forming domains in one subunit[12], and it too is stimulated by volatile anesthetics[13], albeit at high concentrations.

Members of the potentially huge mammalian family of 2P/4TM K^+ channels most likely function as non-voltage-gated background channels whose probability of being open depends on the concentrations of specific modulators (activators and inhibitors) that vary from cell to cell and from channel to channel, setting levels of K^+ conductance that influence cellular activities. However, not all members of this family are activated by volatile anesthetics. Patel and colleagues[2] looked for effects of four volatile agents (isoflurane, halothane, diethyl ether and chloroform) on recombinant TREK-1, TRAAK and TASK homomeric (presumably dimeric) channels expressed in COS cells. All four anesthetics activated TREK-1 channels but had no effect on TRAAK channels. TASK channels, on the other hand, were activated by isoflurane and halothane, unaffected by chloroform and inhibited by diethyl ether.

The mechanism of anesthetic activation of TREK-1 and TASK was probed by using genetic constructs as well as by recording from excised patches. By making chimeras and deletions from anesthetic-sensitive and -insensitive channels, Patel and colleagues deduced that carboxy-terminal (but not amino-terminal) regions were necessary for anesthetic activation; their findings also indicate that additional unidentified regions are involved in binding of anesthetics to the channel and/or in gating the current. Although it is now widely accepted that general anesthetics act by binding directly to proteins, rather than by dissolving in the lipid bilayer as initially proposed, it will be interesting to see if these channels are stereoselectively activated by the optical isomers of isoflurane, as found for the molluscan I_{KAn}[14]. In both inside-out and outside-out excised patches, anesthetic activation persisted in the absence of cytoplasmic second messengers, and so Patel and colleagues[2] conclude that anesthetics act directly on the channels. This may indeed be the case in excised patches, but additional pathways of anesthetic activation and modulation of these channels may exist in intact cells[6–8]. Quantitative comparisons of the effects of volatile anesthetics on excised patches and intact neurons could resolve this issue.

The discovery of volatile anesthetic-activated K^+ channels in mammals increases the number of mammalian inhibitory channels whose activities have been shown to be augmented by anesthetics. Because of the exceptionally large number of 2P/4TM channels in *C. elegans*, it seems reasonable to assume that there are a large number of these background K^+ channels yet to be discovered in man. This argues that their effects on general anesthesia are likely to be important. Although not all members of this family are activated by volatile agents, it seems safe to predict that many are. It will be important to determine which channels are sensitive to which volatile agents and to define their locations at the organ, CNS and neuronal levels. This information, together with the inevitable results from 'knockout' mice (which cannot be far behind) will help to establish the importance of background K^+ channels in the production and maintenance of the anesthetized state.

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This way up: illusions and internal models in the vestibular system

Lawrence Snyder

Two recent papers demonstrate that the vestibular system transforms raw sensory data into a sophisticated internal model of head orientation and movement.

Our intuition tells us that we experience the world directly, but in fact significant processing intervenes between sensation and perception, as demonstrated by the ventriloquist's illusion. The visual cue of the dummy's moving lips influences our perception of where the ventriloquist's voice originates. Thus rather than directly perceiving sights and sounds, we use sensory signals to construct an internal model of the external world, and our perceptions derive from the model rather than from the raw signals. Two recent papers from Hess and Angelaki[1] and Merfeld and colleagues[2] demonstrate that the vestibular system also uses an internal model of how the head is situated in the world to make sense of sensory data. This evolutionarily ancient system thus is capable of much more sophisticated computation than was previously imagined.

