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Miniaturization of Nervous Systems and Neurons

Review

Jeremy E. Niven[1,*] and Sarah M. Farris[2]

Miniaturized species have evolved in many animal lineages, including insects and vertebrates. Consequently, their nervous systems are constrained to fit within tiny volumes. These miniaturized nervous systems face two major challenges for information processing: noise and energy consumption. Fewer or smaller neurons with fewer molecular components will increase noise, affecting information processing and transmission. Smaller, more densely-packed neural processes will increase the density of energy consumption whilst reducing the space available for mitochondria, which supply energy. Although miniaturized nervous systems benefit from smaller distances between neurons, thus saving time, space and energy, they have also increased the space available for neural processing by expanding and contorting their nervous systems to fill any available space, sometimes at the expense of other structures. Other adaptations, such as multifunctional neurons or matched filters, may further alleviate the pressures on space within miniaturized nervous systems. Despite these adaptations, we argue that limitations on information processing are likely to affect the behaviour generated by miniaturized nervous systems.

Introduction

Many animals possess neurons and/or nervous systems that can be described as miniaturized, having undergone an extreme reduction in size during their evolutionary history [1]. Miniaturization of the nervous system typically accompanies miniaturization of the entire body, which may be the result of several evolutionary scenarios, including microhabitat colonization, acquisition of a parasitic mode of life, or reduced developmental time as a result of a rapidly changing environment (Box 1). However it occurs, the extreme reduction of body size has profound consequences for almost all aspects of an animal's biology (Box 2) [2,3], including the structure and function of the nervous system. Despite the widespread occurrence of body miniaturization [4], little is known about miniaturization of the nervous system. For example, how does miniaturization affect the structure of neurons and nervous systems? What are the consequences of miniaturization for information processing within the nervous system? What are the limits to miniaturization of the nervous system? How does miniaturization affect behaviour?

Miniaturized body forms have evolved in numerous animal phyla, including Annelida, Arthropoda, Echinodermata, Mollusca, Nematoda and Chordata [4]. Within the arthropods, highly miniaturized body plans have evolved many times independently but the effect on nervous systems has been investigated for a comparatively small number of species, most of them insects [1,5–8] (Figure 1). In the chordates, miniaturization has primarily been studied in species of fish and amphibians [4]. In all cases, studies are predominantly focused on modifications of nervous system structure [1,4–7,9–13]; little is currently known about the developmental mechanisms for extreme nervous system miniaturization, or the impact of miniaturization on physiological function of neurons and circuits and, consequently, behaviour.

Miniaturization of Computers and Nervous Systems

The process of nervous system miniaturization often draws comparisons with that of computers. Indeed, the term miniaturization was used originally to describe the reduction in size of automated computers and their components [14]. However, such comparisons can be misleading. Early electronic digital computers, such as the Colossus Mark I, had vacuum tubes and paper tape but these were replaced by innovations such as silicon-based transistors [15]. At each stage, computers with equivalent computational power became smaller because smaller components were available. Today's mobile phones contain greater computational power than early computers that occupied entire rooms.

It is important to remember, however, that nervous systems (and biological systems more generally) are more constrained than engineered systems because they must adapt those components they already possess rather than replacing them entirely. The majority of components from which nervous systems are constructed (lipid membranes, G-proteins, pumps, co-transporters, ion channels etc.) predate the evolution of neurons [16,17]. These molecular components typically have similar structures and, therefore, similar sizes in neurons from small as well as large animals. Indeed, there is no experimental evidence to suggest that the structures of components, such as ion channels or G-proteins, are smaller in miniaturized nervous systems. Thus, unlike computers, as nervous systems are miniaturized they contain fewer components, rather than smaller novel components, with consequences for information processing.

