observer, could it be interpreted as a sharing of the pain representation of the demonstrator by the observer (**Fig.1**)? Could this representation of the pain of the other in the ACC be the aversive signal (unconditioned stimulus) in this observational conditioning?

The involvement of the same structure does not prove that the representations are similar in demonstrator and observer. Neuronal networks generating different representations can be intermingled in the same structure. Here is a clear caveat of applying a concept such as empathy to mice: there is no way of assessing the subjective component of the experience. In humans, functional imaging studies have linked the ACC to the experience of empathy for pain[12]. In human studies, however, participants' reports can be used to assess their actual state of mind. In Jeon *et al.*'s procedure[7], the observational conditioning could conceivably happen for reasons other than the presence of a shared representation in both mice. For example, the reactions of the demonstrator mouse as it receives the shocks could aversely affect the observer because they are experienced as a threat. Clearly, feeling threatened by the reactions of another is not the same as sharing that other's pain.

It has been proposed that empathy is based on a perception-action mechanism[2,13]. This implies that observing an action or emotional reaction in another activates some of the same neuronal structures as performing that action or experiencing that emotion for oneself. In the motor system of monkeys, mirror neurons have actually been identified that are active when the animal is making a specific action and when it witnesses the same action being carried out by another[14]. By analogy, emotional mirror neurons could be a fundamental component of empathy, generating a similar emotional representation in an animal witnessing the emotional reactions of another[13]. Neurons responding both to painful stimuli and the observation of painful stimuli applied to others have actually been recorded in the ACC of humans[15]. Such neurons could also be present in the ACC of mice.

There is still a lot to learn about the neuronal mechanisms of empathy. As most of us have probably experienced, human empathy can be modulated by many factors, such as the identity and relationship of the individuals involved, mental imagery, etc.[3]. Are the shared emotional representations activated automatically and then amplified or dampened by the factors influencing empathic responses? Or do some of these influencing factors take an early part in the establishment of the shared representations (discussed in refs. 1–3)?

Jeon *et al.*[7], as well as another recent study[4], show that social modulations in mice can be influenced by the specific relationship the animals share. This implies that, in the observer, sensory information related to the identity of the demonstrator must, at some point, influence the processing of sensory information conveying the demonstrator's specific state. Such behavioral models, along with manipulations such as those employed by Jeon *et al.*[7], could be used to identify the neuronal substrates and mechanisms underlying this integration.

So, are mice capable of empathy? It still depends on the definition that one prefers. But beyond terminology, the present data and other recent results[4–6] convincingly demonstrate that mice and rats show social modulation of emotional responses and learning. The neuronal mechanisms and structures, such as the ACC, that underlie some of these social modulations are beginning to emerge. The fact that the ACC has also been shown to be involved in human empathy suggests that some components of more complex emotional behaviors in humans have counterparts, albeit probably simpler ones, in mice.

COMPETING INTERESTS STATEMENT
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Protecting endangered memories

Guillén Fernández & Marijn C W Kroes

Memories are continually adapted by ongoing experience. A study now suggests that the reactivation of previously stored memories during the formation of new memories is a critical mechanism for determining memory survival.

After a long week in the lab, you and your colleagues are having a drink in a nearby pub when suddenly your supervisor runs in and asks you whether you would be willing to write a News & Views article together. He gives you his home phone number for you to call the next day to discuss details. As the battery of your cell phone is dead, you memorize the number. Shortly after, your colleague, who you've fancied for some time, leaves, but asks you out for a dinner date and gives you a phone number. Excitedly, you memorize the number when, all of a sudden, panic strikes. You cannot remember your supervisor's number anymore! What happened?

For over a century, the question of how we remember and why we forget has been a central theme of scientific enquiry[1]. A prominent theory postulates that memories undergo a time-dependent storage process, after which a memory trace becomes stable[2]. This rather static view on memory has been replaced by more dynamic models in which memories are continuously adapted by ongoing experiences[3–5]. Persistence of memories might then depend on how memories change when new information is learned that overlaps with already existing memories. Consistent with this idea, Kuhl *et al.*[1] found that previously stored memories are reactivated as subjects learn new, overlapping information and that this reactivation protects old memories from vanishing (**Fig. 1**).

The authors are at the Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen, Nijmegen, The Netherlands. Guillén Fernández is also in the Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.
e-mail: g.fernandez@donders.ru.nl

