mHB terminals in the IPN increased exploration of familiar social and nonsocial stimuli without

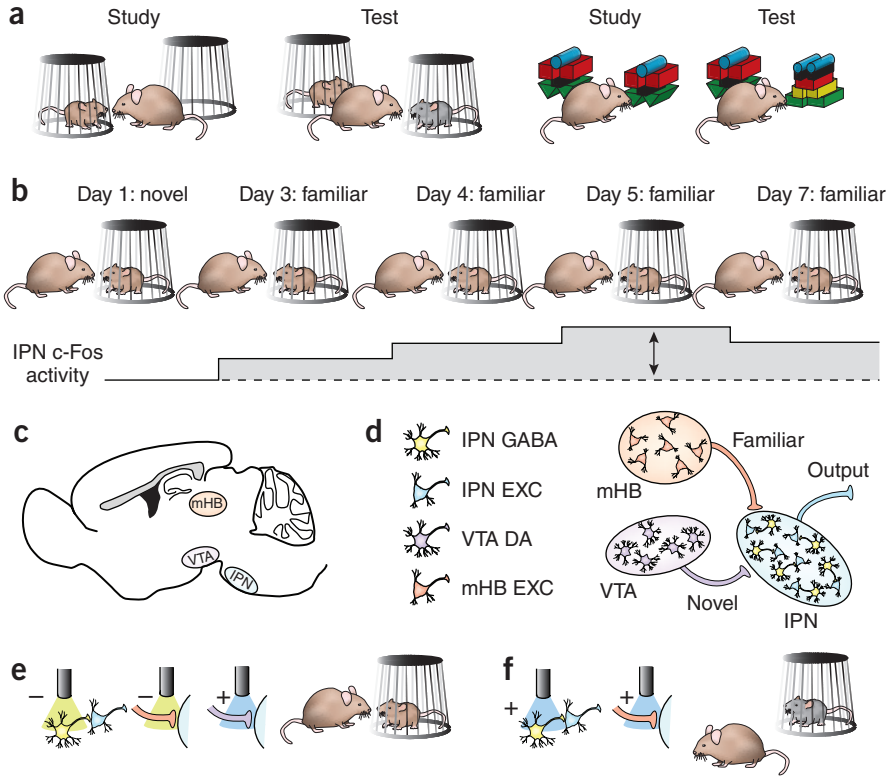

Figure 1 A circuit-based mechanism for familiarity signaling and novelty preference. (**a**) Mammals show a preference for novelty. A mouse will explore an unfamiliar mouse more than a familiar mouse (left) and a novel object more than a familiar object (right). (**b**) Following repeated exposures to the same mouse, shown left to right, c-Fos activity in the IPN increases as 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 or 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 exploration of a familiar stimulus with no impact on exploration of a novel one. Optical activation of VTA input to the IPN also increases exploration of a familiar stimulus, presumably by mimicking novelty. (**f**) Optical activation of IPN interneurons or mHB input to IPN degrades the familiarity signal, decreasing exploration of a novel stimulus with no impact on exploration of a familiar one. DA, dopamine; EXC, excitatory; GABA, GABAergic.

affecting exploration of novel stimuli (**Fig. 1e**, center left). 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 and right). Next, the authors photostimulated the VTA dopaminergic terminals in the IPN. As in the phenomenon of *jamais vu*, this manipulation mimicked the novelty signal, resulting in increased exploration of a familiar mouse (**Fig. 1e**, center right). Interestingly, the photostimulation of dopamine terminals did not affect exploration of inanimate objects. Thus, the novelty signaling pathway may differ for social and nonsocial signals. The authors suggest that different subtypes of VTA dopaminergic neurons may mediate novelty responses to social and nonsocial stimuli.

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[13]. 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, the prelimbic prefrontal cortex and the dopaminergic reward circuit[14]. 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 between *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 neuropsychiatric disorders in which processing of novelty and familiarity are compromised.

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Is population activity more than the sum of its parts?

Jonathan W Pillow & Mikio C Aoi

A study introduces innovative ways to test whether neural population activity exhibits structure above and beyond that of its basic components.

Suppose a fancy new analysis method reveals an (apparently) surprising form of population-level organization in your large-scale neural data set. How can you tell if the observed pattern is truly surprising? Is it the hallmark of a population-level mechanism that reveals the circuit's true function, or is it merely an expected byproduct of things we already knew about neurons contained in the population? To put it bluntly: when are findings of population-level structure 'new science' and when are they merely old knowledge dressed up in new clothes? In this month's issue of *Nature Neuroscience*, Elsayed and Cunningham propose new methods for resolving this question[1].

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Their main contribution is to formalize the notion of primary (or already known) features of a neural population so that claims of surprising population structure can be tested against them. To make this concrete, consider, for example, the recent claim that a neural population exhibits 'rotational dynamics'[2], a contention we'll return to later. Elsayed and Cunningham show that standard shuffling methods do not, in fact, preserve the full set of primary features of a neural population; to address this problem, they introduce two methods for sampling from a properly defined null model, allowing claims of novel population-level structure to be put to the appropriate test.

The starting point for the population-level analyses in question is a collection of peristimulus time histograms, or time-varying firing rates, from multiple neurons across time and across multiple experimental conditions. We can think of these data as living in a 3D tensor (or array) with axes denoting time, neuron and condition (**Fig. 1**). Every entry in the tensor is a number indicating the firing rate of a particular neuron at a single time bin for a particular condition.

What would it mean for this dataset to contain meaningful population structure above and beyond its primary features? Elsayed and Cunningham propose that we should consider as primary the means and correlations along each side of the tensor: temporal correlations, neuronal correlations and conditional correlations. Temporal correlations reflect the fact that, before we say anything about population-level structure, neural firing rates are typically smooth in time. Neuronal correlations, the