Rationale

The nervous systems of only a few lineages that are considered miniaturized relative to a common ancestor have been studied (Box 3). Because of the small size of these nervous systems, their study has been restricted to morphology rather than physiology [1,4–7,9–13]. However, the morphology and physiology of the nervous systems of many insects, which are small in comparison to most vertebrates, have been studied extensively [18–21]. Several studies have specifically modelled small neurons or neural compartments [22–24], and many principles obtained from computational modelling are generally applicable [25,26]. Thus, we use comparisons between small and large nervous systems combined with computational models and the morphology of miniaturized nervous systems to gain insights into neural adaptations to the constraints of small size.

Noise

Noise is defined as random fluctuations or distortions that interfere with a signal and, therefore, with information

[1]School of Life Sciences, University of Sussex, Falmer, Brighton BN1 9QG, UK. [2]Department of Biology, West Virginia University, Morgantown, WV 26506, USA.
*E-mail: nivenje@gmail.com

Box 1

Evolution and development of miniaturized forms.

The invasion of tiny environmental niches may select for miniaturization, as observed for interstitial animals, which colonize the spaces between grains of sea floor sediment and range from 60 μm to 2 mm in size [63], or insect parasitoids, which develop within the eggs or larvae of other species and may be as small as 170–200 μm [5,37]. Paedomorphosis, either through early cessation of growth (progenesis) or a reduction in growth rate (neoteny), appears to be a common mechanism for body size miniaturization [4,38,64]. Selection for paedomorphic development may occur in rapidly changing environments requiring accelerated growth to sexual maturity [4]. To date, developmental studies of miniaturized nervous systems are few, but promise to reveal unusual mechanisms for reducing size while preserving function, such as the removal of neuronal cell bodies apparently while retaining axons and dendrites in *Megaphragma mymaripenne* [5].

transfer. Noise affects all aspects of neural processing from the detection of sensory stimuli to motor control and decision making [26]. In single neurons, noise may arise in several ways. The external stimuli to which the neuron responds, including sensory stimuli and neurotransmitter molecules, contain noise (extrinsic noise). For example, light stimuli contain photon shot noise, whereas variation in the numbers of synaptic vesicles released and neurotransmitter molecules in each vesicle contribute to synaptic noise. Processes within the neuron, such as the spontaneous activation of G-proteins or voltage-gated ion channels, also generate noise (intrinsic noise) [25,27]. Both intrinsic and extrinsic noise affect information processing.

The inability to reduce the size of molecular components has implications for miniaturized nervous systems. The tiny volume of the nervous system will promote fewer, smaller neurons. As neurons get smaller their membrane area and the number of molecular and sub-cellular components (e.g. synapses) will be reduced. With fewer molecular components in smaller neurons, spontaneous activity of a single component will have a greater impact on neural activity, increasing noise. For example, the spontaneous activation of small numbers of voltage-gated Na^+ channels can initiate action potentials if axons are sufficiently narrow, imposing a lower limit on axon diameter [24]. Tracts from small nervous systems have a high proportion of axons with diameters approaching the minimum imposed by this 'channel noise' [28], suggesting that, unless channel properties are altered, signals carried by these axons will be noisy. Thus, with fewer components, small neurons have lower information rates than larger homologous neurons [29].

One means of removing noise in signals from individual neurons is to average across neurons processing information in parallel [26]. Averaging removes random noise that is independent in each neuron being averaged. However, parallel processing requires separate neurons but within miniaturized nervous systems there is little space available for multiple neurons encoding information in parallel. Thus, miniaturized nervous systems will have less parallel processing, compromising their ability to remove noise by averaging.

Energy Consumption

Energy also poses a problem for a miniaturized system. Many aspects of both small and large nervous systems' anatomy, and the physiology of neurons and neural circuits, suggest that they have been under selective pressure to reduce energy consumption [30]. Energy budgets of large nervous systems suggest that the primary processes consuming energy are the generation and maintenance of electrical signalling and synaptic transmission [22,31]. Within small nervous systems, detailed anatomical reconstructions have shown that the placement of neurons and neural components is close to a configuration that would minimise the volume of wire (axons and dendrites) and, consequently, energy consumption [32]. Computational modelling also suggests that neurons from small nervous systems can have energy efficient action potentials [22], whilst electrophysiological recordings show that neurons within small nervous systems adopt efficient information coding strategies [29,33,34].