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The vestibular system is composed of the semicircular canals, which report angular acceleration, and the otolith organs, which respond to linear acceleration (**Fig. 1**). These two sets of sensors are often considered to be independent. Parsimony suggested that this peripheral independence would be respected centrally, for example in distinct angular and linear subsystems of the vestibulo-ocular reflex, which automatically moves the eyes to compensate for head movements, even in the dark[3]. (To appreciate the vestibu-

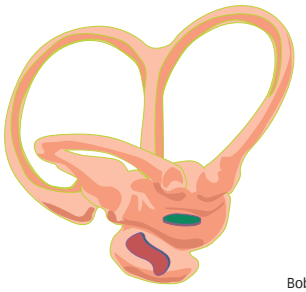

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Fig. 1. Anatomy of the vestibular system. The vestibuluar appartatus consists of three semicircular canals, which detect angular motion, and two otolith organs (red and green), which detect linear motion. The entire structure, along with the cochlea, is encased within solid bone in the inner ear.

lo-ocular reflex, shake your head while reading and compare the outcome to what happens if you hold your head still and move the page instead.) Qualitative verbal descriptions of vestibular perceptions are often unreliable and are not available in non-human subjects. For this reason, reflexive eye movements are often used as an objective, quantitative measure of vestibular sensation.

Both studies use reflexive eye movements to address a long-standing vestibular conundrum. The otolith organs (literally, 'ear rocks') are composed of a matrix of loosely anchored calcium carbonate crystals in the inner ear that is coupled to vestibular hair cells. Neural signals transduce the relative displacement of the crystals. Unfortunately, displacement can result from two completely different physical stimuli[4] (**Fig. 2**). Gravity displaces the crystals in a direction that depends on head orientation. For example, if we tilt our heads up to look up at the ceiling, the crystals will shift, bending the cilia of the hair cells toward the back of the head. However, inertial forces can also displace the crystals. For example, sudden motion in the forward direction will also shift the crystals toward the back of the head. Thus both gravitational and inertial forces produce exactly the same effect on the otoliths.

If gravity and inertia stimulate the otoliths in an identical manner, how is it that we can tell the two stimuli apart? Even with our eyes closed, we never confuse looking up at the ceiling with hurtling forward. (Though the reverse is not true; we can confuse sustained linear acceleration with a change in our orientation with respect to gravity, as fighter pilots soon learn.) The prevailing explanation for this is that we use a frequency-selective filter to differentiate tilt from acceleration when no other cues are available[5]. This filter attributes rapidly changing otolith signals (> 0.5 Hz) to linear acceleration, and more sustained signals (< 0.5 Hz) to tilt. Hess and Angelaki[1] and Merfeld and colleagues[2] show that the method of differentiation is more complex. In the process, they provide convincing evidence that otolith and canal signals are combined in a sophisticated manner to generate an internal model of head orientation and movement.

Hess and Angelaki[1] use eye movements to ask whether monkeys can differentiate tilt from linear acceleration by some criterion other than frequency. Two conditions were compared. In the first, animals slide from right to left and back again twice every second. In the second, animals are first tilted forward by 23 degrees, and then rotated twice per second around an axis along the center of the body, parallel to the spine. Both conditions exert similar periodic forces on the otoliths. The animals are kept in the dark to deprive them of visual cues they might otherwise use to determine what is happening. Can the vestibular system differentiate between these two conditions?

To answer this question, the authors make artful use of a fiendishly obscure property of how the eyes position themselves in the head. About 100 years ago, Helmholtz formalized Listing's law, which describes how eye torsion (rotation around the line of sight) depends on the azimuth and elevation of the eye in the orbit[6]. Recently, Crawford and Vilis discovered that torsion also depends on the tilt of the head with respect to gravity[7]. By measuring all three dimensions of eye position, Hess and Angelaki show that eye

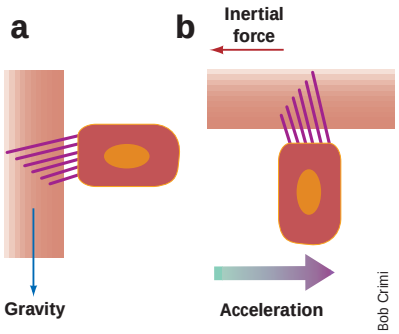

Fig. 2. Gravitational and inertial forces have identical effects on the otolith organs. **(a)** A hair cell from the saccule, stimulated by the effect of gravity on the otolithic mass when the head is tilted nose-up. **(b)** Same hair cell stimulated by inertial force when the upright head is accelerated forward. The hair cell deflections in **(a)** and **(b)** are indistinguishable.