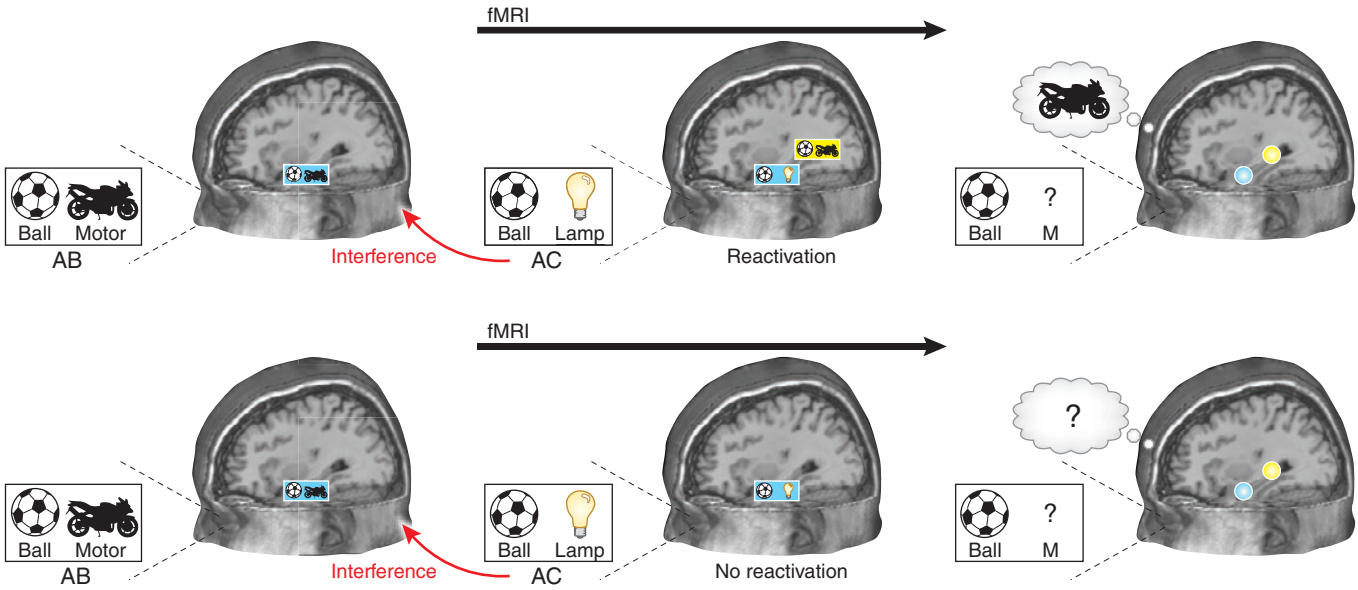

Figure 1 Reactivation protects old memories from vanishing. A graphical depiction of the procedure and findings of Kuhl *et al.*[1]. Learning pairs of items (AB pairs) depends on the anterior hippocampus (left, top and bottom). Next, studying a previously seen cue paired with a novel item (AC pairs) puts memories at risk of forgetting through retroactive interference (middle). As revealed by tracking brain activity with fMRI, the survival of old memories (AB pairs) when at risk of forgetting depends on reactivation of old memories in the posterior hippocampus (top middle). If this reactivation occurs, old memories are more likely to still be remembered in a subsequent memory test (top right). If no reactivation occurs (bottom middle), the old memory is more likely to be forgotten in a subsequent memory test (bottom right).

Memories do not simply decay as time passes; instead, forgetting is thought to be caused by competition between similar memory traces[6]. For example, when you memorize a phone number and then a second similar number, it is likely that you will have difficulty recalling the first number, as the memory trace of the second number competes with that of the first one. This phenomenon is known as retroactive interference[7] and forms the basis of the procedure adopted by Kuhl *et al.*[1]. Subjects were presented with iterating study-retrieval phases while their brain activity was tracked by functional magnetic resonance imaging (fMRI). Subjects initially studied pairs of items (denoted AB pairs) and then memory was tested for these AB pairs by presenting A items as cues. During the next study phase, subjects were presented with new pairs of items that consisted of either two novel items (new AB pairs) or a previously seen cue combined with a novel item (AC pairs). In the subsequent memory test, subjects were cued with A items and asked to recall the most recently associated item (B for new AB pairs and C for AC pairs). Subjects then exited the scanner and were again presented with all A items but were instructed to recall the initially associated item (B). AC learning should jeopardize AB memory, and in the final memory test after scanning, AB pairs that were not followed by AC pairs were better remembered than AB pairs followed by AC pairs. Thus, by causing retroactive interference, this manipulation put memories at risk.

The authors then asked whether there was a neural signature for survival of memories that are at risk of forgetting as a result of retroactive interference. To do this, they tested whether neural activity during AC learning predicted subsequent memory for the corresponding AB pair. Notably, they found greater posterior hippocampal activity during AC encoding for corresponding AB pairs that were later remembered relative to forgotten AB pairs. This finding indicates that, during the learning of new information, posterior hippocampal processing protects similar old memories from forgetting. They confirmed these trial-by-trial findings by demonstrating that subjects who were more sensitive to retroactive interference (those who forgot more AB pairs as a result of AC learning) had reduced hippocampal activation during AC learning compared with subjects who suffered less from interference. Thus, the posterior hippocampus appears to be critical for preventing forgetting when old memories are at risk during learning of new, interfering information.

