took to make the initial choice as a proxy for certainty. However, variance in choice time explained only a minor part of the variance in confidence judgments, indicating that other mechanisms are at work (as is the case in humans[14]). Neurons signaling memory strength in the human hippocampus[15] and posterior parietal cortex[16], which are brain areas involved in memory retrieval, carry a graded familiarity signal that is stronger for high-confidence decisions. This is reminiscent of the synthetic memory decision variable, but it remains unknown whether such neurons exist in rats. Other neurons in the same brain areas, on the other hand, signal decision confidence irrespective of the choice[16,17]. Alternatively, other data indicate that making metamemory decisions requires frontal areas distinct from the underlying memory system[13], indicating the need for simultaneous recordings to examine hippocampal–frontal interactions[18,19]. The availability of a new rat behavioral paradigm now makes it possible to explore these important questions in this model system of memory.

Understanding how a neural or artificial system can gain insight into the reliability of its own memory is of broad significance. Knowing whether we know drives exploratory behavior, curiosity, and learning (among many other behaviors). In humans, confidence attributed to reports from memories has wide significance in a variety of circumstances that includes the law[20]. In medicine, deficits in metacognitive ability are thought to be critical factors in neuropsychiatric diseases. Lastly, it is of paramount importance that we endow artificially intelligent systems with the capability to provide confidence judgments. Deciphering the underlying neural circuitry in rodents has the potential to significantly advance these areas of investigation.

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Cell reprogramming: Nature does it too

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Cell reprogramming is generally considered an artificially induced event. Excitingly, a new study shows that post-mitotic cell reprogramming occurs naturally in the developing fish retina, uncovering a mechanism involved in the generation of cell diversity.

Somatic cell identity has long been assumed to be permanent and irreversible. Over the past few decades, however, ground-breaking studies have shown that cell identity can be altered through various experimental manipulations[1], sparking countless efforts to use cell identity reprogramming for regenerative therapies and disease modelling. For instance, expression of a specific combination of transcription factors can convert differentiated

fibroblasts into pluripotent stem cells[2], which can then be differentiated into various somatic cell types. Similarly, expression of other combinations of transcription factors can reprogram differentiated fibroblasts or glial cells directly into neurons[3,4] or myoblasts[5], without going through an intermediate pluripotent state. Although these are artificially induced reprogramming events, physiological reprogramming, which is generally referred to as transdifferentiation, also occurs endogenously after injury in diverse tissues and organs of 'lower' vertebrates to mediate regeneration, including in the central nervous system (CNS)[6]. Other rare physiological reprogramming events have been reported in developing *Drosophila* eyes[7] and zebrafish dorsal root ganglia[8], but whether transdifferentiation generally takes place in the developing vertebrate CNS has remained unclear. A study published in this issue of *Current Biology* by Engerer, Petridou and colleagues[9] sheds light on this question by showing that spontaneous reprogramming of a type of retinal neuron into another type occurs naturally in the developing zebrafish retina, thereby contributing to the generation of cell diversity in the CNS.

Specifically, Engerer, Petridou *et al.* studied Vsx1-expressing progenitors in the retina, which are generally thought to only produce Vsx1+ bipolar cells, a type of excitatory interneuron. Using a Gal4-driver line to trace the entire lineage of Vsx1-expressing cells, the authors found, however, that almost half of Vsx1+ progenitors actually generate amacrine cells, a retinal inhibitory interneuron, in addition to bipolar cells during terminal neurogenic divisions. Surprisingly, live-imaging revealed that the amacrine cells were not directly produced from progenitors, but rather arose from transdifferentiation of one of the newborn Vsx1+ bipolar cells (Figure 1). After terminal division, one of the Vsx1+ bipolar cells translocated to the inner part of the interneuron layer where amacrine cells reside, changed its morphology to adopt amacrine features, and started expressing amacrine cell markers. Most of these newly produced amacrine cells also lost bipolar markers, although a few rare cells maintained expression