torsion in the translating animal is consistent with an upright head orientation, whereas torsion in the tilting animal is consistent with a tilted head orientation. Thus the vestibular system correctly distinguishes between the two similar patterns of otolith displacement.

How is the distinction made? The conventional answer of a frequency-selective filter can be excluded, because the frequency of stimulation is identical in the two cases. Instead, Hess and Angelaki suggest that a canal signal is used. The canals are stimulated in the tilted, rotating animal, but not in the upright, translating animal. Given a sufficiently sophisticated internal model of the system, canal activity could provide the necessary information to disambiguate the otolith signal. Thus the monkey vestibular system does not maintain separate channels for canal and otolith information, but instead combines these signals to build up a veridical model of head orientation and movement with respect to the external world.

Merfeld and colleagues[2] demonstrate a similar sophistication in the human vestibular system, but with an additional twist. Rather than showing directly that the system can disambiguate tilt from translation, they show that particular combinations of canal and otolith signals can generate an illusion of translation where none actually exists. Because the illusion depends on an interaction between canal and otolith signals, it confirms the idea that these signals are combined within the CNS.

Merfeld and colleagues rotate an upright subject in the dark until the canals completely adapt and the sensation of rotation is abolished (**Fig. 3a** and **d**). This happens because the canals are bony circular tubes, filled with fluid and spanned by a flexible membrane (the cupola), which behave somewhat like a bucket of water. If you pick up a bucket and twist it, the fluid at first stays still, and the bucket turns around it. Friction of the fluid on the moving walls of the bucket eventually causes the fluid to 'catch up' to the bucket. In the canals, the initial lag causes the fluid to exert force on the cupula, which stretches in response. Hair cells register this stretch, which modulates neuronal firing. As the fluid catches up with the canal, the elasticity of the cupula restores it to its resting state, the hair cells no longer sense stretch, and neuronal modulation ceases. This process takes about twenty seconds, but the central 'memory' of the stimulus lasts longer, so the authors wait two minutes for the rotating subject

to lose all sensation of movement. The subject is then decelerated to a sudden stop, which causes hair cells to sense the cupula being stretched in the opposite direction. Because the canals and central circuits were completely adapted to (for example) a counter-clockwise rotation, this deceleration produces exactly the same response as an acceleration in the opposite (clockwise) direction (**Fig. 3b** and **e**). Finally, the subject is tilted nose-up (**Fig. 3c**), and the eye movements elicited by the vestibulo-ocular reflex are used to determine how the vestibular system's internal model interprets this confusing input.

The vestibular system is confronted with a paradox (**Fig. 3f**). From the nose-up position, the sensation of clockwise rotation leads it to expect the head to move so that the right ear is down. However, because no rotation is actually occurring, the head remains nose-up. The otolith organs report that the back of the head, not the right ear, is 'down'. Hence the paradox: the canals report that the head is rotating clockwise and should therefore be turned right ear down, while the otoliths report a gravitational vector aligned with the back of the head, as if no rotation has occurred. To resolve this paradox, the vestibular system postulates a leftward force that would satisfy these conflicting constraints. An illusory leftward inertial force of the correct magnitude exactly accounts for the difference between what the otoliths report—that the back of the head is pointing down—and what the illusory rotation implies—that the right ear is pointing down (**Fig. 3f**). Such a force would be produced if the head were accelerating to the right.

