Seasoned Asexuals

Overall, at least two of the species — *T. tahoe* and *T. geneveviae* (Figure 1) — seem to qualify as long-standing asexuals. Interestingly, *T. geneveviae* also has unpaired chromosomes, another indicator of prolonged lack of sex [5]. They thus join a group of animals that continues to puzzle biologists. On the one hand, there is fundamental skepticism as to whether survival without any sex at all is possible in the long run, and whether the claim of asexual reproduction perhaps just means we haven't looked hard enough. After all, rare sex may go unnoticed and yet be beneficial [2]. On the other hand, if asexuals are real, they pose a challenge and an opportunity for evolutionary biology.

At its heart, evolutionary theory has an economic algorithm, a cost–benefit calculation: if a trait is beneficial for fitness, it will be selected for, when it is costly, it will be selected against. But the near ubiquitous presence of sex has proven to be notoriously hard to rationalise in terms of evolutionary cost–benefit calculations. There is as of now no simple, single-cause explanation for the benefits of sex [18]. On the other side of the equation, the costs of sex are easily spelled out, thanks to John Maynard Smith's notion of the 'twofold cost of sex' [19]: in order to produce the same number of offspring, a sexual species needs twice the number of parents — a father and a mother for each offspring — while an asexual species only needs one. Thus, asexuals should rapidly outgrow sexuals, which they usually don't.

But, if the prevalence of sex means it is so beneficial, how can asexuals — provided they are real — survive? By extension it must mean that the selective pressures that cause sex to persist and prevail are somehow less powerful or counteracted by even larger benefits of asexuality in these organisms. Traditionally, benefits of sex have been grouped into ecological and genetic explanations [20]. So, in an ideal world, a comparison of the genetics and ecology between asexual and sexual species could be expected to yield some hints as to what needs to change within the organism or in its environment to make asexuality (or sexuality) the more successful strategy. This is easier said than done of course, and there's also a double bind: on the one hand, only old asexuals qualify for such comparisons, as evolutionary benefits only play out in the longer run; on the other hand, if lineages have been asexual for a long time, they may have diverged from their sexual ancestors in many different aspects of their biology, making it even more difficult to ascertain which ecological or genetic differences are direct consequences of asexuality and which are unrelated changes that happened along the way.

With their intermediate anciency — older than the many easy-come-easy-go asexual lineages and younger than bdelloids or Darwinulids — the asexual *Timema* stick insects might have just the right age for such comparisons; unless, that is, they turn out not to truly have stuck with asexuality in the end.

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Basal Ganglia: Insights into Origins from Lamprey Brains

The lamprey brain has now been shown to have basal ganglia circuitry, with an output that acts tonically on midbrain and brainstem motor centers and is modulated by ascending dopaminergic input. This condition was believed to represent the tetrapod condition, but now appears to be far more ancient.

Mario F. Wullimann

Lampreys are a global treasure for evolutionary biology. These fish-like, jawless (agnathan) animals represent the most ancestral living vertebrates (Figure 1). Cambrian agnathans originated more than 500 million years ago and gave rise to the first grand craniate radiation in the Silurian and Devonian periods. Todays lampreys may therefore harbour the key for understanding the origins of the craniate/vertebrate radiation, including the evolution of a vertebrate brain and sensory organs [1,2].

Evolutionary neurobiology has suffered historically from various preconceptions. Take cortex evolution, which was once believed to have proceeded from olfactory cortex to hippocampus and isocortex (reflected

