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Perspective

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Three systems of circuit formation: assembly, updating and tuning

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Abstract

Understanding the relationship between genotype and neuronal circuit phenotype necessitates an integrated view of genetics, development, plasticity and learning. Challenging the prevailing notion that emphasizes learning and plasticity as primary drivers of circuit assembly, in this Perspective, we delineate a tripartite framework to clarify the respective roles that learning and plasticity might have in this process. In the first part of the framework, which we term System One, neural circuits are established purely through genetically driven algorithms, in which spike timing-dependent plasticity serves no instructive role. We propose that these circuits equip the animal with sufficient skill and knowledge to successfully engage the world. Next, System Two is governed by rare but critical 'single-shot learning' events, which occur in response to survival situations and prompt rapid synaptic reconfiguration. Such events serve as crucial updates to the existing hardwired knowledge base of an organism. Finally, System Three is characterized by a perpetual state of synaptic recalibration, involving continual plasticity for circuit stabilization and fine-tuning. By outlining the definitions and roles of these three core systems, our framework aims to resolve existing ambiguities related to and enrich our understanding of neural circuit formation.

Sections

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Introduction

Advances in machine learning and systems neuroscience have instilled a widespread and prevailing notion that neural activity during prenatal, neonatal and juvenile stages is critical for the accurate development of functional neural networks[1–4]. In this Perspective, we challenge this assumption based on a detailed scrutiny of the current and past literature, which we argue reveals little evidence for this assumption.

To illustrate how we believe circuits are assembled, without the need for instructive activity patterns, it is useful to discuss – in a more general form – how information is represented and stored in a neural network. Words such as 'knowledge', 'competency' and 'skill' are ubiquitously used in the English language, and it is helpful to constrain their meanings in a more mechanistic and operational context. We think of the 'knowledge base' or 'skill set' of a given animal as a layered set of competencies that allow it to (1) classify specific sensory stimuli of any given modality that are relevant for its effective interaction with the world, (2) generate appropriate motor actions or motor sequences that allow for the execution of adaptive behaviours, and (3) act as an appropriate internal 'switchboard' that connects key sensory stimulus patterns with selective motor sequences. The details of these necessary skills differ between species, and within an individual animal, they need to be deployed in a manner that depends on environmental context, internal state and recent history, among other factors. The concerted and dynamic interaction of these layered competencies can be thought of as the sum of all sensorimotor reflex pathways, as well as the modulatory systems that gate, change and redirect them. Together, they represent the 'cognitive skill set' that the animal possesses and that will allow it to solve problems critical to survival throughout its life.

One central challenge in neuroscience is to explain mechanistically how these layered competencies work individually and how they interact as a whole. Therefore, the overarching question is as follows: how does adaptive behaviour emerge as a consequence of the concerted interactions of the underlying neural circuits?

In the past, models of how such circuits are assembled have been delineated into two main phases. The first phase emphasizes predetermined, genetically driven coarse wiring of the nervous system, and it operates largely independent of neural activity, whereas the second phase is characterized by pruning and refinement through interactions with the environment[5–7]. It is understood that this latter process is heavily influenced by external stimuli and is thought to fine-tune mission-critical neural connectivity[8–10].

However, this model is inconsistent with innate behaviours: it presupposes that shaping neuronal connections through experience is necessary to engage the world in an adaptive manner, but we know that many animals exhibit behaviours that require complex and intricate problem-solving skills immediately after birth[1,11]. This begs the question: how can the nervous system function effectively immediately after development if it relies on experience for refinement? A popular answer is that genetic programs and spontaneous neural activity collaboratively shape the composition and organization of neural circuits before birth, wherein both components serve a critical and instructive role during developmental circuit assembly[12,13]. However, whether such activity patterns, and in particular rewiring induced by spike timing-dependent plasticity, are indeed critical for circuit refinement remains a pivotal, unresolved question that has been notoriously difficult to answer experimentally in a rigorous and conclusive fashion[11]. Additionally, experimental findings demonstrating the capacity for genetic encoding of complex neuronal circuits, as exemplified by the *Drosophila melanogaster* visual system[14,15], led us to reevaluate the presumed instructive role of spike timing-dependent mechanisms in circuit development.

Here, we resolve this conflict of nature versus nurture by proposing a framework of circuit formation in which (1) most, if not all, of the critical knowledge and competence that allows an animal to engage the world is already realized by development, (2) the addition of novel information is not strictly required for successful and competent daily operations, and (3) the crucial role of plasticity is limited to homeostatic feedback stabilization. Thus, we find it useful to separate the assembly of circuits into three different systems that are deployed at different times and in different contexts. We term these systems 'Developmental Maturation' (System One), 'Eureka Moments' (System Two) and 'Staying Tuned' (System Three) and outline each in the following sections.

Throughout this Perspective, we (1) dissect the various facets of learning and plasticity in the context of neural circuit formation, (2) elucidate the reasons behind the attachment of the neuroscience community to the importance of associative and operant learning processes, and (3) offer a more integrated framework that separates the relative contributions of developmental, associative learning and tuning-based factors in knowledge acquisition. By bringing clarity to these complex interactions, we hope to advance the field towards a more nuanced understanding of how neural circuits come to be, adapt and function.

System One — Developmental Maturation

Many animals are born with an astonishing set of innate skills and competencies that must be, somehow, hardcoded into the genome[1]. Evidence for such impressive and innate knowledge can be found ubiquitously throughout the animal kingdom, and in the following, we provide several example behaviours across phyla and species.

Spiders follow a meticulous set of algorithms and patterns that allow them to generate their intricate web masterpieces that, in turn, enable them to snare flying insects, their prey. The interlocking sets of necessary sensory–motor processes are clearly based on dedicated neural circuits in the spider brain, which are assembled following specific instructions from the spider genome. It is generally assumed and accepted that learning and plasticity have no role in this process[16].

One of the most impressive skills displayed by newborn vertebrates is the ability of marine iguanas to detect – and escape from – racer snakes, as featured in a well-known David Attenborough documentary[17]. These hatchlings know how to distinguish friends from foes, presumably with the help of sophisticated visual classification filters, they know to freeze when the predator is still distant and not homing in, and they know – when the predator gets too close for comfort – how to run, with astonishing speed and agility, for the safety of the rocks and ocean. The critical element here is that these behaviours manifest within seconds after the baby iguana hatches from the egg and digs itself out of the ground. As such, it is clear that there was no opportunity to practice or learn.

