for the asymmetric distribution of a signaling substance. During early embryonic development, the 'nodal flow' mediates left-right asymmetry by maintaining a gradient of sonic hedgehog (Shh)[9]. Nodal flow requires actively beating cilia, and left-right asymmetry is accordingly lost in Tg737^{orpk} mutants[10]. However, nodal flow is directed toward the highest concentration of Shh—not away from it as it would be in the case of Slit2 near the adult SEZ.

Thus, the idea that the beating of ependymal cilia contributes to establishment of an endogenous Slit2 gradient in the CSF is not fully convincing. Moreover, cilia are rather short in comparison to the large volume of the lateral ventricle, and it has therefore been suggested that they mediate local mixing rather than contributing to the bulk of the CSF flow[6,11]. Instead, pressure gradients produced by secretion and absorption of the CSF have been thought to underlie CSF flow, and the disturbance of these may actually cause the breakdown of CSF flow in the Tg737^{orpk} mutant mice. Indeed, the mutation also affects epithelial cells of the choroid plexus, which bear cilia as well. Secretion of CSF from the choroid plexus is altered in the Tg737^{orpk} mutant mice, because of increased chloride transport into the CSF followed by a flow of water most likely causing the hydrocephalus in these mice[5]. Thus, it is conceivable that the secretion of Slit2 into the ventricle of Tg737^{orpk} mutant mice is defective, or altered in such a manner that neuroblasts do not get clear instructions to migrate in the rostral direction (**Fig. 1c**). Although the authors checked that choroid plexus cells in the Tg737^{orpk} mutant mice still express Slit2 mRNA, they did not show whether the Tg737^{orpk} mutant choroid plexus could still secrete Slit2 protein and repel migrating neuroblasts.

The multitude of defects seen in the Tg737^{orpk} mice result from a gene trap mutation that affects the protein polaris. This protein is an integral part of the intraflagellar transport particle IFT, which mediates the bidirectional movement of proteins from the base to the tip of cilia. This transport affects Shh signaling in the developing brain (for review, see ref. 12), implying that the cilia are a key signaling compartment of ventricular zone cells. For example, Smoothened, the receptor for Shh, is transported to the tip of cilia, suggesting that the cilia may perceive Shh signals from the ventricle[13]. Other molecules, such as the stem cell marker prominin (also called CD133), located on the apical surface of ventricular zone cells, are released into the ventricle of the developing brain[14], implying that apical processes may participate in both creation and perception of signals communicated via the CSF. On the basis of these considerations, it is conceivable that the defects in polaris and IFT in the Tg737^{orpk} mutant mice affect the ability of ependymal cells to perceive CSF-borne signals. It is important to remember that cilia can act as sensory structures—such as the cilia connected to the pathogenesis of human polycystic kidney disease[15]. According to this model, ependymal cells at the ventricle might sense the CSF flow via their cilia and relay this information to the migrating neuroblasts. Upon disturbance of the CSF flow in the Tg737^{orpk} mutant mice, ependymal cells might then provide misinformation to the migrating neuroblasts—still a non–cell-autonomous effect, but indirectly communicated from the ventricle. Thus, the study by Sawamoto and colleagues has not only identified a key and unexpected role of ventricular signaling, but also casts light on the need to better understand the mechanisms mediating such signaling. Scientific breakthroughs always open many new questions, and this study demonstrates the importance of investigating this long-overlooked part of the brain.

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Rational rats

Nicola Clayton & Anthony Dickinson

Traditional learning theory suggests that animals do not understand that actions cause their consequences. A new paper uses sophisticated behavioral experiments to conclude that rats are capable of causal reasoning.

Many animals are sensitive to the causal consequences of their actions. Indeed, this ability is essential if they are going to learn to control their environment in the service of their needs and desires. Thus in the wild, Israeli black rats learn to strip pine cones to obtain the seeds[1], and in the laboratory, Norwegian rats learn to press levers to get food from a dispenser[2]. However, the crucial question is whether the animals can reason about their actions; in other words, do they understand that their actions cause the food to become available? Traditionally, most psychologists would say no. Within associative learning theory, the food simply reinforces the behaviour as a habit or, at the very most, establishes a simple association between the thought of the food and the action that produced it. In contrast to this tradition, Blaisdell and colleagues[3] in a recent issue of *Science* claim that the humble rat has a much deeper understanding of the causal nature of its actions than previously thought.

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Their experiment, however, is complex and hinges on the inferences that can be drawn from intervening in a causal process. To illustrate this point, consider the following scenario. Suppose you have just hung your washing out to dry in the back garden. A few minutes later, you look out of your front window and see water droplets splashed upon the pane. Clearly the conclusions that you draw from this observation must depend upon the causal attributions you make about the source of this water. If you had turned on your sprinkler in the front garden a few minutes earlier, you would take no further action. The fact that your actions explain the effect you observe leads you to discount the need for any other cause. However, if you cannot attribute the water droplets to the act of turning on the sprinkler, then an obvious inference is that it has started raining—in which case, you should scurry into the back garden to rescue the washing. This is essentially the intervention test used by Blaisdell and colleagues with their rats (**Fig. 1**).

