example, an individual might insure a car used to drive to the casino. Such observations have led to more complex shapes of utility functions[4] and other elaborations of utility theory[5]. People and animals tend to be risk-prone when the choice involves potential losses[5,6], but risk-averse when they face potential gains or when the animal's energy intake is sufficient for its daily metabolic requirement[7].

Economic and psychological theories of decision-making can successfully account for a broad range of human and animal choice behaviors, but the neural basis for this fundamental aspect of life is only beginning to be understood. Given the central role of utility in formal theories of decision-making, it is not surprising that much effort has been devoted to identifying neural signals related to the utility of choices made by the animal. Indeed, signals resembling utility have been found in many brain areas, including the posterior cingulate cortex[8] targeted in McCoy and Platt's new study[2]. However, it has not been possible to determine whether such signals are actually related to utility (subjective value) or to the objective value of reward (such as its size). This can be accomplished by presenting a decision-maker with the task of choosing between two alternatives with the same mean outcome, one of which has a fixed outcome and the other of which has an uncertain outcome. This is precisely the approach used in McCoy and Platt's study.

Monkeys were trained to choose between two targets, indicating their choice with an eye movement. Choosing one of the targets delivered a fixed amount of juice reward, but the amount of juice available from the other target was uncertain. By choosing the risky target, the animal had a 50:50 chance of receiving a larger or smaller reward than the mean, although the average reward was always the same for both targets. There were no other differences between the targets, so only the riskiness of the animal's choice differentiated the two. Risk was systematically manipulated by changing the difference between the smaller reward and the larger reward available from the risky target. The monkeys tested in McCoy and Platt's experiment systematically preferred the risky target, and the riskier the target, the more likely the animals were to choose it. Remarkably, the animals continued to show a bias for risky choices even when the probability of obtaining a larger reward from the risky target was reduced so that the risky choice led to a smaller average reward.

McCoy and Platt also recorded the activity of individual neurons in the posterior cingulate cortex while the animals were making their choices, and found that more than half of the neurons signaled not only the animal's choice but also the riskiness of that choice. Because the animals were risk-prone in this experiment, the utility of the risky target must be larger than the utility of the average reward. Therefore, neurons responding more strongly to a risky target might have been signaling its utility, rather than merely the size of the expected reward. This is indeed what McCoy and Platt found. They reasoned that such quantities as utility or expected reward size must be estimated from the animal's recent experience[9–12]. However, they found that the activity in the posterior parietal cortex did not encode the size of reward in the previous trial. They then estimated the utility of each target on a trial-by-trial basis according to the sum of reward size and risk, and found that this was more reliably reflected in the neural activity.

The study of McCoy and Platt raises several exciting questions for future studies. First, by providing quantitative data regarding the risk preference of monkeys, it lays the foundation for further neurobiological studies of risk preference in primate brains. It would be interesting, for example, to determine whether monkeys are intrinsically risk-prone, or whether their risk preference can be manipulated by any environmental or cognitive factors[6,7]. Second, this study will stimulate similar future studies in other brain regions, as an animal's ability to make adaptive decisions depends on cooperation among multiple cortical and subcortical areas[11–15]. For example, are risk-related signals found in the present study first generated in the posterior cingulate cortex? If not, what is the function of risk-related signals represented in this particular brain area? How do signals related to risk or utility ultimately influence the choice of the animal? As McCoy and Platt demonstrated, answers to many of these questions may be within reach now. As with any other choice in our stochastic environment, the decision to study the neural basis of risky choices might be risky, but such studies will be surely rewarding.

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Wnts send axons up and down the spinal cord

Barry J Dickson

Certain Wnts attract ascending somatosensory axons up the spinal cord toward the brain. A study in this issue shows that other Wnts guide corticospinal axons down the spinal cord, not by an attractive mechanism but by repulsion through the receptor Ryk.