A more disturbing example of an innate and sophisticated behavioural skill is that of a freshly hatched cuckoo bird murdering its step-siblings[18]. The complexity of this behaviour, and its efficient execution, would be even more impressive if it did not come with such horrific contextual associations.

While on the topic of innate knowledge in birds, there are two other examples that deserve to be highlighted. First, there is the ability of migratory birds to identify the direction and path of their long-distance

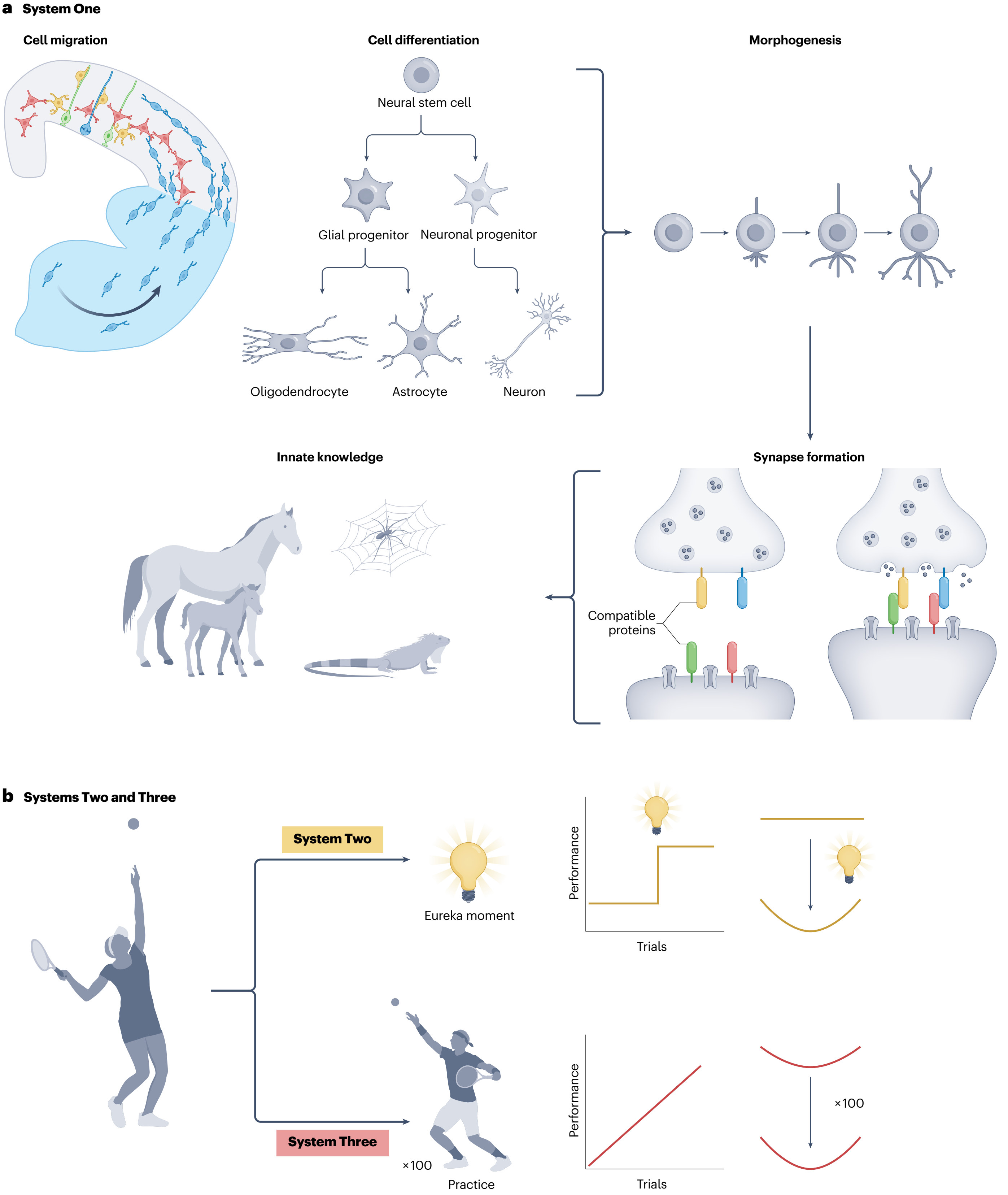
a System One
Cell migration
Cell differentiation
Neural stem cell
Glial progenitor
Neuronal progenitor
Oligodendrocyte
Astrocyte
Neuron
Morphogenesis
Innate knowledge
Synapse formation
Compatible proteins
b Systems Two and Three
System Two
Eureka moment
System Three
×100
Practice
Performance
Trials
Performance
Trials
×100

Fig. 1 | The three systems. a, In System One, the complexity and precision of brain wiring, and its resultant innate knowledge base (bottom left), emerges from sequential neurodevelopment steps. First, migration and differentiation programs define a diversity of cell types (top left). Then, the inherent genetic programs of neuronal cell types determine the morphogenetic program of a cell (top right), thereby establishing a pool of local cell partners. Finally, neurons make decisions on their synaptic partners through surface membrane protein compatibility programs (bottom right). **b**, In System Two, observing a novel event, such as a tennis serve, can lead to a eureka moment (left), leading to a rapid, step-like increase in performance following the observation (centre), probably coincident with the generation of a new dynamic or structural attractor state (right). Alternatively, System Three can take over during the practice of the tennis swing (left), which coincides with a gradual, ramp-like increase in performance with trials (centre), leading to a deepening of available dynamical and structural attractor networks (right). The migration image in part **a** is adapted from ref. 96, Springer Nature Limited.

journeys to better climates, which is truly impressive and the topic of extensive research in various disciplines[19,20]. Second, the ability of many bird species to build nests with structures that can be of almost arbitrary complexity and sophistication never fails to astonish. A particularly fascinating example is that of male bowerbirds, which are known for building elaborate 'palaces' that are ornamented with colourful decorations of various sorts to attract females in a harsh competition of sexual selection[17].

Finally, we would like to draw the attention of the reader to the ability of a newborn horse, which, after a brief period of calibration and tuning, knows how to run, how to find food, how to escape predation and how to respond to the calls of its mother[21]. These are all critical skills that are both necessary and sufficient to survive in a harsh and antagonist world and that are most probably hardwired into the genome because there is very little opportunity for practicing such complex skills within the womb.

These examples should illustrate that there is a vast and extensive amount of innate and genetically encoded knowledge present in many, if not all, animals.

