Let's add to the list of biological disciplines the idea of computational modelling. Although I don't do it myself, I think such approaches will be vital in guiding a way forward to understanding the human mind and brain, as well as the minds and brains of other species.

What are the most pressing questions the cognitive sciences face right now? There is a long-standing debate between nativism and empiricism, as well as an equally long-standing debate between hereditarians and environmentalists. Both debates suffer from polarization and a lack of understanding of the middle ground. Nativists and hereditarians (who are not necessarily the same people) argue that their opponents believe in a 'blank slate'. I don't think that's true, or at least it hasn't been true for decades. The other possibilities are constructivism (but with theory that long ago transcended Piaget) and a respectful and disciplined search for exactly how genes and environment interact.

If you could ask an omniscient higher being one scientific question, what would it be and why? For me, a lot of the fun in science is the lure of the chase. I love detective novels, and puzzles, and like to work things out myself. It's just frustrating that each experiment takes so long. My idea of paradise is that I could formulate a question, and a study or experimental design, press a button and get data and analyses. Those might not answer my question of course, if it was poorly formulated or the study was poorly designed. But since paradise is eternal, presumably I'd gradually get warmer, or at least I'd like to think so.

I have asked a few colleagues whether they like this vision or would prefer to read the definitive textbook on the field in paradise. Some people opt for the latter. I see the attraction, but I prefer the quest.

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Quick guide

Cerebrospinal-fluid-contacting neurons

Adeline Orts-Del'Immagine and Claire Wyart

First, what is cerebrospinal fluid? The cerebrospinal fluid (CSF) is the complex solution, mainly secreted by the choroid plexuses, that fills the cavities surrounding the central nervous system (CNS) — the brain and spinal cord (Figure 1A). First described by Hippocrates when examining cases of hydrocephalus, the CSF was later referred to as an "excremental liquid" by Galen and as the "spirituous lymph" by Swedenborg. The CSF has been long assumed to form a passive fluid, an ultra-filtrate of plasma, providing nutriments and ensuring the mechanical protection and chemical homeostasis of the brain by transporting secreted molecules and removing toxic waste. As the CSF composition reflects the activity of the CNS and its health status, analysis of CSF content is commonly used to detect pathogen invasion or to diagnose neurological disease.

What signals are carried by the CSF? The CSF contains diverse chemical cues which have the potential to modulate CNS activity, mediating a long distance and slow mode of communication referred to as 'volume transmission'. Neuro-active substances, such as neurotransmitters, neuromodulators (serotonin, dopamine, noradrenaline) or neuropeptides (vasopressin, β-endorphin and oxytocin) can act on extra-synaptic receptors on distant targets. Interestingly, the CSF contains exosomes as well as an aggregation of secreted molecules known as Reissner's Fiber, and these could be involved in the specific recognition, transport and stabilization of some of these active components.

The CSF is mainly produced by the choroid plexuses via a process that involves the transport of sodium, chloride and carbonate ions from the blood into the ventricles of the brain. Compounds can passively diffuse into the CSF from neurons and glial cells in the parenchyma, or be actively secreted into the CSF by the choroid plexuses or other neurosecretory glands, such as the pineal gland, the superior commissural organ, or neurons that contact the CSF throughout the brain and spinal cord.

What roles do CSF chemical cues play during development? Recent findings point to the CSF playing an active role during brain and spine development via the oriented transport of chemical cues. The choroid plexuses secrete chemo-repulsive (Slit 2) and chemo-attractive (Shh) molecules that are transported by CSF flow and required for the proper migration of neuroblasts along the rostral migratory stream. During early stages of brain development, the choroid plexuses secrete growth factors, morphogens and exosomes that act on ciliated progenitor cells in contact with the CSF to regulate their proliferation and neurogenesis. As development progresses, the CSF protein and exosome content decreases in line with the decrease of neurogenic capacity. Recent evidence indicates that CSF flow is important in body axis formation at the embryonic stage and also spine curvature at the juvenile stages, though the molecular mechanisms underlying this are not known.

Does CSF content influence behavior? Surprisingly little is known on the effects of CSF on behavior. In 1913, Legendre and Pieron suggested that CSF modulates sleep, after observing that injection of CSF from a sleep-deprived dog into control animals induced sleep that lasted for 2–6 hours, something they were able to reproduce in goats and cats. This effect may involve prostaglandin D2, an endogenous sleep-promoting compound secreted by the choroid plexuses and whose CSF concentration fluctuates with the sleep–wake cycle, or other CSF factors known to have effects on sleep, such as orexin-A, TGF-β, cardiotrophin-like cytokine and melatonin. CSF injections in farm animals have further suggested that CSF content modulates appetite,

a phenomenon that could involve insulin, leptin or the anorexigen peptide glucagon-like-peptide-1, produced by the small intestine and nucleus tractus solitarius.

Together, these studies indicate that CSF signals circulate and act throughout the nervous system. But it is still not known how secretion into the CSF from the various contacting neurosecretory structures is regulated, how chemical cues are transported to reach their targets, and which receptor cells integrate the signals from the CSF to modulate behavior.