The developing spinal cord is a major highway for growing axons. Axons enter and exit the highway at specific points, and, when appropriate, cross over to the other side. But the main traffic flow, as on any highway, is in both directions along the longitudinal axis—up to or down from the brain. What are the guidance cues that send these axons up or down the spinal cord? Over the past decade, researchers have uncovered many of the molecular signposts that regulate axon entry, exit and crossing over. Yet, until recently, the signals that direct axons up and down the spinal cord had been elusive. The first breakthrough came a couple of years ago, when the Zou group demonstrated that Wnt proteins are important in directing axon growth toward the brain[1]. Now, further work from the same group, by Liu *et al.* in this issue[2], suggests that other Wnt

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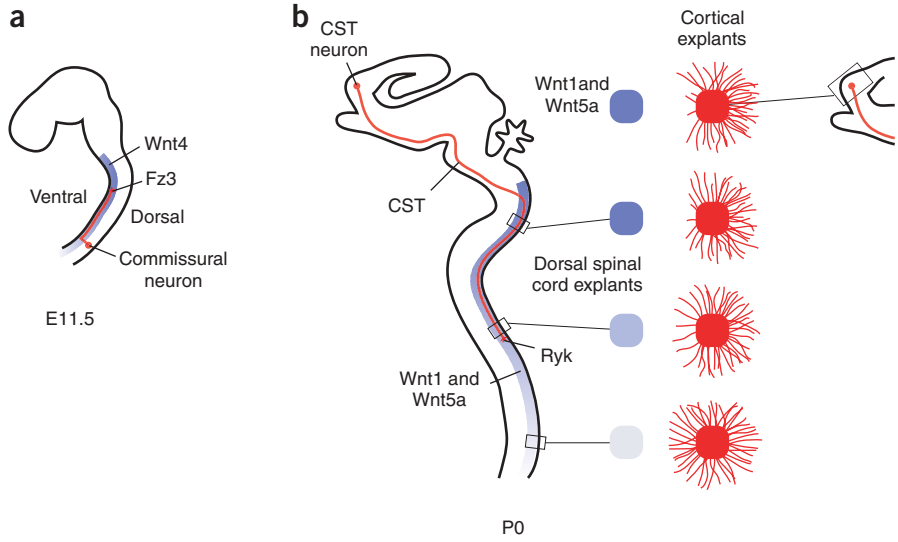

Figure 1 Wnts guide axons up and down the spinal cord. (**a**) Commissural axons turn anteriorly after crossing the floor plate. This turn seems to be mediated in part by Wnt4, and possibly by other Wnts, which are expressed in an anterior-posterior gradient in the floor plate and signal attraction through the Fz3 receptor[1]. (**b**) After passing through the mid- and hindbrain, corticospinal tract axons cross the midline and grow down the spinal cord in the dorsal funiculus. Growth down the spinal cord seems to be mediated in part by Wnt1 and Wnt5a, which are expressed in an anterior-posterior gradient in the dorsal spinal cord and signal repulsion through the Ryk receptor[2].

proteins direct axons in the opposite direction, down the spinal cord.

Wnt proteins seem unlikely candidates for axon guidance cues. They are far better known for their roles in cell-fate specification and cell proliferation, which have been the focus of intense investigation for more than two decades. It thus came as a major surprise when clever genetic studies identified a Wnt protein, Wnt5, as a key factor in axon guidance in *Drosophila melanogaster*[3]. Specifically, Wnt5 was found to determine whether commissural axons—those that extend across the midline of the CNS—take the anterior or the posterior commissure of each segment. A further remarkable finding was that Wnt5 does not seem to act through a Frizzled (Fz) protein, the typical seven-transmembrane-domain receptors for Wnts. Instead, Wnt5 signals through a completely unrelated single-pass transmembrane receptor of the Ryk family, called Derailed (Drl).

While this *Drosophila* work was going on, members of the Zou group were looking for factors in vertebrates that instruct commissural axons to turn anteriorly after crossing. Remarkably, they too stumbled on Wnt proteins, including Wnt4, which are expressed in the floor plate at the ventral midline in an anterior-high to posterior-low gradient[1] (**Fig. 1a**). Their report provided compelling evidence that Wnt proteins can also act as axon-guidance factors in vertebrates, just as they do in *Drosophila*[3]. But there were also some intriguing differences. First, *Drosophila* Wnt5 clearly acts as a repellent cue for commissural axons as they cross the midline, whereas mammalian Wnt4 instead seems to guide commissural axons by attraction, and only after they have crossed. Second, whereas *Drosophila* Wnt5 acts through a Ryk family receptor, mammalian Wnt4 seems to act through Fz receptors, including Fz3. Thus, a model emerged in which various Wnt proteins might act either as axonal attractants or repellents, depending upon whether a Fz or a Ryk receptor was involved, respectively[4].