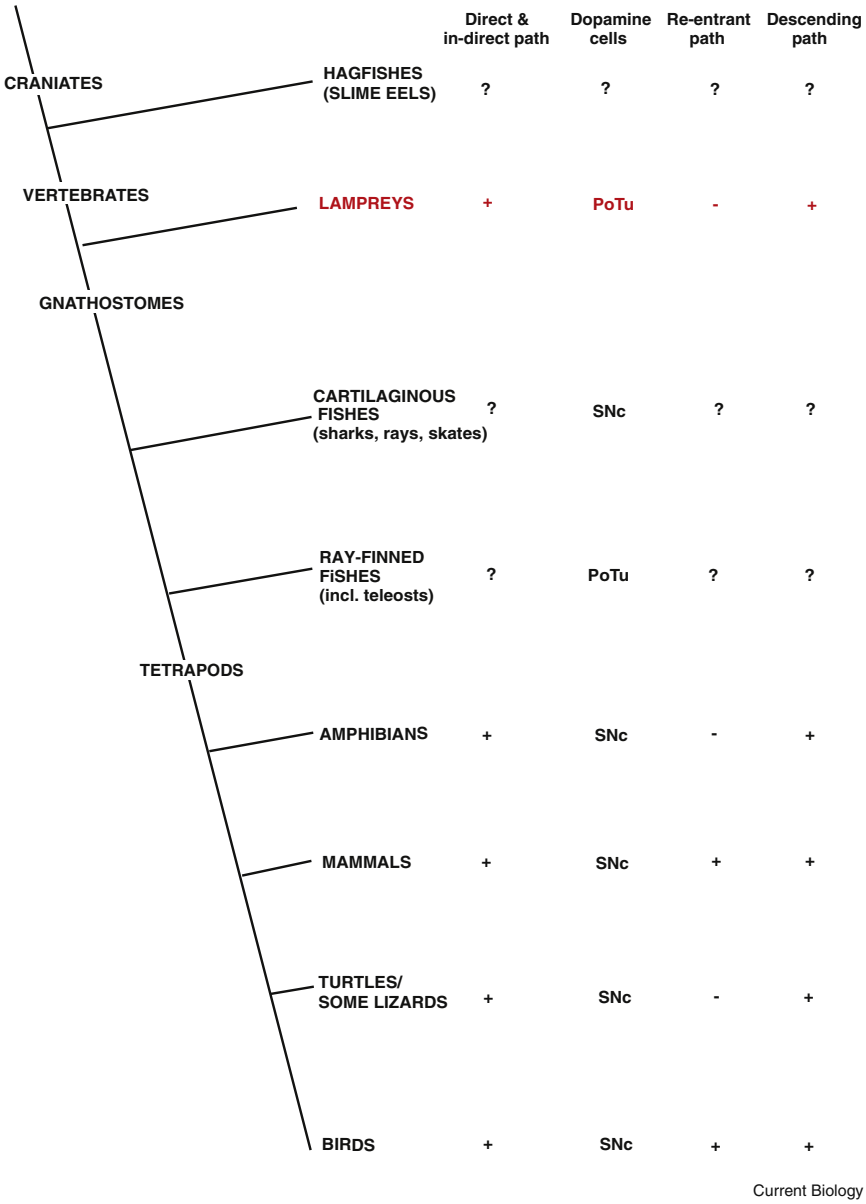

Figure 1. Simplified cladogram of extant craniates and some basal ganglia features.
SNc, compact substantia nigra; PoTu, posterior tuberculum. See text for details.

in outdated paleo-, archi-, and neocortex terminology). This is clearly inconsistent with the fact than not only primates, but all placental mammals, and even marsupials and egg-laying platypus/echidnas possess all three types of cortices [3].

Some people may recall a feeling of humiliation associated with the observation that juvenile chimpanzees are taught by conspecifics how to prepare straws and use them to collect termites. Such complex motor learning leading to acquisition and later activation of fine motor skills was formerly believed to be unique to human behavior. Its underlying neural machinery is the so-called motor loop of basal ganglia circuitry. The isocortex activates the striatum, which has two different inhibitory neuronal populations giving rise to the direct and indirect pathways, respectively.

The direct pathway starts out from GABA/Substance P-containing striatal cells and thus inhibits the reticular nigral substance and the internal pallidal segment. Because the latter two structures are also GABAergic, they will in consequence disinhibit a dorsal thalamic (glutamatergic) nucleus which, in turn, acts back excitatorily on the premotor-motor cortex.

The indirect pathway arises from GABA/enkephalin-containing striatal neurons and runs via sequential synapses through external pallidal segment (GABAergic), subthalamic nucleus (glutamatergic), internal pallidal segment (again GABAergic) to thalamus. Therefore, activation of this indirect pathway has an inhibitory effect back onto isocortex. In behaviorally relevant situations, the dopaminergic compact nigral population of the basal midbrain releases dopamine onto both striatal GABAergic populations.

However, these two neuronal populations exhibit different dopamine receptors: the direct pathway cells have D1 receptors, and the indirect pathway population carry D2 receptors. The D1 receptors activate an excitatory intracellular signal in striatal direct pathway cells which supports the excitatory feedback of the direct pathway onto cortex. In contrast, D2 receptors trigger an inhibitory cellular signal in striatal indirect pathway cells, changing the sign of the resulting activity back onto cortex, which becomes then also excitatory. Thus, release of dopamine leads to activation of planned motor behavior through the basal ganglia motor loop in mammals [4].