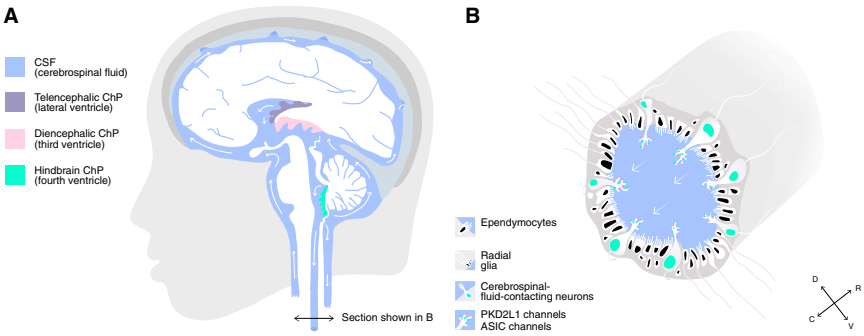

Figure 1. Organization of the cerebrospinal fluid (CSF) and the cerebrospinal-fluid-contacting neurons (CSF-cNs) in vertebrates.
(A) The CSF is produced by the choroid plexuses (ChPs) in the brain. Spinal CSF-cNs are surrounding the central canal at the level of the brain stem and spinal cord. (B) Section of the spinal cord shows the organization of cells surrounding the CSF in the central canal: radial glia, ependymocytes and CSF-cNs, which possess on their apical extension bathing in the CSF the ASIC and PKD2L1 channels that detect changes in CSF pH and osmolarity. R, rostral; C, caudal, V, ventral; D, dorsal.

So what are CSF-contacting neurons? Nearly 100 years ago now, Kolmer and Agduhr described bipolar cells contacting the CSF at the level of their apical extension around the third ventricle and the central canal in the spinal cord of over two hundred vertebrate species (Figure 1B). The ciliated morphology and location of these CSF-contacting neurons (CSF-cNs) suggested a sensory function in the detection of CSF composition or flow. Morphological and molecular analysis of CSF-cNs revealed these cells originate from two progenitor domains in fish and mouse and can be identified by the morphology of their apical extension as well as their local axonal projections. The lack of molecular markers for CSF-cNs long hampered investigations of their function, until Charles Zucker's group noticed that these neurons express a transient receptor potential channel identified in sour taste receptors of the mouth. This channel protein, PKD2L1, has been since identified as a specific marker of spinal CSF-cNs across vertebrate species. Genetic targeting combined with optical techniques to monitor and manipulate activity of CSF-cNs has transformed our understanding of these cell types in the zebrafish larva.

So are CSF-cNs chemosensory and/or mechanosensory cells? Due to their peculiar morphology and their close contact with the CSF, Kolmer and Agduhr had postulated that CSF-cNs constitute a sensory organ of the medullo-spinal area—suggesting even they could constitute a third ear in the spinal cord. The discovery that PKD2L1 is a marker of CSF-cNs led to a number of *in vitro* studies of the cells, pH sensitivity. Electrophysiologically, CSF-cNs are highly resistive, responding to small variations of pH away from neutral values. Because of their high input resistance, the opening of PKD2L1 and ASICs channels, enhanced respectively by alkalinisation and acidification, is sufficient to trigger CSF-cN spiking.

That CSF-cNs may have a role in mechanoception is suggested by *in vivo* physiological studies, which showed that the cells respond to mechanical bending of the spinal cord via the PKD2L1 channel (Figure 2). While dorsal CSF-cNs detect lateral bending of the spinal cord, ventral CSF-cNs respond to longitudinal contractions. Further support for spinal CSF-cNs having a mechanoceptive function has come from *in vitro* studies with the lamprey. Further studies will be needed to establish whether CSF-cNs can chronically respond to CSF pressure or flow, and mediate the connection between CSF flow and body axis formation and spine curvature during development.

Do CSF-cNs modulate spinal circuits that control locomotion and posture? Mosaic labeling and optogenetic stimulation of CSF-cNs in zebrafish has revealed that these GABAergic neurons send ipsilateral ascending projections to local spinal circuits in order to modulate locomotor central pattern generators. Optogenetic-mediated connectivity mapping combined with *in vivo* patch-clamp recording of targeted spinal interneurons showed that CSF-cNs synapse onto V0v glutamatergic interneurons involved in locomotion and motor neurons involved in postural control (Figure 2). A fine morphological analysis has revealed that these targets received exclusive inputs from dorsal and ventral CSF-cNs, respectively. Interestingly, both dorsal and ventral CSF-cNs project onto glutamatergic sensory interneurons, suggesting a common pathway for the integration of sensory feedback.