From genes to knowledge

This innate knowledge is stored in the neural circuits that enable the animal to solve all survival-critical problems. As such, we need to discuss how genetic information is deployed to assemble these circuits during embryonic development (Fig. 1a). We find it useful to separate this process of assembly into roughly three stages. In the first stage, neuronal precursor cells differentiate into their final phenotype and migrate into the correct position[22–25]. In the second stage, neurons send axon growth cones across the brain, wherein they navigate sophisticated morphogenetic gradients to connect with appropriate target regions[26,27]. In stage three, these growth cones make decisions on which subclass of postsynaptic targets to contact, and this process is governed by a range of close-contact ligand–receptor pathways and adhesion molecules (such as protocadherins)[28–30].

Although it may seem like these assembly processes are insufficient to define the complexity and precision of brain wiring, a critical insight here lies in the realization that development does not use 'explicit addressing', in which genes stand for 'which neuron to connect to'. Rather, neural circuits assemble algorithmically, with genes providing a list of instructions that control all of these three stages of development[1,31–33]. For instance, cell types can be seen as stable states in transcription factor regulatory dynamics[22]. This indicates that gene regulatory networks can precisely code a broad spectrum of cell identities, which then generate local morphogenetic gradients and equip individual cell types with the ability to uniquely navigate these gradients. This, in turn, defines the arborage and projection patterns of a neuron[34,35]. As such, morphogenesis can be seen as responding to chemical cues and contact-based neurite interactions to achieve the correct sequence and frequency of neurite branching[36,37]. Similarly, synaptic specificity emerges from cell–cell recognition events driven by physical interactions between surface protein repertoires of neurons[38,39]. In this process, neural activity[4,40,41], especially activity that emerges spontaneously during early stages of development[3,42], can have a role in these cell-to-cell signalling mechanisms, and thus might modulate the formation of some circuits in some species. Such activity-dependent signalling mechanisms, which include subthreshold voltage fluctuations and the spontaneous release of vesicles, probably impact circuit assembly in many contexts[43,44] and contribute to the specification programs of the neurons involved.

Although these principles have been established for roughly a century, how the exact mechanisms play out across all three stages in detail and how they lead, eventually, to the intricate complexity and heterogeneity of the mature brain remain one of the most exciting frontiers in neurodevelopment[45].

Taken together, we observe that neurodevelopment contains sufficient complexity and precision to fully define the genetic and connectomic identity of a neuron and, thus, by extension, any and all neural circuits. Truly, even the human brain could be hardcoded in this fashion[1,46]. Although surprising at face value, this statement would barely be contentious for any other organ in the body; thus, why do we find it so hard to believe for the brain? Indeed, the ability of these processes to generate a network structure that equips an animal with what we can call knowledge, competency or skill is as much of a survival necessity as developing a functional heart.

Innate and hardwired does not mean inflexible and stereotypical

It is important to note that even if circuits and behaviours are 'innate' or 'hardwired', it does not necessarily imply that they are inflexible and stereotypical. The dynamic flexibility with which many, if not all, hardwired networks can respond fluidly to perturbations and settle into a new stable minimum does not necessarily require any synaptic or neuronal plasticity, but it can rely exclusively on negative feedback-dependent error minimization[47].

Consider how any autonomous vehicle, be it a self-driving car or an aeroplane on autopilot, can self-stabilize when faced with perturbations in the feedback from the environment[48]. The networks that control such systems can be trained by unsupervised or supervised reinforcement learning algorithms, and this might give the impression that synaptic plasticity is critical for this process. However, the learning in such systems happens generally before the agent is deployed, and it serves just for the initial assembly of the circuits. Such a pre-deployment tuning process is analogous to the iterative adjustment of biological neural networks that occurs over evolutionary time periods and that ensures that once the agent is deployed to interact with the world, the circuits with all their optimized connections are already fully operational.

Similarly, the rapid stabilization of *Drosophila* flight patterns in the face of critical perturbations such as wind gusts or notches in the wing does not require synaptic plasticity in the network that controls and stabilizes flight[49]. Rather, the resulting mismatch errors of these perturbations are fed back directly into the motor control circuits for immediate correction and error minimization, very much in the same way that a feedback system in engineering or electronics does not require a change in gain or set point.

Desert ants that will navigate back to the nest after foraging for food for extended time periods in featureless environments have been shown to use path integration, dead reckoning and counting steps to accomplish this feat[50]. A realistic circuit model that explains how this may be implemented does not require any form of learning or synaptic plasticity. The integration and all other critical computations are executed through various ring-attractor and line-attractor networks that acquire their long time constants simply based on the intrinsic properties of the recurrent networks[51,52]. None of the synaptic connections in this implementation need to be updated or changed, so no plasticity is required in any form.

Very similar principles are at play when our hatchling iguanas run over uneven terrain, a process that requires constant correction and stabilization and that would be impossible to jibe with a purely feedforward control system[17,50]. Again, the feedback errors that are probably deployed here do not require any synaptic plasticity to engage appropriately adjusted motor commands.

In humans, the immediate and effortless adjustment of grasp strength when picking up objects of unknown weight is governed by feedback control systems located in the spinal cord and brainstem that can operate largely independently of synaptic plasticity[53]. This phenomenon is of course not restricted to humans but extends to all animals that need to pick up potentially fragile objects of various sizes and weights with their hands, feet or jaws. An illustrative example of this process is that of a lioness gently picking up her cubs by the scruff of the neck and carrying them to safety.

Finally, we point out that many – if not all – innate behaviours will only get released in the appropriate context and certainly do not all present spontaneously. There are countless examples wherein very specific 'releasing stimuli' are required, such as pup calls that trigger retrieval behaviour in female mice[54], or the presentation of an erratically moving target, such as the spot of a laser pointer as wielded by a playful human, which triggers hunting behaviour in a young and inexperienced kitten that has not seen such a stimulus before.

Often the procession through specific postnatal developmental stages is necessary before such trigger stimuli can become potent releasers of specific behavioural programs[55]. For example, many mammals, including humans, will start displaying stereotypical mating behaviour[56] only once the releasing stimuli become salient after the onset of puberty.

Crucially, the core structures and connections that are established during development not only support all these behaviours apparent at birth but also provide the backbone of neural circuits capable of learning, as we detail in the next two sections.