Guided by such a model, Liu *et al.*[2] hypothesized that if Fz receptors could attract axons up a Wnt gradient in the spinal cord, then Ryk receptors might repel axons down a Wnt gradient. To test this idea, they focused on axons of the corticospinal tract, a major descending pathway from the brain that courses through the dorsal region of the spinal cord (**Fig. 1b**). As it turned out, their prediction was spot on. They first found that several other Wnts are indeed expressed in an anterior-high to posterior-low gradient in the neonatal dorsal spinal cord, and that two of these Wnts—Wnt1 and Wnt5a—are potent repellents for corticospinal tract axons *in vitro*. Dorsal spinal cord explants themselves also repel these axons *in vitro*, and just like Wnt1 and Wnt5a expression, this effect tapers off in more caudal regions of the spinal cord (**Fig. 1b**).

The authors then went on to show that Ryk, the vertebrate homolog of *Drosophila* Drl, is indeed expressed on corticospinal tract axons. Moreover, by using anti-Ryk antibodies to block Ryk function, they show that Ryk is indeed required for the repulsion of corticospinal tract axons *in vitro*, in response both to Wnts and to dorsal spinal cord explants. Finally, Liu *et al.* show that injection of antibodies to Ryk directly into the spinal cord interferes with the posterior growth of corticospinal tract axons. Overall, this series of experiments make a compelling case that endogenous Wnts, most likely including Wnt1 and Wnt5a, act through Ryk to help guide corticospinal tract axons down the spinal cord. In the future, genetic manipulations of the *Wnt1*, *Wnt5a* and *Ryk* genes will be required to confirm and extend these findings.

One intriguing aspect of this study is that corticospinal tract axons grow for some distance in the brain before they enter the spinal cord, and so actually have to grow up a very steep Wnt gradient as they first enter the cord. This is not the response one would expect these axons to show when confronted with such a potent repellent! The explanation, it seems, is that young corticospinal tract axons are evidently insensitive to the repellent action of Wnts, and only acquire this sensitivity at about the time they enter the spinal cord[2]. Presumably, by this time corticospinal tract axons have passed the point of no return, and now have no choice but to continue on down the spinal cord. Such tight temporal regulation of guidance responses is a recurring theme in axon guidance, and has been particularly well documented for commissural[5,6] axons. These axons switch their responses to several guidance cues as they cross the CNS midline, possibly even becoming attracted by Wnt4 only after crossing[1]. In this regard, it is interesting to note that corticospinal tract axons also cross the midline just before they enter the spinal cord, and so it is tempting to speculate that midline crossing of corticospinal tract axons might similarly trigger the onset of Ryk expression and aversion to Wnts.

This new work also adds to the growing evidence that Ryk proteins, like Fz proteins, are receptors for at least some of the Wnts[3,7,8]. An open issue, and a matter of some debate, is whether Ryk and Fz proteins are part of the same multifunctional receptor complex or are independent receptors with distinct functions. A recent report[7] has argued that Ryk and Fz are part of the same receptor complex, though it should be noted that the case rests largely on evidence from overexpression studies in cell culture. In contrast, the studies discussed above clearly indicate that the axon guidance functions of Ryk and Fz receptors are mutually independent[1–3]. A similar conclusion has

also come from recent studies of Ryk and Fz function in cell fate specification in the *Caenorhabditis elegans* vulva[8]. Thus, on balance, the evidence seems to favor a model in which the two receptors can signal independently. Nevertheless, comparisons to another well-known family of bifunctional guidance cues, the netrins, may be helpful. Like Wnt proteins, netrins also signal attraction and repulsion through different receptors—DCC and Unc5, respectively. Although these two receptors can clearly act on their own[9–11], they may also sometimes function together as part of a single receptor complex[11–13].