Reducing the size of neurons and increasing their packing density within miniaturized nervous systems will increase the density of membranes and synapses, thereby increasing the density of energy consumption. However, a reduction in neuron volume will reduce the available space for mitochondria, which are necessary for generating the energy needed for neural signalling. Evidence from large nervous systems shows that narrower axons with fewer mitochondria

Box 2

Implications of body miniaturization for oxygen supply.

When considering the miniaturization of the nervous system, it is essential to consider the consequences of miniaturization of the body in which the nervous system is situated [2,3]. Miniaturization influences the means by which the nervous system (and other organs/tissues) is supplied with the oxygen and nutrients needed to generate the energy necessary to support information processing and maintenance. Smaller nervous systems possess larger surface area to volume ratios, increasing the area over which oxygen and nutrients can diffuse into the tissue. The smaller volume of the nervous system also allows oxygen to diffuse through the tissue rapidly. Thus, miniaturized species do not require such extensive oxygen supply networks such as capillaries or tracheal ramifications. The reduction or loss of oxygen supply networks will free space for other tissues and reduce the need for active pumping, which itself consumes energy.

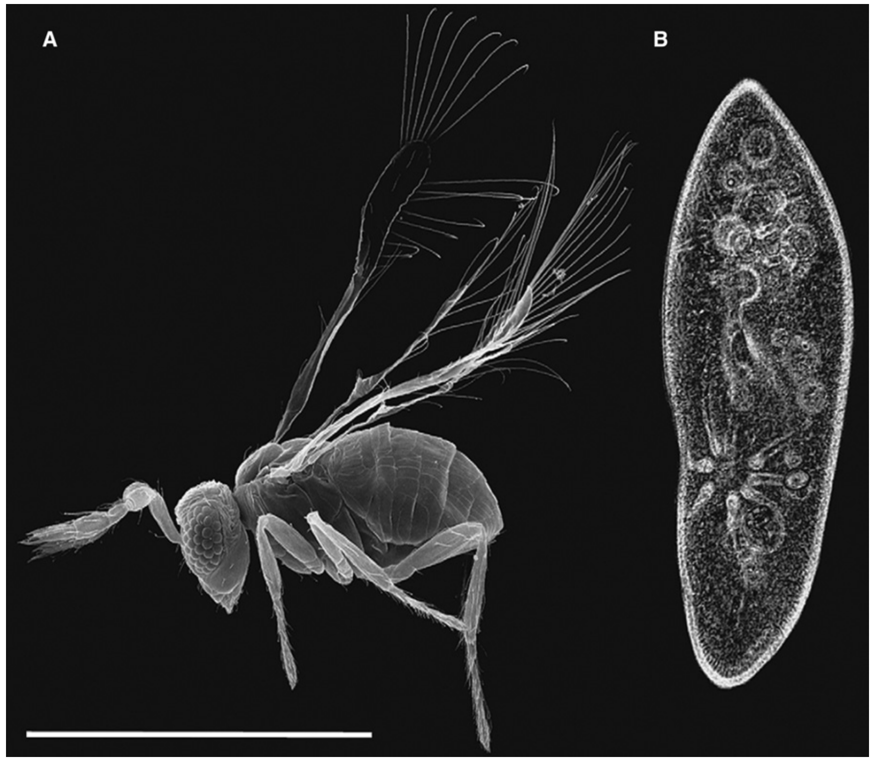

Figure 1. Extreme reduction in body size in an insect.

(A) SEM of an adult *Megaphragma mymaripenne* parasitic wasp. (B). The protozoan *Paramecium caudatum* for comparison. The scale bar is 200 μm. Adapted from [5].

have lower firing frequencies [28]. Thus, narrow axons within miniaturized nervous systems may be unable to sustain high firing frequencies due to energy limitation. Although information processing in smaller neurons is more energy efficient [29], fewer mitochondria are likely to limit the energy available for maintaining electrical processing and synaptic transmission impacting upon information processing.