System Two — Eureka Moments

To survive and reproduce, most, if not all, animals need to go beyond the execution of hardcoded innate motor programs that turn a releasing stimulus into a fixed action behaviour. In many cases, it is necessary to flexibly adjust and adapt the behaviour to changing environmental contexts, which often are impossible to predict or anticipate. This need is served by the fact that brains are plastic and that they can learn. It is generally assumed that a lot of the knowledge, skill sets and competencies that an individual species possess is based on this ability of the nervous system to integrate novel information through associative or operant learning processes (Fig. 1b). We define this remarkable feature of biological neural networks as System Two, and below, we provide a series of examples that serve to illustrate this phenomenon.

Drosophila larvae adapt their behavioural repertoire in response to environmental cues to navigate complex environments. This learning capability is apparent in their response to innately aversive carbon dioxide (CO_2), which, when paired with a reward signal, can become an appetitive stimulus. Interestingly, in such experiments, the effect of associative conditioning on the learning of an individual larva is switch-like: the associative memory does not form gradually through repeated training but is instead learned in an all-or-none manner. This means that larvae that have undergone training but have not yet shown a behavioural shift behaved in a manner similar to those that had not been trained at all[57].

Honeybees, which are equipped with the innate skill to classify flowers on the basis of shape and colour, are known for their ability to effortlessly and quickly learn to assign value to specific combinations of colour, taste and smell. In fact, the capacity of flowers to generate specific colours, shapes and chemical attractants has clearly co-evolved with this remarkable power of their pollinators to form value-based associations between the specific colours and smells of the leaves and the reward that is hidden beneath the petals[58]. Bees are master learners when it comes to forming associations between different multimodal stimuli, and their System Two must be adapted to these critical needs.

In laboratory mice, a striking example of System Two at play is their capacity to hunt live prey. If the only food source available are live crickets or beetles, hungry mice will learn within a few trials to become expert hunters[59]. Interestingly, the first trial can last up to several hours, during which the mouse extensively explores the behavioural space. However, a single successful hunting event can induce an instantaneous transition in knowledge, whereby subsequent trials take only a few seconds to complete. Clearly this is an example of fast, single-trial learning, in which a critical piece of information, namely, that crickets are good to eat, gets updated into the knowledge base of the animal.

An example that illustrates this point in primates is the anecdotal story of a low-ranking female capuchin that learned how to clean the dirt off a sweet potato by dipping it into water rather than scrubbing the earth off with her hands[60]. The updated knowledge of this efficient cleaning process then spread rapidly through the entire colony, another example of how animals can imply their System Two to quickly learn critical skills, in this case by imitation. An informative detail about this particular intra-species transfer of knowledge was that it occurred only horizontally through the monkey hierarchy: it took high-ranking alpha males many weeks to learn the new trick, whereas similarly low-ranking females picked it up on the day of the original 'eureka moment'.

In mammals, the cortex and hippocampus have probably evolved to implement System Two. These structures allow sophisticated learning, which in turn allows many layers of abstraction and generalization[61]. The circuit structure of these regions and the mechanisms by which such learning events are implemented are subject to many studies in which great leaps of progress have been made in recent decades[62]. The theory is that knowledge updates are implemented by modifying the connections between a pre-established 'sensory motif' and a pre-established 'motor motif' or by changing the weights of the connectivity patterns between different sensory representations[63]. We argue that these motifs are innate and part of the hardcoded knowledge base because changing them, in either the sensory or the motor domain, is very difficult. For example, it is easy for a mouse to learn to associate the object class of 'cricket' with the motor skill of 'chasing and biting', whereas it would be very difficult to teach a mouse the motor skill of riding a unicycle. On the sensory side, it is very difficult to teach a human to echolocate or to follow an odour trail that is left behind by a fugitive criminal[64,65].

As we are on the topic of humans and System Two, our species is certainly an outlier on the spectrum of all animals that need to leverage their ability to learn new things to survive and reproduce. Most, if not all, episodic and semantic memories in humans are encoded and transferred through language, which is unique to the human condition. As such, almost everything we consider knowledge is semantic and language-based and relies exclusively on System Two.

For example, humans can effortlessly recognize and classify tens of thousands of objects that did not exist a few hundred years ago and that, therefore, cannot be part of an innate knowledge base. This skill is probably related to our supercharged ability to form language-based associations, and it is doubtful that other animals will have comparable experiences about the richness of the world when contemplating their environments. We think that this unique ability in *Homo sapiens* has led to a widespread insistence that learning through System Two is critical also for all other species. We refer the reader to the 'Perspectives' for a more detailed treatment of this topic.

In conclusion, we propose that System Two learning events occur rapidly within just one or very few trials and that they have the flavour of eureka moments, in which the 'penny suddenly drops'. In an experimental context, this would manifest as a sudden step in the learning curve, rather than an incremental and stochastic ramp.

We further argue that these critical updates happen rarely (sometimes never) in most species. Specifically, we propose that these events serve to update the innate knowledge base and equip the animal with the ability to solve a newly emergent, critical problem that is not readily covered by the innate and hardwired set of competencies and skills. The example of a naive human learning to serve in tennis, as discussed in the next section, serves to illustrate this point: the initial understanding of the problem and the first execution can be viewed as a eureka moment that occurs extremely quickly, but the appropriate tuning and calibration can then take a lifetime. Learning how to ride a bicycle, play the piano, or learn a language all can be separated similarly into an initially instantaneous understanding of the problem, followed by extensive tuning and calibration.

We recognize that the cortex and hippocampus, which are thought to implement System Two, emerged relatively recently in evolution and that these brain areas were then deployed to facilitate and accelerate the process of quickly associating contextual cues with each other, and implementing them into long-term memory. Hippocampal place cells that can update their firing properties rapidly with changes in context are a good example of a possible concrete implementation[66].

Here, we argue that, as impressive as such 'System Two knowledge-updating' abilities may be, they are probably irrelevant for a mouse – or any other animal for that matter – as it goes about its daily business of escaping predation, finding food, competing with conspecifics, initiating reproduction or raising the young. None of these critical skills probably require any of these associative learning events.

In the next section, we discuss how the problem of executing difficult sensorimotor transformations smoothly in an ever-changing environment can be facilitated via a different system implementing what we think is a distinctly different form of activity-dependent plasticity.

System Three — Staying Tuned

The processes underlying all sensorimotor knowledge, including all behavioural policies that allow us to solve critical problems and switch between behavioural strategies, require constant tuning and calibration (Fig. 1b). Once an animal is born, or hatches, it must engage the world, wherein it will receive constant feedback during and after the execution of motor programs. Specifically, environmental streams of mismatch or error signals will allow it to recalibrate sensory motor gains to ensure smooth operation. In the following section, we provide various examples of animals that use innate knowledge to adaptively interact with the environment and to solve survival critical problems. We further explain how this process requires constant tuning and calibration to ensure stable and efficient execution of all motor sequences.