Another important area for further research will be to define the signaling pathways that act downstream of Fz and Ryk receptors in axon guidance. Fz proteins activate at least three distinct pathways, of which the so-called 'planar cell polarity' and 'calcium' pathways provide the more plausible links to the cytoskeleton[14]. Signaling pathways for Ryk receptors are still unknown. These proteins have a cytoplasmic domain that resembles tyrosine kinases, but evidently lacks kinase activity. This cytoplasmic domain is required in Drl for axon guidance in *Drosophila*[15], but not in Lin-18/Ryk for cell fate specification in *C. elegans*[8]. Clearly, there is still a lot of work to do, and it would certainly help to develop *in vitro* growth cone turning assays for Wnts—a method that has proven particularly useful for other guidance cues such as netrins.

Finally, might these new results be of any help in efforts to develop therapies for the treatment of spinal cord injuries? It remains to be seen how, or whether, Wnt proteins and their Fz and Ryk receptors might act in the adult spinal cord. But, surely, learning how axons grow up and down the spinal cord during development can only increase the prospects for encouraging severed axons to do the same in the adult.

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GABA puts the brake on stem cells

Arnold R Kriegstein

In the adult brain, new neurons are generated from neural stem cells residing in the subventricular zone. Newborn neuroblasts release the transmitter GABA, which reduces the proliferation of stem cells—and thereby neurogenesis—by a nonsynaptic mechanism.

Uncontrolled proliferation of immature cell types can have devastating consequences, including cancer. Tight regulation of neurogenesis in the adult brain is therefore essential. Neurons destined for the olfactory bulb are produced in the subventricular zone (SVZ) and added continuously through adulthood. However, the regulatory mechanisms that control neurogenesis are poorly understood. A variety of signaling molecules, including EGF, Shh, BMPs and the Eph/ephrin family, promote neurogenesis in SVZ cells, and at least one pathway, involving Notch signaling, seems to suppress SVZ neurogenesis (for review, see ref. 1). In this issue, Liu and colleagues[2] use a wide variety of electrophysiological approaches to show that nonsynaptic, nonvesicular release of the neurotransmitter GABA provides negative feedback to neural stem cells, inhibiting their production of new neuroblasts through inhibition of cell-cycle reentry.

These results build upon prior observations on the role of GABA in both embryonic and adult neurogenesis. During embryonic stages of cortical development, GABA influences the proliferation of neural progenitor cells. Its net effect is to inhibit the number of cells entering the cell cycle[3,4]. GABA affects embryonic neurogenesis at ages after GABAergic neurons are produced, but before the development of synaptic GABA transmission. The new report is consistent with these studies of embryonic neurogenesis, showing a GABA-mediated feedback regulation of adult neurogenesis controlled by nonsynaptic GABA release. This is also in line with observations that elimination of neuroblasts stimulates the proliferation of GFAP-positive neural stem cells, suggesting that a feedback signal produced by neuroblasts may normally inhibit stem cell proliferation[5]. SVZ neuroblasts can synthesize and release GABA[6,7], and the current report extends these observations by providing evidence that GABA may act as an inhibitory feedback signal to suppress neural stem cell proliferation. It is now clear that this neurotransmitter, once thought only to mediate signaling at synapses, is also important for regulating neurogenesis at both adult and embryonic ages.

Liu and colleagues very nicely characterize the electrophysiological properties of neuroblasts and GFAP-positive astrocyte-like neural stem cells. They find that the GFAP-positive cells are gap junction–coupled into small clusters and express functional $GABA_A$ receptors. They further show that nonsynaptic, nonvesicular GABA release by neuroblasts (type A cells) inhibits proliferation of GFAP-positive progenitors (B cells; **Fig. 1**). The new findings, as with many new observations, raise more questions than they answer. One question concerns the role of C cells in the GABA regulatory pathway. These GFAP-negative cells are generated by B cells and serve as intermediates in neuroblast generation (**Fig. 1**). The C cells are thought to act as transit-amplifying cells and are known to undergo rapid cell cycling. There are few reliable characteristics that can help identify C cells at present, perhaps the best being the highly invaginated nucleus with a reticulated nucleolus[8], but this feature is best visualized by electron microscopy. Do the C cells synthesize and release GABA? Do they respond to GABA? Does GABA regulate C cell proliferation? Answering these questions will be difficult until better cell-specific markers are available to identify these cells *in vivo*. Another question involves the importance of GABA-mediated feedback regulation *in vivo*.

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