Morphological Consequences of Miniaturization

Miniaturization of the nervous system has primarily been studied at the gross anatomical level, and from these data a number of features emerge as seemingly universal adaptations to extreme reductions in body size. First, and perhaps surprisingly, a negative allometric relationship between brain and body size in both vertebrates and invertebrates results in a larger relative brain size as body size decreases [7,8,35]. This speaks to strong functional constraints on minimum brain size in most vertebrates and invertebrates. Interestingly, it has been postulated that the increased relative brain size associated with miniaturization may lead to increased encephalization if the lineage later evolves to include larger species [36].

The relatively large brains of the smallest animals gives rise to the problem of accommodating larger brains within the head, further complicated in vertebrates and arthropods by the need to enclose the brain within a rigid skull or head capsule. In both groups of animals, the relatively large brain may appear tightly packed or condensed, and tightly fills the cranial area (Figure 2) [35,37]. Neural tissue may be further accommodated by displacement of surrounding head structures, invasion of neighbouring head and body spaces, or both. In plethodontid salamanders, which can be as little as 14 mm long [38], the enlarged eyes protrude anteriorly and deform the anterior surface of the skull, while the enlarged hindbrain and otic (ear) capsules displace bones of the upper jaw [35]. Similar skull morphologies have arisen independently in miniaturized frogs [39]. In miniaturized insects lacking a constricted neck, the brain may be partially or totally displaced into the thorax or abdomen [11,37,40–42] (Figure 2A), while in spiders, where the head and thorax are fused into a single cephalothorax, the enlarged nervous system of miniaturized species distends ventrally and invades the proximal segments of the legs and pedipalps [7].

Few studies have addressed the effects of miniaturization on functional regions within the brain, although those that do exist suggest that the impact of reduced size is similar to that on other morphological elements such as bones

Box 3

What is miniaturization of the nervous system?

Miniaturization implies that the nervous system, a population of neurons or a single neuron, has undergone an extreme reduction in size in comparison to the homologous structure hypothesised to have been present in an ancestral species. There are, however, no definitive criteria about which ancestor the comparison should be made with and, therefore, the node within the phylogeny that is used for the comparison. This is made more complicated when phylogenetic origins are uncertain. There are also no firm criteria about how extreme a reduction in size must be to qualify as miniaturization rather than a less dramatic reduction of nervous system size, which has been hypothesised to have occurred in many lineages. This definition of miniaturization means that the nervous system of a particular lineage may be described as miniaturized even though it is larger than those of other lineages that are not considered to be miniaturized. Thus, although vertebrate nervous systems are large in comparison to those of many invertebrates, some vertebrate lineages may still be described as miniaturized in relation to an ancestor. Conversely, despite possessing small nervous systems in comparison to vertebrates, many insects possess much larger nervous systems than basal apterygotes (e.g. silverfish) and so, with reference to this node of their phylogeny, they are not miniaturized.