System Three is in place across practically all phyla, and it needs to kick into operation the moment the animal starts to engage the world. One example that illustrates this point is that of the larval zebrafish, which leverage System Three as early as 7 days after fertilization. Young fish need to stabilize their position in moving currents to avoid getting swept down the river. To solve this problem, they engage in the optomotor response, a robust and innate behaviour in which the direction and strength of whole-field visual motion is computed and the information is used to execute appropriate swim behaviours that minimize retinal slip[67,68]. If the feedback between swim vigour and resulting reduction in backward visual motion is perturbed, then fish will rapidly adjust their swim strength to compensate for and reduce the unexpected increase in the feedback signal. This allows them to adjust the gain of their swim vigour if they encounter environmental impediments such as increased water viscosity and bodily encumberments such as notched or broken fins, or if they simply gain weight or experience changes in body shape that modulate their hydrodynamic properties. The critical point here is that baby fish also can, and need to, use their System Three to adjust internal sensory motor gains if feedback error signals exceed the recommended operating range.

Probably the most famous example of gradual re-tuning of a sensory system after a critical perturbation is the plasticity in ocular dominance that is readily observed when one eye is closed for an extensive period in a newborn monkey[69] or kitten[70]. Here, the visual system will re-tune itself to maximize efficiency in the active channel, such that smooth and efficient operation of the pathway stays in place.

A similar phenomenon can be observed in the barn owl when the visual system is mis-calibrated by the permanent placement of prismatic goggles on the beak of juvenile birds. This perturbation leads to a remarkable re-tuning of the auditory pathways, which can serve as a clear and well-understood example of System Three in play. A particularly impressive feature of this story is that here the neural circuit implementation is understood at a level and to a degree that is rare in other organisms (Box 1).

System Three is also impressively at play in a newborn horse right after it emerges from the mother and engages the world for the first time. The foal clearly knows how to run and walk in principle, as one can deduce from its first bumbling attempts at standing up, walking and searching for the food source. Remarkably, it will take the foal only a couple of hours to turn the initial clumsy steps into smooth walking, running and jumping. This process illustrates how the existing motor

Box 1 | System Three in barn owl fixations

To properly illustrate System Three in action, here, we discuss an example in which the auditory and visual pathways are aligned and matched within the avian tectal circuitry. Barn owls know how to turn their heads quickly and accurately to fixate on a sound-emitting object of interest, say, a squeaking mouse, and they can do this even in complete darkness[97]. To that end, they leverage their innate and hardwired ability to use interaural time differences, that is, the delay of soundwave arrivals between the left and the right ear, and they can use this information to accurately triangulate the location of the sound source. Once the 'squeak-induced' ballistic head rotation comes to rest, the visual system of the owl comes into play. The circuitry within its optic tectum will engage and classify objects of appropriate valence. In this case, there is dedicated and hardwired circuitry in place that responds preferentially to the image of a mouse. Critically, if the sound-dependent head-orienting reflex works well, then the position of the image comes to rest close to the centre of the retina, wherein dedicated ganglion cells encode it with appropriately configured receptive fields. If a separate set of ganglion cells fire at the end of the head rotation, namely, cells that code for a stimulus that sits at a lateral offset, then this constitutes an error or mismatch signal that informs the owl that the head rotation was insufficient. It could have over-rotated and the image is displaced to one side, or it under-rotated and the image is displaced to the other. Either way, the amount of 'angular offset' from the centre serves as an accurate error signal that informs the owl about how much the current movement was 'off' and by how much the next movement needs to be adjusted to land on target. This automated and instantaneous correction of a slightly faulty reflex motion is the core and hallmark of System Three. The error signal, in this case, the firing rate of the 'off-target' sensitive ganglion cells, serves as an instructive 'teaching' signal that is probably relayed through climbing fibres into cerebellar Purkinje neurons, which then adjust the sensorimotor gain controlled at the parallel fibre to Purkinje synapses, by exactly the correct amount[98]. This — usually small — mismatch between predicted and actual outcome of sound-induced head rotation in an owl can be artificially enhanced by putting optical prisms on the head of a juvenile barn owl and, thereby, shifting the whole visual world of the bird by, say, 20°. Now, if the owl turns its head for the first time in response to a directional sound cue, a significant mismatch, or error signal between the visual and auditory cues, is introduced: the visual object will not come to rest in the centre of the retina once head movement is complete, but it will be offset by about 20°. Under such conditions, the owl will learn quickly, within a few seconds, to adjust the amount of its head rotation[99]. It takes just a few trials to learn the new head angle that allows visual fixation of the target. This process harnesses the extensively studied cerebellar system that all vertebrates use for rapid motor learning and feedback gain. The same process is at play during the vestibular ocular reflex in most vertebrates, including humans. The only difference here is that the prediction about how much visual displacement will take place originates not from an acoustic signal but from vestibular output that measures rotational head acceleration directly.

In fact, if you take the prisms from the owl and put them on a human subject, you will find that they adjust their vestibular ocular reflex with the same speed and accuracy as barn owls will do for their sound-evoked head saccades[100]. A more direct example that illustrates how System Three incrementally adjusts sensorimotor feedback gain can be tested in person: procure 20° prism goggles and put them on, ask someone to hold a pencil out in front of you, and then try to reach out and touch the pencil with your index finger. You will find that your first attempt misses the target by about 20°, but subsequent attempts rapidly converge on the correct pointing action. This process emulates what is described in the barn owl experiments above. However, what makes the owls much more extraordinary and impressive compared to their human counterparts is that their fine-tuned auditory system, which allows them to identify and hunt potential prey in complete darkness, will adjust to rematch the auditory tuning to the prism-induced visual shift over the course of several weeks. This remarkable and well-studied plasticity requires incremental updating of synapses in the tectum of the bird and allows precise calibration of this essential orienting behaviour[101–103]. All three examples, sound-triggered head saccades in owls, the vestibulo-ocular reflex in all vertebrates, and the reaching-for-target in humans, are excellent examples of System Three at play, and they illustrate how specific feedback error signals can be used to accurately adjust feedback gain and ensure smooth and flexible operations.

control machinery can be quickly calibrated and tuned, using the ubiquitous feedback gain mechanisms of System Three.

