loss was observed, neurons appeared smaller. Basal synaptic transmission was normal, but there was an impairment of hippocampal long-term potentiation and a decreased threshold for hippocampal long-term depression.

Notably, the DKO mice also showed behavioral deficits for two tasks that are frequently used to assess hippocampal-dependent memory: the Morris water maze and contextual fear conditioning. In the contextual version of Pavlovian fear conditioning, mice learn the association between foot shock and the training cage environment. When normal mice are placed back into the training cage after 24 h, they freeze, which is an indicator of fearful memory. Successful training in the Morris water maze depends on the ability of mice to navigate to a submerged platform in murky water.

The involvement of DNA methylation in memory has been proposed previously[11]. A contextual fear conditioning task induced a transient increase in DNA methylation levels of protein phosphatase 1 (*Ppp1*), a gene that is considered to repress memory, 1 h after learning. The increased levels of DNA methylation were accompanied by a transient elevation of Dnmt expression (after 24 h, these levels returned to normal). This pattern of DNA methylation suggests an active and gene-specific demethylation mechanism, whose identity remains elusive. Feng *et al.*[7] could not confirm or disprove that a transiently high pattern of DNA methylation and demethylation was a requirement for learning and memory. However, they found strong genetic evidence that specific patterns of DNA methylation are critical for the long-lasting preservation of neuronal functions and morphology, including those supporting memory.

Defining the specific demethylation mechanisms in postmitotic neurons has also been controversial[14], with inconsistent and isolated reports implicating different putative DNA methylases in mammalian cells. Passive mechanisms for DNA demethylation have also been proposed. A study[15] of oxidative stress in neurons proposed that DNA damage induces a DNA base-excision and repair cascade, producing a repaired, but unmethylated, base. In this model, DNA methyltransferases (including Dnmt1 and Dnmt3a) cooperate with the DNA repair machinery to restore neuron type–specific DNA methylation patterns. Feng *et al.*'s results[7] are certainly consistent with this model.

Feng *et al.*[7] had two particularly interesting results. First, DNA methylation patterns in specific, postmitotic neuronal populations were altered in DKO mice. Consequently, this genetic manipulation caused the alteration of both DNA methylation patterns and gene expression, suggesting that Dnmts indeed are required for the maintenance of DNA methylation in postmitotic neurons. Second, they were able to link a distinctive behavioral deficit to these altered DNA methylation patterns in defined neuronal populations in otherwise normally functioning mutant mice. It is fair to conclude that Feng *et al.*[7] were able to alter brain function by direct alteration of gene expression in specific neurons via an epigenetic mechanism. These data indicate that fine-tuning of epigenetic program in postmitotic neurons is possible without disruption of basal synaptic transmission and without grossly altering brain function. The phenotype of the DKO mice is subtle and the mice retain both short-term memory and the ability to learn.

The implication of DNA methylation in psychological memory is intriguing. Future work should answer the pressing question of which genes show methylation patterns that are critical for the mechanism(s) underlying synaptic plasticity and memory. Genome-wide screening should help to unveil candidates, including those proposed by Feng *et al.*[7]; however, it appears that a 'one-gene-at-the-time' approach will be required to assess such mechanistic aspects. Another pressing question is how the specificity of DNA methylation patterns can be maintained. The repression mechanism driven by methylated DNA is also largely unknown. One of the proteins that directly binds to hypermethylated CpG is MeCP2 (ref. 9). However, despite initial biochemical indications that MeCP2 may repress methylated promoters, genetic data does not confirm that prediction[9].

In conclusion, Feng *et al.*[7] confirm the importance of DNA methylation for neuronal function and morphology. Their research opens new avenues for epigenetic studies of relationships between epigenetically encoded cellular memory in postmitotic neuronal populations and cognitive functions in the context of both normal brain processing, as well as in mental disorders.

COMPETING FINANCIAL INTERESTS
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Mouse brains wired for empathy?

François Grenier & Andreas Lüthi

A study in this issue reports that mice can be fear conditioned through observation of other mice receiving aversive stimuli and identifies some of the brain regions involved in this observational fear learning.

Do mice have empathy? This question may elicit a wide range of answers, including "yes, of course", "impossible" and "we'll never know". One of the reasons behind such a diversity of opinions is simply a matter of definition. Empathy implies at least some emotional sensitivity in an individual to the affective state of another. But emotional sensitivity to another can refer to many specific phenomena. Some are automatic, such as emotional contagion (for example, babies starting to cry when they hear another baby crying), whereas others have a strong cognitive component, such as sympathy and compassion. Some apply the term empathy to a wide range of these phenomena (for example, see refs. 1,2). Others prefer to restrict it to a more specific case with criteria such as a similarity between the emotional states of the observer and the observed, and

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the understanding that the affective state of one was produced by observation of the other (for example, ref. 3). The latter definition would seem to apply almost exclusively to humans. So what about some form of empathy in mice?

Recent reports have indicated that rodents can display social modulation of emotional behavior and responses[4–6]. These social modulations correspond to at least a broad behavioral definition of empathy. Can we infer in a behavioral mouse model some of the affective components of empathy, such as a representation of the emotional state of one individual in the other? Can we learn something from mouse models about the neuronal mechanisms of empathy, or at least some simple form of it?

A study by Jeon *et al.*[7] sheds some light on these questions. The authors built on the classical fear-conditioning model to develop an observational fear-learning procedure in mice that fits into a broad behavioral definition of empathy. Furthermore, they identified some of the neuronal mechanisms involved in that learning. In classical fear conditioning, an animal experiences an aversive stimulus, the unconditioned stimulus. It then learns to associate fear with the environment (context) and any sensory cue (conditioned stimulus) that was paired with the unconditioned stimulus. It will display fear responses if it is returned to the learning context or presented with the conditioned stimulus alone. The level of fear experienced by the animal can be inferred from various physiological and behavioral parameters, such as the amount of time it remains immobile, the freezing response.