Subjects do not report translation, perhaps because they are too disoriented by the unusual sequence of stimuli to properly sort out their sensations. However, their eyes betray them. Merfeld and colleagues compare evoked movements when clockwise or counterclockwise rotation precedes a particular head tilt. After subtracting out the reflexive response to the illusory rotation and the subsequent tilt, a residual signal remains. This residual eye movement is consistent with a response to an (illusory) head translation. Thus, much as the ventriloquist manipulates visual input to generate an auditory illusion, Merfeld and colleagues manipulate the vestibular canal signal to generate an illusion of translation.

These two sets of experiments have several important implications. First, eye movement responses to rotation and translation of the head are not mediated by two distinct systems, but instead by a single integrated system[8]. Second, otolith signals are not interpreted as reflecting tilt or translation based on a simple method such as a frequency filter. Instead, canal signals are combined with otolith signals to produce a consistent measure of head orientation and movement. Merfeld and colleagues argue that such a circuit should be considered an internal model. It is a good bet that this circuitry lies at least in part within the oldest part of the cerebellum, the vestibulocerebellum, portions of which have long been implicated in vestibulo-ocular reflex adaptation and, more recently, in the extraction of rotational information from otolith signals[9,10]. On the current evidence, however, it is not possible to rule out involvement of the vestibular nucleus.

The vestibulo-ocular system has already provided several less-complicated examples of internal models. The central 'velocity storage' mechanism that maintains the sense of rotation for a minute or more after the canals have adapted[11] is itself a simple internal model. This model gets input from other sensory channels. If you open your eyes after adapting to constant-velocity rotation with eyes closed, then the visual signal accesses the vestibular circuits, and the sensation of rotation returns with a jolt[12]. Although previous work had demonstrated internal processing and integration of visual and vestibular sensory signals, these computations could be modeled by simple circuits. In contrast, the disambiguation of gravitational from inertial forces demonstrates the sophistication of vestibular processing and recommends the vestibular system as a model for understanding how raw sensory data are transformed to support perception.

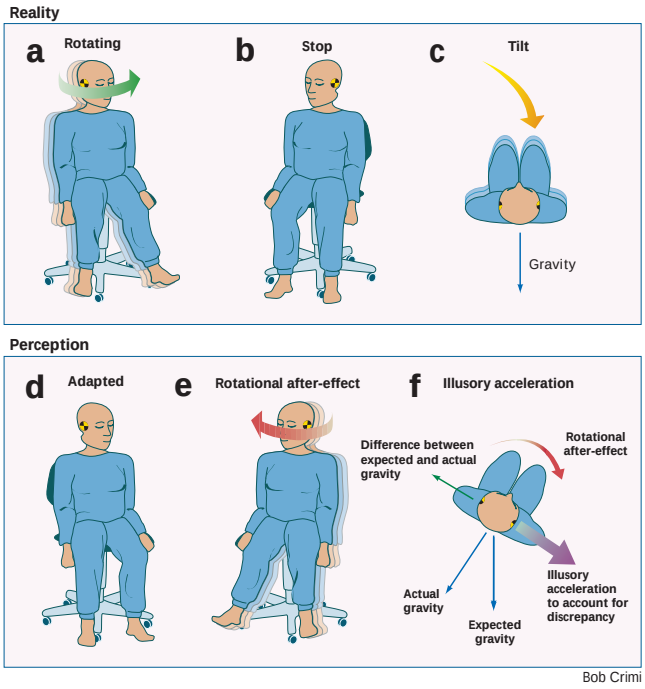

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Fig. 3. Experimental design of Merfeld and colleagues. The subject is rotated counter-clockwise for two minutes **(a)**, until the vestibular canals have adapted, so that the subject no longer perceives movement **(d)**. Then the rotation is stopped abruptly **(b)**, which stimulates the canals in the opposite direction, producing an illusion of clockwise rotation **(e)**. During this illusion, the subject is tilted nose-up **(c)**, and the vestibular system compensates for these conflicting signals by experiencing another illusion, that the body is accelerating toward the right **(f)**. See text for details.

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