In the first stage, the rats observed that presentations of a light were sometimes followed by a tone and sometimes by food. This stage was intended to be equivalent to learning that rain (the light) causes both splashing on the window panes (the tone) and soaking of the washing (the food). The second stage uses this causal knowledge to investigate the rat's ability to reason about its actions. One group of rats were equivalent to our episode of looking out of the front window and seeing the water on the window pane. These rats simply observed presentations of the tone (wet front windows), which led them to go and search for food, just as we would have rushed outside to retrieve the washing. The explanation is that perceiving the tone led the rats to infer that the antecedent cause must have occurred, in this case the light, and therefore so must the other effects of this cause, namely the food.

The other group of rats experienced a scenario that was similar to the episode in which you had turned on the sprinkler in the front garden. For these rats, the tone was presented whenever they pressed a lever so that they could attribute the occurrence of this tone to their actions, thus allowing them to discount the possibility that the tone had been caused by an unobserved light. In turn, this inference would lead to the conclusion that there is no reason for them to expect food, in just the same way as knowing that you had turned on the sprinkler in the front garden led you to discount the possibility that your washing in the back garden would be wet.

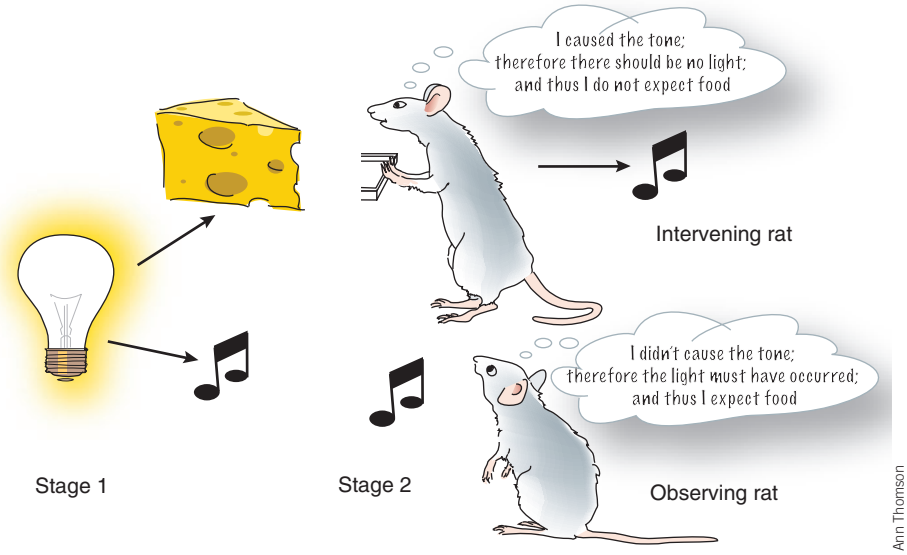

Figure 1 Design of the experiments of Blaisdell and colleagues. In the first stage (left), the rats learned that a light predicted a tone and the appearance of food. In the second stage (right), rats that heard the tone proceeded to search for food, while rats that pressed a lever to cause the tone did not search for food.

Blaisdell and colleagues presented other rats with a number of controls to evaluate alternative explanations for what seemed to be causal reasoning. For example, one control was equivalent to looking out the back window rather than the front. In this case, if you did see water droplets, then you would be worried about your washing, irrespective of whether it had been soaked by the rain or by your sprinkler. Similarly, when presented with a noise that had previously predicted food, the rats searched for food irrespective of whether this noise was caused by a lever press or happened independently of the rat's actions.

What makes these experiments even more compelling as evidence for causal reasoning is that human participants draw the same kinds of inferences from interventions and observations in analogous scenarios as the rats do[4]. In humans, the ability to understand the causal power of actions seems to develop relatively early in infancy[5].

Indeed, the basic claim that an animal's action can be based on causal beliefs is not a new one. One of us has argued that there are two reasons why goal-directed actions are based on causal beliefs. The first is the absence of any adequate associative account of these actions[6], and the second draws on the similarity between the processes underlying instrumental learning by animals and the acquisition of causal beliefs by humans[7]. That being said, these theoretical claims never anticipated the sophisticated causal inferences that apparently underlie the behavior of Blaisdell's rats.