Finally, let us consider a human learning to do a tennis serve. The initial part of getting the idea across to the subject is usually very quick and just requires a demonstration by an expert. This initial process of acquiring the skill and executing the first clumsy but representative motor sequence is implemented by the mechanisms we have summarized under single-shot learning in System Two. However, after this quick and effortless acquisition of the basic behaviour, the player needs to practice diligently for hundreds, if not thousands, of hours to fine-tune and hone that skill. We argue that all the elements of the latter part fall squarely into the category of System Three, which is ubiquitous in all animals.

We propose that System Three is active in all brain areas, including the periphery, the autonomic and the enteric nervous system, and that it is active all the time and in all animals. We also point out that the periphery, be it sensory or motor, is probably the exclusive domain of System Three, and that the engagement of System Two is restricted to central brain areas that coordinate between sensation and motor output.

It is important to note that the tuning and stabilization processes implemented by System Three are a critical feature not just of animals with a nervous system but of all living systems. In contrast to engineered systems, biological networks need to constantly update their weights to cope with environmental noise and biological drift. Every cell in the body needs to stabilize critical variables such as organelle size, ionic concentrations of internal and external milieu, and countless other parameters. Therefore, the ability to stabilize the physiology and behaviour against the drift into unstable regiments is a universal and ubiquitous feature in biology, and System Three, as defined here within the boundaries of the nervous system, is just one of many manifestations.

In summary, most of these incremental plastic changes that modulate the gain and transduction efficacy in neural networks, as described in the examples above, serve to continuously stabilize the operation of a behaviour in the face of changes and drift in environmental conditions. This is an absolutely critical and fundamental feature without which any biological system would quickly drift into unstable domains, and many forms of non-declarative memory, such as habituation, desensitization, and many aspects of adaptive procedural learning, can thus be placed into the category of System Three.

We suggest that most, if not all, standard learning assays currently used to study neural plasticity in rodents and non-human primates in the laboratory serve to elucidate and investigate mechanisms that are related to System Three. Because the specific behaviours under these conditions are mostly generated by incremental shaping of specific motor patterns, the quick and rare updating that is the hallmark of System Two rarely makes an appearance.

At best, quick associative learning events might occur when a mouse realizes that a lever is important and carries associative valence, but such events are most certainly lost in the noise of the behavioural data if the number of required trials to reach significant performance number in the thousands. In other words, whether the learning occurs incrementally and the learning curves look like ramps (System Three) or whether learning occurs in a stepwise fashion (System Two) is often hard to distinguish because everything looks like a ramp if many trials across many animals are averaged[57].

Perspectives

Neural implementation – the role of plasticity in all three systems

How these three systems are implemented by biological hardware is one of the most pressing and exciting questions in modern neuroscience. In the following section, we try to summarize how concrete and existing neural plasticity rules can explain how neural circuits get assembled, updated and tuned.

With respect to System One, such plasticity rules are reduced to the set of signalling pathways and developmental processes that govern the initial assembly of neural circuits during development. This initial assembly, as described above, will follow roughly three stages, which maintain their own extensive research field. In the first stage, neurons need to differentiate into their specific cell type and migrate into their final location[22]. During the second stage, cells send out axons and dendrites which will migrate and project, led by growth cones that serve as the critical sentinels, into their ultimate target regions[26,71]. Finally, presynaptic axon terminals and postsynaptic dendrites need to find and recognize each other to form the specific connectivity patterns[28] from which the fully assembled network draws its computational power.

A particularly impressive feature of these developmental processes is their robustness to perturbation, rather than their precision in execution. The ability for self-correction in the face of perturbations is important because errors can occur at several levels during neural circuit development and need to be corrected to avoid drifting into unstable regimes. Especially during the differentiation of class-specific morphologies and circuits, mistakes in wiring frequently need to be detected and corrected. This process is evident in aspects such as neurite targeting and the positioning of axons and dendrites, for example, in the developing ventral nerve cord of *Drosophila*. Here, systematic errors in the appropriate targeting of axons and dendrites can be introduced by relocating presynaptic elements to abnormal positions[30]. Nonetheless, dendritic postsynaptic partners are still able to locate and establish appropriate connections, even if neural activity was silenced throughout. Also in *Drosophila*, but this time in the mushroom body in the CNS, genetically altering the number of the principal neurons of the circuits, named Kenyon cells, shows that presynaptic axonal processes remain adaptable whereas postsynaptic dendrites remain stable, ensuring the correct levels of contacts and synapses required to general functional circuits for accurate odour discrimination[72]. These examples illustrate that the ability to detect error – or mismatch – signals and feed them back into generative mechanisms in a corrective fashion is ubiquitous throughout the developing nervous system and can occur in the absence of any spiking activity.

The role of synaptic plasticity with respect to the implementation of System Two can be found in practically all neuroscience textbooks[73], wherein spike timing-dependent plasticity is elegantly linked to various forms of associative Hebbian learning. Maybe the most famous example of how synchronous presentation of a conditioned stimulus with an unconditioned stimulus can lead to the implementation of new knowledge is that of Pavlov's dog that learned an entirely new meaning about the sound of a bell. The fundamental insight, popularized largely by Donald Hebb, is that the synchronous activity of the auditory neurons that represent the sound of the bell on the one hand and the olfactory neurons that encode the smell of the food and unconditionally trigger the flow of saliva on the other hand leads to a selective and spike timing-dependent enhancement of the synapses that connect the auditory with the drool-inducing neurons[73].

In System Three, neural plasticity is always at play, it serves to stabilize function, and it minimizes feedback errors. In this context, it is useful to think of the circuit as a control system that relies heavily on feedback gain, specific set points, and dynamically changing input parameters.

The core properties of this system are probably 'baked in by evolution', and the role of plasticity is to continuously adjust the weights and to minimize feedback errors. Often, these set points are moved to different values in the face of gradual or sudden changes in feedback gain. These updates in set point values can be implemented at the neuronal level in various ways. One way of achieving such temporal stability in neural networks is by leveraging the local attractor structures that are already present in the circuits assembled through System One, which are equivalent to a minimum in the 'energy landscape' of network activity. In such a case, plasticity can serve to 'deepen the well' of the attractor and accelerate the movement back to the local minimum in the face of perturbations.