The authors adapted this standard fear-conditioning procedure for observational fear learning. A mouse (demonstrator) received a series of electrical shocks (unconditioned stimulus) in a chamber. A second mouse (observer) witnessed the event from an adjacent chamber. The observer mouse actually showed signs of fear (freezing) when the conditioning occurred. The observer also froze when put back in its observing chamber the next day, an indication that witnessing the reaction of another mouse to aversive stimuli led to fear conditioning in the observer. Notably, not all demonstrator mice were equal. The intensity of the conditioning in the observer mouse depended on its relationship with the demonstrator; the effect was stronger when demonstrator mice were long-term mating partners or siblings of the observer.

Are these behavioral results completely unexpected? There has been at least one early report of emotional reactions to the pain of others in rats[8]. More recently, pain sensitivity was found to be modulated in mice by the presence of other mice showing pain responses, as long as these mice were cage mates rather than strangers[4]. Fear conditioning has been shown to be increased in rats if they were exposed to rats that had already been conditioned just before being fear conditioned themselves[5]. Mice that witnessed another mouse being presented with a tone and shock pairing subsequently showed increased freezing to presentations of the tone alone[6]. Jeon *et al.*[7], however, also tried to identify the neuronal structures involved in this observational fear learning.

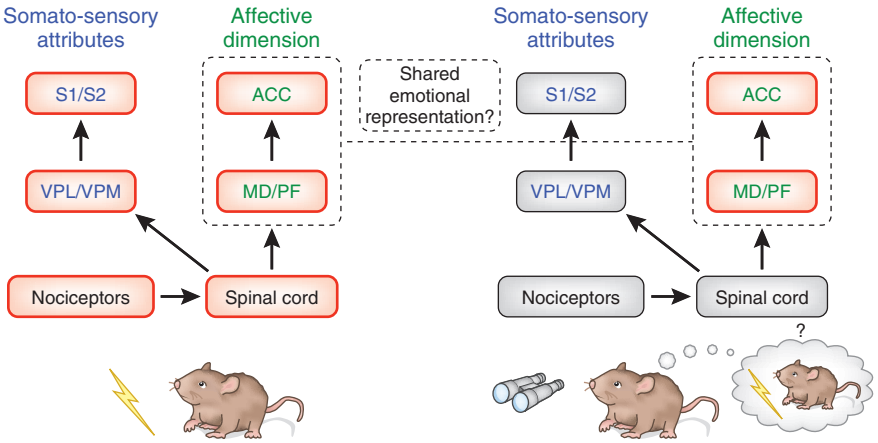

Figure 1 Possible substrate for a shared representation of pain in a demonstrator mouse receiving a foot shock and in an observer mouse witnessing the event. The demonstrator mouse is on the left. Above each mouse is a simplified scheme of some of the components of the neural circuitry involved in pain representation. The structures that are expected to be activated during the event are boxed in red. The structures that are thought to represent the sensory attributes of the stimuli are in blue and those that are involved in the affective or unpleasantness component are in green. Structures activated in both mice could underlie a shared representation of the situation. ACC, anterior cingulate cortex; S1/S2, cortical somatosensory areas S1 and S2; VPL/VPM, thalamic ventroposterior lateral and medial nuclei; MD, mediodorsal nucleus; PF, parafascicular nucleus.

The authors relied on what is known about the mechanisms of fear conditioning[9] and the representations of painful stimuli in the brain[10] to identify candidate structures. The lateral nucleus of the amygdala is essential for the formation of classical fear conditioning. Painful stimuli are represented in the forebrain by two main systems: the lateral system, which is thought to represent the location, intensity and quality of painful stimuli and includes the cortical somatosensory areas S1 and S2 and the ventral posterolateral (VPL) and posteromedial (VPM) thalamic nuclei of the thalamus, and the medial system, which is thought to encode the affective dimension or unpleasantness of noxious stimuli and includes the anterior cingulate cortex (ACC) and mediodorsal and parafascicular nuclei of the thalamus.

Using pharmacological and genetic manipulations, Jeon *et al.*[7] inactivated some of these structures in the observer mice during learning and the memory test. The lateral nucleus of the amygdala was found to be essential for both the acquisition and the expression of observational fear, as it is for classical fear conditioning. Pharmacologically inactivating a component of the lateral pain system (VPL/VPM) had no influence on observational learning. In contrast, inactivating any component of the medial pain system (ACC or mediodorsal or parafascicular nuclei) during learning blocked the acquisition of fear, whereas inactivating them only before memory retrieval did not block fear expression. Thus, the medial pain system is essential for the acquisition of observational fear conditioning, but not fear expression once it has been acquired.

This suggests that the medial system could be transmitting the aversive nature of the situation to the lateral nucleus of the amygdala during observational learning. The ACC and lateral nucleus of the amygdala are known to be interconnected. Jeon *et al.*[7] tested their possible interaction during observational fear learning with field potential recordings in the observer mouse. They indeed found a strong increase in amplitude and synchronization of theta oscillations between the lateral nucleus of the amygdala and ACC during observational learning, suggesting that a functional interaction occurs during the process.

Has a neuronal substrate for a shared emotion been identified between observer and demonstrator? It has been proposed that the ACC represents the unpleasantness of a painful stimulus in rodents[11]. It is therefore expected to be activated in the demonstrator mouse during the shocks. Jeon *et al.*[7] found that the same structure was essential for observational learning in the observer mouse. Clearly, the full experiences of demonstrator and observer mice are not identical. But if the same structure, which is thought to encode the affective dimension of pain, is activated in both demonstrator and

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.

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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**).

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