The intriguing question is whether this posterior hippocampal region, activated during the learning of new AC pairs and predicting AB memory, is associated with reactivating AB memories. Capitalizing on an ingenious design twist, the authors found that contextual information related to AB learning was actually reactivated. During the initial study phase, the presentation of AB pairs was preceded by cues indicating a high or low monetary reward for correct recall in the immediate memory test. During AB learning, several regions that are sensitive to reward processing showed greater activation for AB pairs associated with high reward than pairs associated with low reward. Critically, greater activation in these reward-related areas during AC study predicted better memory in the final test specifically for those AB pairs associated with high reward at study. In further support, greater activity during AC study in these reward-related regions for remembered compared with forgotten AB items correlated with posterior hippocampal activity for later remembered AB items. These findings indicate that corresponding old memories were reactivated together with their specific study context (reward) during new learning and that the strength of this reactivation is indicative of whether old information is later remembered or doomed to be forgotten.

Kuhl *et al.*[1] interpret their findings in the context of pattern completion (the reconstruction of memory from sparse input) and pattern separation (the identification of unique elements between similar input)[8,9]. The finding that contextual information of AB pairs is reactivated during AC study suggests that AB memory is reconstructed from partial input (item A) and is coherent with a pattern completion account. Pattern completion is considered to be an essential aspect of retrieval,

whereas pattern separation might subserve encoding[10]. Thus, it is interesting to note that a subsequent memory effect was located in the anterior hippocampus during AB study, a region previously associated with novelty and memory encoding[11,12], whereas the subsequent memory effect for AB pairs during AC study was located in the posterior hippocampus and parahippocampal gyrus, regions that are considered to support retrieval[11,12]. In addition, the greatest subsequent memory effect for AB pairs during AC study in the between-subjects analysis was found in the medial prefrontal gyrus, an area previously associated with pattern completion and memory retrieval[13]. Although interesting, this pattern completion interpretation remains speculative. Pattern separation in the dentate gyrus is thought to precede and enable pattern completion in hippocampal CA1 region[9]. Thus, as the authors note, both may have occurred in this task; however, the spatial resolution of fMRI does not allow them to be separated.

In sum, Kuhl *et al.*[1] provide us with a convincing demonstration that memories of old information can be reprocessed when new, similar information is learned and that this reactivation is critical for the fate of the old memory. A central question that remains is whether the reactivation as detected reflects a restrengthening of memory through replay[3] or an active trace change, as described for reconsolidation[4] and schema-dependent updating[5]. Replay occurs off-line and usually without perceptual input. When reactivation occurs in the presence of perceptual input, reactivated traces become unstable (a process that is critically dependent on the posterior hippocampus[14]) and require reconsolidation[4]. However, Kuhl *et al.*[1] found the opposite: reactivation during novel learning protects memories from being forgotten, although on a much shorter time scale. A potential interpretation of these seemingly contradicting findings is that the reactivated memory and the current perceptual input can be integrated in such a way that the old memory is updated. Such integration has been shown to depend on the hippocampus and pre-existing knowledge[5,15]. Determining which of these processes underlie the findings of Kuhl *et al.*[1] requires further investigation. Regardless, a neural correlate of memory reactivation has been very difficult to detect thus far, as the timing of reactivations is unknown. Now, Kuhl *et al.*[1] provide the neuroscience community with the opportunity to track reactivated memories and the ability to investigate the dynamic nature of memory.

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Speedy rod signaling

Rod photoreceptors in the mammalian retina allow vision under dim light conditions, when cones are not sufficiently activated. The rod light response, however, is relatively slow. Rods transmit their signals mainly to two effector cell types—to the ON bipolar cells by means of a synapse consisting of metabotropic glutamate receptors, and to adjacent cones by means of gap junctions. A third type of contact has been reported as well, between about 20% of rods in the mouse retina and a particular subset of OFF bipolar cells, the b2 cells. It was, however, not clear whether these contacts formed functional synaptic connections.

Now, Li, Chen and DeVries, on page 414 of this issue, characterize the electrophysiological properties of these contacts in slices from ground squirrel retina. The b2 bipolar cells, in contrast to the rod ON bipolar cells, express fast ionotropic AMPA-type glutamate receptors in their postsynaptic endings and could therefore mediate faster signaling.

The picture shows a b2 OFF bipolar cell (green) contacting a rod (red). The outer segment of the rod cell is stained blue for rhodopsin. Recording from such cell pairs, the authors found that kinetics of synaptic transmission between these cells is as fast and transient as transmission between cones and b2 bipolar cells and five to ten times faster than transmission between rods and rod ON bipolar cells or rods and cones. In other respects, too, such as synaptic vesicle replenishment, the rod–b2 OFF bipolar cell synapses resemble cone–b2 OFF bipolar cell synapses.

Although this study does not tease out any specific contribution of the new fast transmission circuit component to rod-mediated vision, the discovery of fast rod signaling is surprising in itself. One may speculate that at intermediate light intensities, cones and a subset of rods collaboratively activate the b2 cell–driven OFF circuitry. We look forward to future work revealing the physiological significance of this new input.

Annette Markus