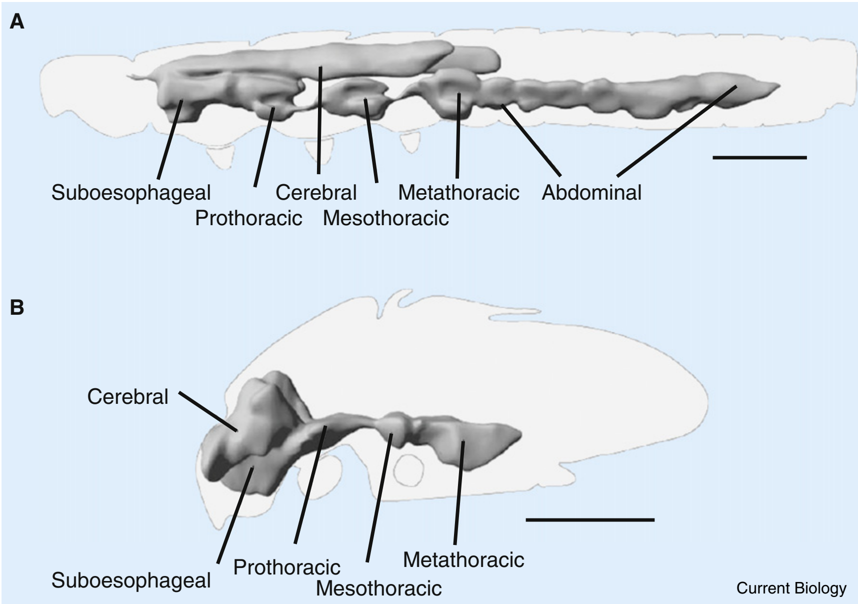

Figure 2. The brain and nervous system of tiny insects.

The first instar larval (A), and adult brain (B) and ventral nerve cord of the beetle, *Mikado* sp. The grey line shows the outline of the insect, the shaded grey region shows the central nervous system. The cerebral ganglion (brain) extends into the thorax due to insufficient space within the anterior segments. The scale bars are 50 μm. Adapted from [6].

within the skeleton. For example, miniaturization in amphibians causes skeletal elements to become simplified due to loss or fusion of components, often resulting in novel morphological features [38,39,43]. Similarly, the optic tectum of caecilians (limbless amphibians) has a simpler structure in miniaturized species, showing reduced lamination and cell migration [44]. In leaf-cutting ants, the smallest workers have fewer antennal lobe glomeruli than do larger workers and lack a specialized macroglomerulus, although this difference may also be related to the different behavioural roles and odour processing needs of small and large workers [45]. Chalcidoid wasps include some of the smallest insect species, and belong to the Order Hymenoptera, whose brains are typically characterized by large learning and memory neuropils called mushroom bodies with doubled, convoluted input regions called calyces [46,47]. The calyces appear to be reduced in chalcids, either through complete loss of one calyx or reduction and fusion of two calyces into a single neuropil [47].

Neurons and Networks in Miniaturized Nervous Systems

The size of individual neurons is also reduced in miniaturized nervous systems. The diameter of neuron somata in miniaturized insects may be as little as 1–2 μm, a limit likely imposed by the size of the nucleus (Figure 3) [7,37,40]. Reduction of neuron size and dense packing of somata is also observed in miniaturized salamanders, although genome size also influences soma size in these species [9]. The size limit of somata in insects is overcome in a unique manner by the parasitoid wasp *Megaphragma mymaripenne*, which has an adult body size of 200 μm, rivalling that of some unicellular organisms (Figure 1). During metamorphosis, 95% of neuronal cell bodies lyse, leaving a nervous system composed primarily of anucleate neurons (Figure 3). The adult brain thus contains only about 200 cell bodies compared with approximately 37,000 in the brains of slightly larger related species [5].

Insect neurons possess unique features that may reflect the relatively small size of most invertebrate nervous systems, and the need to maximize functional capacity within a small space. The neurons of insects, like many other invertebrates, typically have a passive soma attached to the axonal and dendritic arbours through a thin neurite, whereas vertebrate neurons typically have an active soma interposed between dendritic and axonal processes [18,21,48]. At the very small soma sizes reached in miniaturized nervous systems, passive soma membrane properties combined with their position on side branches may be advantageous. By removing the soma from the main dendritic-axonal information processing axis, its miniaturization is unlikely to affect information processing. Additionally, the spontaneous activation of voltage-gated ion channels in small neural compartments and processes can cause spontaneous action potentials [24]. In the absence of changes to the biophysical properties of the voltage-gated ion channels, miniaturization of the soma would further increase the rate of spontaneous action potentials, thereby increasing energy consumption and disrupting signalling.