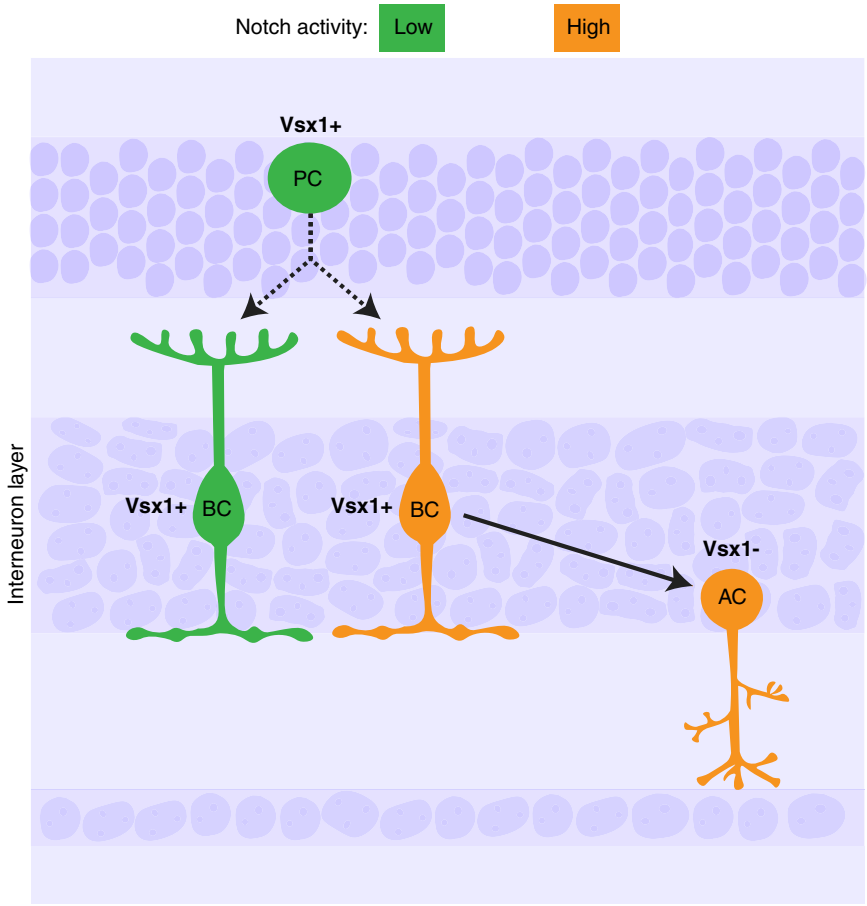

Figure 1. Bipolar to amacrine cell conversion in the *vsx1* lineage of the developing zebrafish retina.
Schematic representation of findings by Engerer, Petridou and colleagues[9]. A retinal progenitor cell (PC) of the *vsx1* lineage gives rise to two bipolar cells (BC) in terminal neurogenic divisions, as shown with dotted lines and arrows. One of these cells, with low Notch activity (green), will maintain a bipolar identity, while the other, due to high Notch activity (orange), will convert to an amacrine cell (AC), represented by the black line and arrow.

of Vsx1. These data indicate that a considerable fraction of Vsx1+ bipolar cells undergo transdifferentiation to an amacrine identity shortly after their initial generation. Interestingly, some of the reprogramming cells expressed the progenitor marker GFAP, suggesting that they might transiently adopt some progenitor features.

To investigate the mechanism underlying this bipolar to amacrine cell conversion, the authors focused on Notch signaling, which was previously implicated in cell fate decisions[10] and reprogramming[11]. Using a Notch activity reporter for live-imaging, they found that amacrine cells of the *vsx1* lineage had higher levels of Notch activity compared to surrounding bipolar cells. In a series of elegant *in vivo* time lapse recordings, the authors found that Notch activity was low in Vsx1+ progenitors, but gradually increased in post-mitotic cells, and significantly more so in the amacrine cell sibling of the amacrine–bipolar cell pairs, suggesting that Notch could mediate reprogramming. Accordingly, inhibition of Notch activity reduced the number of amacrine cells produced in the *vsx1* lineage, whereas stimulating Notch activity in post-mitotic cells had the opposite effect, with more bipolar cells converting to amacrine identities. These experiments show that Notch signaling confers some level of plasticity in early post-mitotic bipolar cells, allowing conversion into amacrine cells (Figure 1).

Could this Notch-induced plasticity be exploited to enhance bipolar cell conversion into different retinal cell types? To address this, Engerer, Petridou *et al.* first induced Notch activity in the *vsx1* lineage, together with overexpression of Ptf1a, a key amacrine fate determinant. These manipulations induced a ~28-fold increase in the number of amacrine cells generated compared to wild-type conditions, and a ~4-fold increase over Ptf1a expression alone, indicating that Notch signaling potentiates the effect of Ptf1a, likely by allowing bipolar–amacrine cell reprogramming. To investigate whether bipolar cells could be converted to other cell types, the authors stimulated Notch activity and overexpressed Atoh7, a key retinal ganglion cell fate determinant, while knocking down *ptf1a* to inhibit the amacrine fate. Remarkably, they found that these manipulations induced conversion of bipolar cells to retinal ganglion cells, which was not observed with Atoh7 expression alone. Therefore, elevated Notch activity induces a period of plasticity in post-mitotic bipolar cells that can be used to promote conversion into different cell identities via expression of specific fate determinants.

Altogether, this work by Engerer, Petridou *et al.* identifies a novel type of plasticity in the developing vertebrate CNS, adding to the complexity of mechanisms used to generate cell diversity. Indeed, this study challenges the concept that progenitor cells are the lone source of cell diversity during CNS development and brings to light the idea that spontaneous cell reprogramming also plays a part. These findings also imply that genetic manipulations performed in progenitor cells and their progeny may induce post-mitotic identity conversions, rather than directly acting in progenitors. Many studies addressing the mechanisms of cell-fate decisions involve manipulations of gene expression in progenitors, which results in modified expression in both progenitors and their progenies. The work by Engerer, Petridou *et al.* and others[9,12–14] now suggests that early post-mitotic identity switches could occur and may account for differences in progeny composition, calling for caution in the interpretation of such experiments.