Do CSF-cNs form a secretory organ in the CSF? On the basis of ultrastructural studies, Vigh and Vigh-Teichmann suggested that spinal CSF-cNs may constitute a neurosecretory system that controls the levels of neuroactive substances in the CSF. Dense granules were observed under the apical extension contacting the CSF as well as in the axon forming neurohormonal-like nerve endings, indicating that CSF-cNs could release bioactive substances into the central canal, as well as onto neuronal targets in the spinal cord and into the meningeal vessel. Large granular vesicles were also observed in CSF-cNs perikarya and dendritic processes, suggesting a possible uptake of active molecules

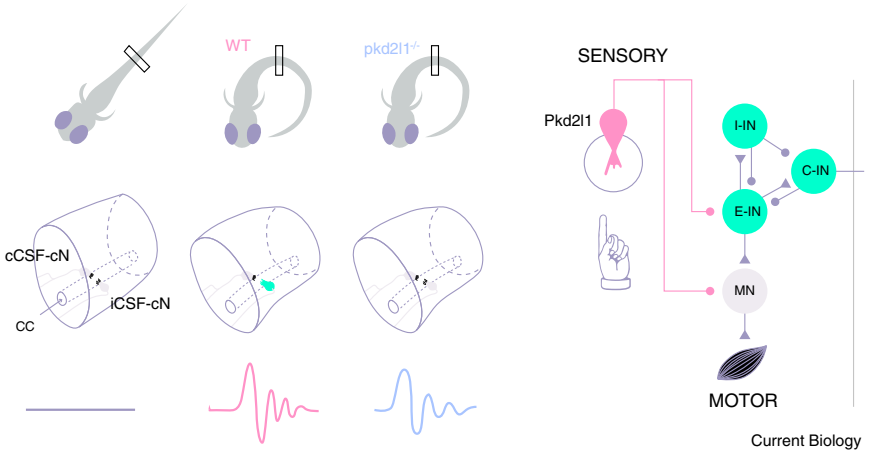

Figure 2. In zebrafish, CSF-cNs have been shown to detect curvature of the spinal cord via the channel Pkd2l1.
Left panel: zebrafish larvae swim by bending their tail, which leads to an activation of CSF-cNs on the side of bending (ipsilateral, iCSF-cNs, green; contralateral, cCSF-cNs, grey; CC, central canal). This activation is not observed in *pkd2l1* homozygotous mutants. Consequently, *pkd2l1* mutants swim with altered kinematics — slowing down their escape response. Right panel: once activated by bending, CSF-cNs (pink) project onto specific target neurons, namely excitatory premotor interneurons (E-IN) and motor neurons (MN) but not inhibitory premotor interneurons (I-IN and C-IN), within the motor circuits controlling locomotion and posture in the vertebrate spinal cord.

from the CSF through the dendrite. Although multiple studies confirm expression of peptides and secreted proteins in these cells, it remains to be demonstrated whether CSF-cNs could regulate through an active secretion process the composition of CSF.

There is thus converging evidence that medullo-spinal CSF-cNs constitute a highly conserved sensory system in vertebrates. Studies in mouse spinal cord identified pH and osmolarity as strong modulators of these cells. New optical approaches in zebrafish have revealed their mechanosensory function and projection pattern onto spinal circuits involved in locomotion and posture. The location of CSF-cNs at the interface between CSF and the parenchyma sets them as great candidate neurons to detect changes in the CSF and, in return, to adjust the excitability of motor circuits and the properties of the CSF itself. Further studies will investigate the role of these cells for organogenesis of the body axis and spine curvature. While the relevance of these cells to behavior has been mainly investigated in zebrafish, the connectivity map of CSF-cN and physiological roles in mammals remain to be established.

Where can I find out more?

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Primer

Habits

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What is a habit? One problem with the concept of habit has been that virtually everyone has their own ideas of what is meant by such a term. Whilst not eschewing folk psychology, it is useful to re-examine dictionary definitions of 'habit'. The Oxford Dictionary of English defines habit as "a settled or regular tendency or practice, especially one that is hard to give up" and also "an automatic reaction to a specific situation". The latter, reassuringly, is not too far from what has come to be known as stimulus–response theory.

The stimulus–response habit is a very old concept deriving from Thorndike's Law of Effect as a fundamental mechanism underpinning instrumental or 'purposeful' behavior, by which animals appear to gain mastery over their environment. The fundamental idea is that, through repetition and learning, environmental stimuli come to automatically elicit responses that are initially made spontaneously by the animal, and that this associative learning between stimulus and response is mechanistically bound together by the 'reinforcing' action of the significant consequences of that response, such as food for a hungry animal (Figure 1).

Note that this learning is therefore somewhat distinct from Pavlovian conditioning, in which responses are not spontaneous, but are also automatically elicited by stimuli predictive of reinforcers, including the environmental context. It is also distinct from goal-directed learning, by which animals learn directly that their actions have valuable consequences, and hence have knowledge of instrumental contingencies of specific outcomes and their current motivational values for the animal. The latter is termed goal-directed behavior (or action–outcome learning). Behavioral output overall is presumably usually an optimal combination of these two controlling systems, which are coordinated in certain circumstances, but can be placed into competition in others.

In this Primer, we shall explore how this dual control system for action