Placing somata on the outside of the nervous system will also reduce the distances between dendrites and axons, which will be further reduced as nervous systems are miniaturized. Insect neurons are also more densely packed than are vertebrate neurons, increasing the number of neurons that can be accommodated within a small space [37,48]. Thus, neural processes can be shorter, reducing the space they occupy, the conduction delay of signal transmission and the energy they consume. The shorter distances over which voltage signals must be propagated may permit graded potentials rather than action potentials to be used for information transmission [49]. Graded potentials, which cannot be used for transmission over long distances, are more energy efficient than action potentials, potentially making further energy savings [33]. Non-spiking neurons, which transmit information with graded potentials, appear to be more widespread in small insect nervous systems than in larger vertebrate nervous systems, where they are often restricted to peripheral sensory systems, such as the retina [18,50].

Invertebrate neurons may also be multifunctional, operating in multiple circuits and contributing to multiple behaviours [51]. Though to some extent this is true for many neurons, such as motor neurons that contribute to the generation of many movements (e.g. walking, jumping and kicking), in some cases, these multifunctional neurons contain domains that can function relatively independently

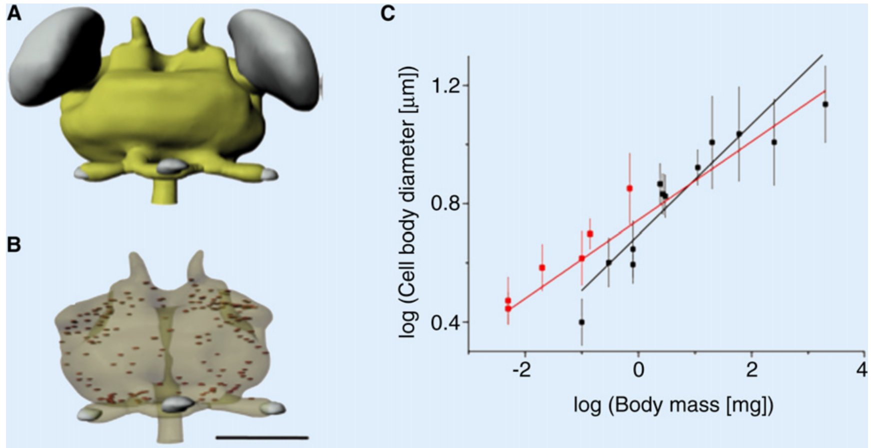

Figure 3. Miniature nervous systems have fewer, smaller neurons.

(A) The adult brain of the parasitic wasp *Megaphragma mymaripenne*. The brain (yellow), optic lobes (upper, grey) and occelli (lower, grey) are visible. (B) Nuclei are absent from many neurons in *M. mymaripenne*. The ~200 nuclei that remain within the brain are visible as small dots. (C) Scaling of cell body diameter in orb-weaving spiders. Data are from adults and nymphs (red) or only adult males and females (black). Lines show the scaling relationship for adults (black) and for pooled data from adults and nymphs (red). The small volumes occupied by the cell bodies save space. The scale bar is 25 μm. Adapted from [5] and [7].

of one another and may even have two or more spike initiation zones [19,52]. In addition, single processes may possess both pre- and postsynaptic specializations providing both inputs and outputs to local circuits [48,53]. Thus, a single neuron may effectively function as two or more neurons. Although there is no direct evidence that these multifunctional neurons are more prevalent in smaller nervous systems, the majority have been characterised from invertebrate neural circuits.

Numerous multifunctional or polymodal neurons have been characterised in the nervous system of the nematode *Caenorhabditis elegans*, which at 1 mm adult length possesses only 302 neurons. Indeed, the morphology of the entire nervous system is greatly streamlined and is only weakly centralized, consisting of dorsal and ventral nerve cords and a circumesophageal ring. In addition, neuronal processes are typically unbranched, though there are exceptions, particularly in males. These processes form *en passant* chemical synapses onto other neurons and muscles, and electrical synapses with neighbouring cells appear far more common than in larger invertebrates or vertebrates [54]. This suggests that many aspects of neuronal morphology may be altered in miniaturized nervous systems. Reducing the numbers of chemical synapses may save space in tiny nervous systems but it is likely to have major consequences for computation within the neural circuits and the behaviour they generate.