Seeing how elegantly toucans or parrots use their beak for manipulating small food items, it is easy to believe that comparable basal ganglia circuitry is also found in birds [5]. Reptiles (turtles, some lizards) follow suit [6], although their motor loop is not completed directly. The major output of the reptilian basal ganglia does not lead through thalamus back to dorsal cortex, but goes to motor centers of pretectum, midbrain and brainstem. This descending pathway is present in birds, in addition to the so-called re-entrant pathway through thalamus back to dorsal pallium (Wulst), as similarly seen in mammals. Completing the tetrapods, amphibians show essentially the reptilian situation because they also lack the re-entrant pathway, but show the other elements of the motor loop described above, including the descending output pathway [7].

In an exciting paper in this issue of *Current Biology*, Stephenson-Jones and colleagues from Sten Grillner's

lab [8] report the presence of core elements of basal ganglia circuitry, neurochemistry and neurophysiology in the river lamprey. This work identifies two neurochemically different striatal GABAergic neuron populations co-expressing either Substance P or enkephalin. Combined tracing and neurochemical studies demonstrate furthermore that these striatal populations show selective connectivity patterns consistent with the presence of a direct and indirect pathway, including a GABAergic pallidum and a glutamatergic subthalamic nucleus. Finally, this circuitry converges into a descending output pathway (Figure 2).

From a tetrapod viewpoint, it is of critical functional importance that lamprey pallidal output cells to the optic tectum exhibit spontaneous tonic activity which is not dependent on synaptic input, but may be silenced by striatal GABAergic input — both are shown in this work with combined pharmacological and neurophysiological experiments. However, analysis of tetrapod basal ganglia revealed that the re-entrant pathway of the basal ganglia motor loop has apparently independently evolved in mammals and birds (Figure 1) and that it is not seen in the ancestral tetrapod condition [5–7]. This makes it highly unlikely that a re-entrant pathway is present in lampreys, but rather that their basal ganglia are similar to the basal tetrapod organizational pattern.

Stephenson-Jones *et al.* [8] propose the evolutionary hypothesis that additional associative, limbic and cognitive loops may have evolved in other vertebrates through duplication of this basal ganglia motor loop. While strong evidence for at least a motor and limbic loop exists for all tetrapods outside mammals, the adult situation for ray-finned and cartilaginous fishes is not well investigated. Developmental genetic markers suggest the presence of separate pallidal and striatal areas in teleosts [9]. Furthermore, goldfishes have the core parts of a limbic system, namely a hippocampus homologue related to place memory formation and retention and a pallial amygdala related to fear recognition [10], which makes the presence of associated

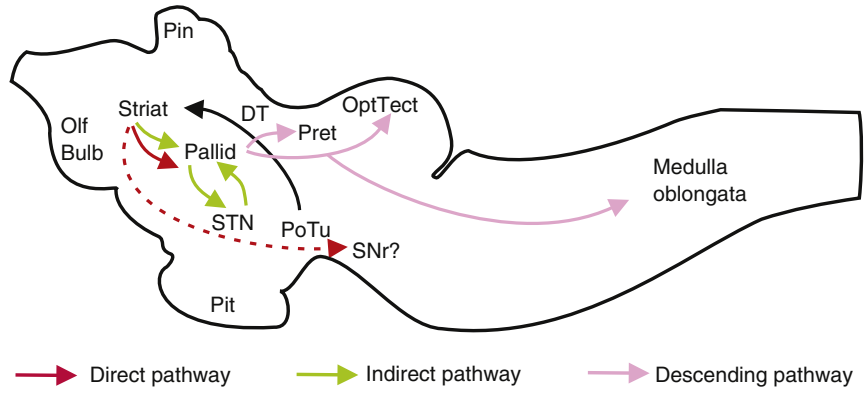

Figure 2. Schematic lateral view of a lamprey brain with basal ganglia circuitry as described in this issue by Stephenson-Jones *et al.* [8].

Olf bulb, olfactory bulb; OptTect, optic tectum; Pallid, pallidum; Pin, pineal; Pit, pituitary; PoTu, posterior tuberculum; SNc, compact substantia nigra; SNr, reticular substantia nigra; Striat, striatum; STN, subthalamic nucleus.

limbic basal ganglia circuits likely in teleosts. Since a functional pallidum appears now even present in lampreys, the noted absence of diagnostic pallidal gene expression must be revisited (see discussion in [11]).

Large basal midbrain dopaminergic cell populations (compact nigral substance) are present in all tetrapods and in cartilaginous fishes (Figure 1). However, lampreys together with ray-finned fishes lack such midbrain cells, but both groups have ascending dopaminergic projections from a more anterior diencephalic region, the posterior tuberculum [12]. These posterior tubercular cells are momentarily either interpreted as a diencephalic extension of midbrain basal plate nigral dopamine cells [13] or of cells corresponding to mammalian A11 dopamine group [14]. Only in the first case would the ascending dopamine projection be homologous among all vertebrates.