This work also raises numerous interesting questions that remain unanswered. For instance, how is Notch asymmetry generated in sister bipolar cells to induce conversion of one of the siblings? A possible mechanism is the asymmetric inheritance of Notch signaling inhibitors during division. The Notch antagonist Numb, for example, was previously shown to be required for production of asymmetric neurogenic divisions in the mouse retina[15], but Engerer, Petridou *et al.* have found that asymmetric Numb distribution is not involved in generating differential Notch signaling in the *vsx1* lineage. Thus, Notch asymmetry may instead be achieved by the unequal activity of transcription factors, Notch ligands, or other negative regulators of Notch activity.

Another interesting question pertains to the purpose of bipolar to amacrine conversions. The authors propose that transdifferentiation could fine-tune the balance between excitatory (bipolar) and inhibitory (amacrine) circuits in the retina. Interestingly, reduction of overall amacrine cell numbers via knockdown of *pft1a* resulted in more amacrine cells generated in the *vsx1* lineage compared to control. This suggests that environment-sensing mechanisms are in place to regulate bipolar to amacrine conversions, which may be necessary to obtain the appropriate number of both cell types within the tissue.

It also remains to be determined whether direct identity conversions are widespread in zebrafish, for instance in other lineages of the retina, and in other CNS regions. It will additionally be interesting to investigate whether transdifferentiation takes place in other vertebrates. The greater plasticity of lower vertebrates, exemplified by their ability to regenerate their CNS[6], could possibly render them more prone to cell conversion. In this case, manipulating Notch signaling may confer similar plasticity in higher vertebrates.

The extraordinary malleability of post-mitotic cells depicted in this work implies that cell state changes may occur more readily than previously believed. Could aberrant cell conversions be involved in diseases? In some cancers, the epithelial-to-mesenchymal cell transition is a well-known mechanism underlying the excessive ability to proliferate, which apparently represents an exacerbation of a normal plasticity process[16]. Thus, could similar abnormal cell state reprogramming be involved in other diseases? Notch signaling has been implicated in cancers[17] and a number of other diseases and developmental malformations[18], suggesting that common cell state reprogramming mechanisms may be at play.

The discovery of cell identity reprogramming has revolutionized our understanding of somatic cell states. The novel findings that differentiated cells undergo transdifferentiation in the normal developing nervous system[7–9] suggests a previously unappreciated level of plasticity in post-mitotic cells. Accordingly, it will be necessary to review the concept of differentiation, a process previously associated with the generation of a terminal cell state.

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Evolution: Ant trail pheromones promote ant–aphid mutualisms

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A new study shows that trail pheromones produced by an invasive ant species suppress the dispersal and stimulate the reproduction of cotton aphids that the ants can 'milk' for honeydew. Aphids use these pheromones as a signal of ant presence and respond adaptively, analogous to early stages of animal husbandry where animals were attracted to human settlements.

We are used to thinking of animal husbandry as an exclusively human endeavor, but some animals have predated us in evolving forms of animal husbandry millions of years ago. Some of the best-known examples are ant species that 'farm' aphids, 'milking' them for honeydew. This is a mutualistic relationship, since the ants protect the aphids on the plants where aphids are feeding, and the honeydew produced by aphids is the ants' major source of carbohydrates[1]. The mutualism between ants and certain aphids can cause problems for human agriculture where invasive species overlap, as is the case for red imported fire ants (RIFAs, *Solenopsis invicta*) and cotton aphids (*Aphis gossypii*). It is known that establishment of mutualistic interactions with invasive RIFAs is one of the reasons for cotton aphid outbreaks, but the proximate mechanism of the mutualism was unclear. In this issue of *Current Biology*, Xu *et al.*[2] describe such a mechanism for the mutualism between RIFAs and cotton aphids. In a series of elegant experiments, these authors show that two ant-produced semiochemicals (Z,E-α-farnesene and E,E-α-farnesene) suppress aphid dispersal (although long-range dispersal by flying is not affected), and additionally that one of these chemicals (Z,E-α-farnesene) increases aphid reproduction and leads to faster aphid population growth.

Ant–aphid interactions have multiple origins, and the outcomes of these interactions range from parasitic to mutualistic and from obligate to facultative[1]. It is, however, unknown how the specific interaction between RIFAs and cotton aphids evolved. Both partners in this interaction can be invasive outside their home range and are widely distributed. RIFAs are known to have originated in South America[3], but the origin of cotton aphids is less clear, with Asia being a possibility[4]. There is some circumstantial evidence that aphids play a more important role in invaded regions than in their native ranges and that mutualistic associations have since been established with other ant species with which aphids have not previously coevolved[5]. This suggests that the aphids perceive a common suite of chemicals that signal the presence of ants, which in turn provide aphids with protection. In support of this hypothesis, Z,E-α-farnesene is a chemical typically found in the trail pheromones of multiple ant species from different genera (Xu and Turlings, personal communication).

In the new study, Xu *et al.*[2] found that increases in ant population sizes benefit the aphids, and the protection conferred by ants allows aphids to reach a higher density than they could in the absence of ants, where higher densities would make aphids an easy target for predators. On the other hand, a larger and a denser aphid population also increases the feeding efficiency of ants on aphid honeydew, concomitant with protection