The plasticity rules that are at play in System Three are distinctly different from the classic spike timing-dependent plasticity mechanisms that are extensively studied in the context of associative learning in the hippocampus and cortex. There, a single-shot learning event would be described by the synaptic weight structure settling into a new attractor state, or a new minimum in the energy landscape. This is greatly facilitated if the network is pre-configured by evolution to already present a set of such attractor states that are readily found by a directed perturbation.

By contrast, System Three probably uses plasticity rules that are 'anti-Hebbian' in nature and that are at play in cerebellar plasticity wherein the complex spikes in climbing fibres serve as 'errors' or 'teaching signals' that minimize mismatch generated in the parallel fibres that connect granule cells with Purkinje cells[74]. However, such incremental and gradual updating of synaptic weights is probably not restricted to cerebellar circuitry within a motor adaptation framework and can be found across neural contexts, such as homeostatic plasticity, non-associative learning (habituation, sensitization and so on), cortical mismatch calculations[75], and the stabilization and (re-)tuning of receptive fields across all sensory modalities. Furthermore, mismatch signals that are used for gain control in motor sequence generation have been described in primary auditory centres in the song bird[76] and in the visual cortex of mice[77]. Beyond these well-studied organisms and assays, we believe that such feedback control loops are prevalent in all circuits and all animals because every living organism is exposed to biological drift and noise that must be controlled in some format for many critical metabolic processes.

The widespread prevalence of System Three, many parts of which are already put into place during prenatal development, makes the young and developing nervous system sensitive to perturbations. As such, many experiments that aimed to investigate the role of spike timing-dependent activity in the formation of circuit assembly[78,79], and that rely usually on a wide set of different perturbations to test for causal relationships[80,81], might inadvertently discover critical and substantial phenomena that do help to understand how proper development can be hampered and compromised by aberrant neural activity. However, many, if not all, of these effects and phenotypes might very well be related to System Three engaged at recalibrating and re-tuning the network to find a new stable set point. As we have previously argued[11], this Perspective aligns with a substantial body of research involving developmental perturbations – such as eye suturing, prismatic goggles, sensory deprivation, and genetic silencing of neural activity – that indicate that neuronal activity has a crucial role in brain development. Importantly, these studies often focus on localized (rather than global) disruptions of plasticity and introduce competitive imbalances between different sensory modalities or mixed input channels. For example, in the monocular deprivation experiments of Hubel and Wiesel, suturing one eye closed led to the open eye dominating the visual cortex[70,82], but when both eyes were sutured shut before eye opening, the visual cortex remained largely normal[83], a result reproduced in monkeys[69]. Even the remaining aberrations of visual cortex neurons can be explained by the fact that perturbed visual inputs are outcompeted by other, non-visual modalities, such as motor-related or auditory signals, which have been demonstrated to contribute to primary visual cortex processing[75,84]. Similarly, visual pathways can innervate the auditory cortex in ferrets when normal thalamic inputs are surgically removed[84,85], and in mice, blocking a single olfactory receptor causes significant synaptic rearrangements, whereas blocking all receptors results in minimal circuitry changes[86].

However, in studies in which all spiking activity, including action potentials in innervating axons, was suppressed across the cortex, precise targeting of neuronal projections still occurred[87,88]. These findings suggest that although spiking activity may be necessary in certain contexts, discerning whether its role in neural circuit formation is instructive or merely permissive remains challenging[89].

Unlocking innate behaviours: the onset of System Three

The exact time point in which an animal is born or hatches from an egg is somewhat arbitrary, depending largely on evolutionary constraints, such as the safety of the environment at the moment of birth or the need for mobility in the mother. Here, we choose the moment of birth (or hatching) as the time point for the completion of System One and the transition to System Three. Iguanas, ducks and horses, as discussed above, are almost immediately ready to fully engage the world after birth, which implies that most developmental programs have been completed. However, in many other animals, such as eagles, mice and apes, this transition happens much later, which we would interpret as a continuation of brain development (that is, System One) after birth. In such cases, animals are simply born 'too early', System One is not completed, and the animal is not ready to engage the world.

Another example that illustrates the point of 'premature' birth is the incompetence of human babies, who need to get pushed 'prematurely' through the birth canal before the head gets too big and who have only four crucial motor policies in place at birth: screaming, sucking, sleeping and pooping. Most other circuits are still in the process of developing and will come online progressively during the first years (such as speaking, grasping and walking).

We note that the capacity for feedback-dependent gain control needs to be put in place already prenatally, as System Three needs to be ready to be deployed once the animal is born. Think of the newborn horse or the freshly hatched iguana, which both need a fully operational System Three in place to function appropriately. The hypothesis put forth here is that these System Three mechanisms are merely 'idling' during the late stage of System One (final assembly before birth) without serving any necessary role in circuit formation. In fact, as System Three must already be in place and ready to engage prenatally, it stands to reason that, as discussed above, early perturbation and deprivation experiments, such as silencing of regional spontaneous activity, monocular eye closure in kittens, or sensory isolation of juvenile zebra finches, can already have pronounced effects.

Even postnatally, System Three will be idling for a considerable fraction of the time. Whenever the animal is not engaged in a particular task and does not generate specific predictions nor receive corresponding error or mismatch signals, then activity is not instructive, and little plasticity will occur. This implies that a lot of 'spontaneous' or 'ongoing' activity that is recorded in essentially all neurophysiological experiments in all animals can be assigned to such idling of a critical neuronal process that is currently not engaged in solving any particular task or problem.

Addressing the widespread belief that activity-dependent plasticity is critical for circuit assembly

Finally, we would like to discuss the widely accepted notion that patterned activity has a necessary and instructive role in shaping neural circuits. We think that this is probably owing to several factors, which are discussed below.

Postnatal development and maturation. The delayed development observed especially in human babies, when compared with other species, offers a reason for the prevailing emphasis on learning and plasticity. As human infants go through extensive periods of maturation post-birth, the assumption is that most of their neural circuitry is shaped by learning and plasticity. An alternative view is that humans are simply born too early and that the genetically determined developmental programs continue to unfold after birth. For example, many aspects of an emergent skill, such as the ability of a human baby to walk or delicately pick up small food items and guide them to the mouth for consumption, are thought to necessitate System Two. Here, we question this premise and propose instead that many aspects of these behavioural refinements can be explained by a developmental restructuring of the neural circuits. This hypothesis generates concrete predictions for experiments whereby the animal is prevented from engaging in any extended and extensive training sessions, and then testing whether the skills, such as walking, grasping or running, will spontaneously emerge given the right context and the right set of releasing trigger stimuli. Preliminary confirmation of this hypothesis can be found in human newborn babies, in whom it has been shown that if you raise their body upright, while holding most of their weight, and then gently push them forward, they will start 'walking', a test commonly done to babies days after they are born[90]. A distinctly more informative experiment would be to reversibly silence all activity in all neurons in a developing mouse embryo, then relieve the block at birth, and check whether appropriate behaviour is displayed by the newborn pups. Such an experiment is in principle already within reach, as a universal activity block through the elimination of neurotransmitter release from synaptic vesicles has already been implemented in prenatal mice[91], with the only caveat that the approach taken to achieve this (Munc18-1 silencing) was not implemented in a reversible fashion. In the meantime, we invite the still-skeptical reader to consider and observe the rapid acquisition of walking and running skills in a newborn horse.