What is less clear, however, is whether complex reasoning about generic causation, as demonstrated in these experiments, extends to reasoning about domain-specific causal processes, which has been the primary focus of comparative cognition ever since Kohler's pioneering studies of the use of tools by apes[8]. Comparative psychologists have been concerned with the extent to which animals, mostly primates, show causal insight in their construction and deployment of tools. Although a number of species learn to use tools effectively both in the wild[9] and in the laboratory[10], the jury is still out on the issue of whether and, if so, to what extent, animals understand the physical processes by which these tools are effective. The most compelling evidence to date that animals understand the causal properties of physical objects comes surprisingly not from the nonhuman primates but from corvids[11]. Although, Povinelli's chimpanzees are often just as likely to select an ineffective tool as an effective one[12], a New Caledonian crow named Betty spontaneously bent a piece of ineffective straight wire into an effective hook tool for retrieving food[13]. And when it comes to learning to avoid maneuvering food into a clearly visible and inaccessible trap, a non–tool-using species of corvid, the rook,

learns surprisingly rapidly[14], whereas chimpanzees and capuchin monkeys seem to take many trials to learn a similar task[12,15].

It remains to be seen whether chimpanzees and corvids show the sophistication of Blaisdell's rats when reasoning using the general principles of causation. As Blaisdell and colleagues point out, it may be that an animal's apparent failure to display causal understanding in some tasks of physical cognition is a reflection of the demands that the task places on an animal's knowledge of the physical world, rather than on its capacity to reason about causes. It may seem surprising that the humble rat is capable of such causal understanding. Perhaps even more surprising is that this cognitive sophistication was manifest within the artificiality of the Skinner box, which has been claimed to functionally decorticate the rat. Clearly, this is not the case.

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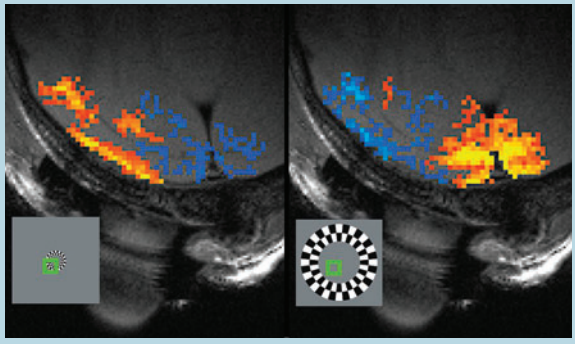
Going down BOLDly



Attractive pictures from functional brain imaging studies showing localized increases in hemodynamic responses have been the belle of the ball, but task-induced decreases in hemodynamic responses have been treated as something of the ugly stepsister. Part of the reason for this neglect is that much less is understood about the basis of such decreases. A new study on page 569 of this issue puts this negative hemodynamic response under the spotlight.

Functional MRI studies commonly measure the blood oxygenation level–dependent (BOLD) signal, and increases in this signal are thought to reflect increases in the underlying neural activity. However, fMRI studies often find a negative BOLD (the BOLD signal dips below the resting baseline) in response to certain tasks, and it is unclear if this negative BOLD response also reflects neural activity or a non-neural process. Although there is experimental support for the view that the negative BOLD response reflects suppression of neural activity, the competing 'vascular blood steal' hypothesis claims that such reductions are due to decreased blood flow with a vascular origin, and the negative BOLD response has little direct relation to underlying neural activity.

Amir Shmuel and colleagues used simultaneous functional MRI and electrophysiological recordings in monkeys to show that the negative BOLD signal is closely coupled to decreases in neural activity. These researchers directly recorded neural activity in primary visual cortex V1 using electrophysiological recordings, while also recording BOLD responses through MRI. During these recordings, the animals saw stimuli that either did or did not overlap with the receptive fields of neurons near the recording site. (The picture shows the circular checkerboard stimuli used, and the green square represents the aggregate receptive fields of these neurons.) As expected, the stimulus overlapping with the neuron receptive fields elicited a positive BOLD response (orange in left panel). However, the nonoverlapping stimulus resulted in a negative BOLD response (blue in right panel). In accord with previous work, the positive BOLD response correlated with increases in neural response as indexed by the electrophysiological recordings. However, the nonoverlapping stimulus resulted in decreases in neuronal activity in the same region of V1. Crucially, the negative BOLD correlated with these decreases in spiking activity and local field potentials.

Although this result suggests a neural origin for the negative BOLD response, it does not completely rule out the vascular blood steal hypothesis: decreased blood flow could result in hypoxia, preventing neurons from maintaining their baseline activity. Decreased blood flow would then also result in a negative BOLD response—the relationship between the negative BOLD and the decreases in neural activity would then be due to an unrelated third factor. However, the onset of the decreases in neural activity closely followed the stimulus presentation, similar to the dynamics of the increased neural activity. The negative BOLD response also lagged behind the decrease in neural activity (also similar to the lag between increased neural activity and the positive BOLD response), making it unlikely that reduced cerebral blood flow is the cause of these results. These findings therefore strengthen the view that the negative BOLD response is connected to underlying decreases in neural activity. Further work is needed to confirm that this explanation applies to areas outside V1 as well. Nonetheless, these results help strengthen the idea that negative BOLD responses also yield useful information about neuronal activity.

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