In any case, the important work of Stephenson-Jones *et al.* [8] shows that lampreys exhibit an ancestral basal ganglia machinery possibly used in motor learning and performance and homologous in phylogeny throughout vertebrates. Thus, once again the river runs deeper than expected when it comes to the evolution of basic components of the vertebrate brain. This teaches us that presence or absence of derived neural systems cannot be established by inference from the phylogenetic position of a particular species, but only by detailed analysis of the system of interest [15].

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Phagocytes: Fussy about Carbs

A new mechanistic model based on the formation of a phagocytic synapse explains how immune cells detect and respond to direct contact with fungal pathogens.

Ann M. Kerrigan and Gordon D. Brown

Specialised receptors on immune cells recognise invading pathogens and trigger a series of signals culminating in protective responses that can include internalisation of the organism and the generation of anti-microbial reactive oxygen species (ROS). Inappropriate activation of these responses can, however, be damaging to the host, causing tissue injury and inflammation. It is therefore crucial that the host cell can distinguish direct microbial contact from the detection of soluble material shed from microbes at a distance, and respond appropriately. Recent work published in *Nature* by a team at Cedars-Sinai Medical Center has given insight into how the host can achieve this distinction. This investigation by Underhill and colleagues [1] focused on the immune receptor Dectin-1 and its recognition of β-glucans, carbohydrates commonly found in fungal cell walls. The findings resulted in their proposal of a model mechanism through which immune cells can distinguish between direct fungal contact and detection of soluble fungal-derived components [1].

Dectin-1 is a pattern recognition receptor expressed predominantly by myeloid cells. It recognises fungi by detecting β-glucans and triggers a variety of immune responses through signalling via its atypical immunoreceptor tyrosine-based activation motif (ITAM). A great deal of *in vitro* work has suggested an antifungal role for Dectin-1 and, indeed, recent studies in mice and humans have established an important function for the receptor during fungal infections (see [2,3] for recent reviews covering Dectin-1). Dectin-1 was originally identified as a β-glucan receptor by studies using zymosan, a β-glucan-rich yeast-derived particle [4]. β-glucans themselves have been of interest since the 1960s when their immune-stimulating activities were discovered, and the administration of purified β-glucans has since been shown to protect against tumour development and to boost resistance to various infections [5]. The β-glucan components of zymosan also account for its observed immunostimulatory effects and it has consequently been widely used for many studies of immune function. Following the identification of Dectin-1 as the principal β-glucan receptor on leukocytes, subsequent investigations demonstrated that it is in fact the key receptor involved in mediating the immunomodulatory effects of these carbohydrates.

Although there has been considerable progress regarding Dectin-1 and its significance in immunity, some aspects of its recognition of β-glucans have puzzled researchers. For example, the mechanism underlying its recognition of carbohydrates is still unclear. Furthermore, although small soluble β-glucans such as laminarin bind specifically to Dectin-1, they function to block rather than activate the receptor [6]. In general, intermediate-sized soluble β-glucans, such as glucan phosphate, do not appear to directly activate leukocytes *in vitro*, although there is evidence that in some instances they can induce cytokines and transcription factors, and they seem to possess biological activity *in vivo* [6]. Conversely, there are several examples demonstrating that large particulate β-glucans, such as zymosan and curdlan, can directly activate leukocytes, thereby stimulating phagocytosis and the production of inflammatory mediators and ROS. These general observations regarding the relationship between the molecular weight of β-glucans and their biological activity raised the idea that larger molecules were required to provide a greater degree of receptor cross-linking to permit Dectin-1 activation.

Underhill and colleagues [1] explored this idea by comparing whole glucan particles (WGP), a particulate yeast-derived β-glucan preparation, with various soluble yeast-derived β-glucans ranging from low to high molecular weights. They examined the activities of the β-glucans in the context of phagocytosis, and the induction of cytokines and ROS. Using various cell types they found that WGP induced robust Dectin-1 signalling and downstream responses, whereas all soluble β-glucans (including high molecular weight glucans) failed to elicit similar responses. These observations demonstrated that increasing the size of the β-glucan is insufficient to activate Dectin-1 signalling and prompted the group to investigate whether the way in which β-glucans are presented to a cell may be an important factor. They investigated this by examining responses from cells stimulated with soluble β-glucans immobilised on the surface of plates or beads. Using this approach they demonstrated that the size of the β-glucan is unimportant, but that in order to trigger cellular activation it must be presented to Dectin-1 in an immobilised form such as on a yeast cell.

The researchers likened the requirement of immobilised β-glucans for Dectin-1 activation as being similar to the situation with the ‘immunological