Human subjective experience. There is a deeply ingrained belief, shaped by our subjective experience, that all human knowledge is learned over the course of our lifetimes. However, this anthropocentric lens may not fully capture the fact that most of our knowledge has to do with controlling and operating our bodies in an efficient and economical fashion and that our cognitive, semantic and episodic knowledge base is dwarfed by the underlying operating system that needs to solve the problems of day-to-day operations (see Moravec's paradox below).

Human language and semantics. The ability of humans to express complex thoughts through language adds another layer to the puzzle. Unlike other animals, which primarily rely on non-verbal behaviour to communicate, humans have the capacity for semantic language. This can lead to the projection of our complex language faculties on other species, thereby reinforcing the belief that learning and plasticity are universally critical to neural circuit formation.

Machine learning success. The success of artificial intelligence, particularly in its ability to surpass human experts at complex games such as chess and Go[92], has reinforced the idea that learning from experience alone can lead to sophisticated behaviour in models with minimal initial structure. Given that these models abstract the biological phenomenon of experience-dependent rewiring of neuronal circuits, machine learning successes have contributed to a common belief that neural circuits in biological organisms are similarly predominantly shaped by activity-dependent plasticity and learning[1]. However, this interpretation overlooks the significant role of innate structures and evolutionary adaptations in shaping neural circuits. This discrepancy between knowledge representation in humans versus non-human animals is nicely illustrated and highlighted by Hans Moravec who formulated this in his well-known paradox: "Encoded in the large, highly evolved sensory and motor portions of the human brain is a billion years of experience about the nature of the world and how to survive in it. The deliberate process we call reasoning is, I believe, the thinnest veneer of human thought, effective only because it is supported by this much older and much more powerful, though usually unconscious, sensorimotor knowledge. We are all prodigious olympians in perceptual and motor areas, so good that we make the difficult look easy. Abstract thought, though, is a new trick, perhaps less than 100 thousand years old. We have not yet mastered it. It is not all that intrinsically difficult; it just seems so when we do it"[93].

Conclusions

In this Perspective, we proposed that the assembly of neural circuits is governed by a tripartite framework of algorithms and rules.

System One: Developmental Maturation

We suggest that the first phase of circuit assembly occurs exclusively based on genetic information and unfolds entirely under transcriptional control. Spike timing-dependent plasticity is neither necessary nor instructive. Nonetheless, we think that such a network, once fully assembled, is capable of supporting all critical behaviours that are necessary for the survival and reproduction of an animal. Generally, System One (Fig. 1a) dominates during prenatal development and, in many animals, is concluded at birth. After birth, the animal is ready to engage the world and, through a series of subsequent maturation events, becomes fully equipped to solve all the important problems that are critical for survival and reproduction, including feeding, fleeing, fighting and mating. We define the combined set of all of these innate skills as the knowledge base with which the animal is born.

System Two: Eureka Moments

We fully acknowledge that all animals have the capacity to update their innate knowledge base by means of classical or operant conditioning, thereby adding new information and critical behavioural policies into their repertoire (Fig. 1b). These processes are described in the context of basically everything that comes up in the context of learning and memory. Examples include episodic, semantic and almost all forms of associative memories. However, we argue that the necessary updates to neural networks required to include these novel memories happen very rarely, and when they happen, they happen quickly, as in the form of one-shot learning. Moreover, we think that such updates occur only when the events that cause them are critical elements of the 'Umwelt' of an animal, that is, when they provide an adaptive context that is relevant to the survival of the animal.

System Three: Staying Tuned

All biological neural networks and circuits require constant plasticity for calibration, stabilization and tuning. The need for homeostatic plasticity and stabilization of set point values is not just a basic feature of neural networks and synapses but also critical for all of biology wherein most parameters and values need to be stabilized to avoid drift into unstable regiments. We propose that there is always a synaptic plasticity-dependent process at play that serves this need (Fig. 1b). This process must be present in all animals, it must be there all the time, and it must come online the moment the animal starts to interact with the world.

Key messages

We conclude by leaving the reader with several core messages to consider.

(1) Respect the power of System One. It probably holds the secret for most questions on how neural circuits lead to all adaptive behaviour, including higher-order processes such as decision-making, perception and general problem-solving.

(2) Be aware that System Two is hard to study in the laboratory. The phenomenon of fast and sparse network re-configuration, which is the defining feature of this system, is not easy to access experimentally. The synapses that are changed in this process

are probably few in number, and they will be distributed across several brain areas, such as the hippocampus, basal ganglia and cortex in mammals. In addition, it is often not clear, a priori, which neurons specifically need to be targeted for detailed investigation. Furthermore, the process happens rapidly and is, therefore, difficult to catch in the act, and a learning event will occur only once per animal in a given learning task. This means that a new subject will have to be recruited for each trial. In combination, these factors make designing a controlled experiment a significant challenge, and great care needs to be taken to define and spell out a concrete hypothesis before embarking on an extensive experimental project.

(3) Be aware that a lot of ongoing activity that is ubiquitously observed in most brain recordings is probably because of System Three idling in the background. Furthermore, any mismatch or error signals that are introduced to the experiment – either explicitly and deliberately or inadvertently – will engage System Three and introduce plastic changes. This plasticity will result in changing the neural dynamics to minimize this mismatch or error signal and can introduce significant changes in the firing properties of the small number of neurons that are usually available for experimental readout. The explicit consideration of this process can often help explain findings that otherwise might be cryptic or puzzling.

In summary, we believe that these considerations will be crucial discussion points in studying the boundary between nature and nurture, especially as big data approaches allow neuroscientists and machine learning experts to connect emerging connectomics, high-resolution behaviour and brain-wide neuroimaging datasets[94,95].

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Competing interests

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