Behavioural Consequences of Miniaturization

Despite numerous adaptations to increase the space available for miniaturized nervous systems, changes in the structure and function of neurons and neural circuits should affect behaviour. Fewer, smaller neurons should reduce the resolution of sensory systems and the accuracy of motor systems [55]. These changes would be expected to reduce behavioural accuracy. There may also be fewer layers of neural processing, which may prevent neural circuits from computing derived variables. However, quantitative comparisons of the precision of web construction in miniaturized *versus* larger orb-weaving spiders have failed to find the predicted greater inaccuracy of miniaturized species [56,57]. There may be several explanations for the inability to detect a behavioural deficit. One possible explanation is that limb movements during web construction may be co-ordinated by relatively few interneurons that modify the output of individual limb controllers and that are sufficiently important to be retained even in the smallest spiders. An alternative explanation is that miniaturized spiders have maintained the accuracy of web construction at the expense of other behaviours.

One consequence of miniaturization is a change in the demands on the skeleton. The substantial reduction in body mass means that miniaturized animals experience smaller forces with consequences for behaviour [2,3]. For example, inaccurate limb placement in miniaturized animals, which may cause them to fall, is unlikely to cause injury so that they may have less need for sensory information about their limb placement than larger species. Changes to the structure of the body may also simplify control, reducing both the computations needed and the energy costs involved. In arthropods, the control of appendages can be performed by a variety of innovative mechanisms, although these mechanisms are not restricted to miniaturized animals. Appendages may be controlled by muscles operating against springs or through hydrodynamic extension, whilst high-speed synchrony may be achieved by cuticular structures [58,59].

Miniaturized animals may also resort to heuristics to reduce their computational burden, allowing them to produce behaviours that seem to require numerous computations through ‘rules of thumb’. Though such strategies are certainly not restricted to miniaturized animals, they may be more prevalent. Numerous behaviours in arthropods have been shown to rely on assumptions that reduce the computations underpinning behaviour [60–62]. Moreover, the lifespan of many miniaturized animals is short, in the case of insects, sometimes just hours or days. In such cases, the need for associative learning and memory formation may be reduced.

Conclusions

Noise and energy pose challenges for the processing and transmission of information within miniature nervous systems. Yet despite these challenges, miniaturized nervous systems have evolved that are smaller than unicellular organisms (Figure 1) or single neurons within larger nervous systems. This remarkable miniaturization is possible at least partly because of numerous adaptations that alleviate the potential effects of noise and energy on information processing in two ways; by increasing the space available for the

nervous system (specifically neural processes) within the animal or by reducing the information processing necessary for generating behaviour. However, these adaptations are unlikely to circumvent entirely the basic constraints of noise and energy that miniaturized nervous systems are subject to, suggesting that future studies will reveal severe behavioural deficits in miniaturized species.

References

1. Eberhard, W.G., and Wcislo, W.T. (2011). Grade changes in brain-body allometry: Morphological and behavioural correlates of brain size and miniature spiders, insects and other invertebrates. Adv. Insect Physiol. *40*, 155–214.
2. Bonner, J.T. (2006). Why Size Matters: From Bacteria to Blue Whales (Princeton: Princeton University Press).
3. Schmidt-Nielsen, K. (1984). Scaling: Why is Animal Size so Important? (Cambridge: Cambridge University Press).
4. Hanken, J., and Wake, D.B. (1993). Miniaturization of body size: organismal consequences and evolutionary significance. Annu. Rev. Ecol. Syst. *24*, 501–519.
5. Polilov, A.A. (2012). The smallest insects evolve anucleate neurons. Arth. Struct. Dev. *41*, 29–34.
6. Polilov, A.A., and Beutel, R.G. (2009). Miniaturisation effects in larvae and adults of *Mikado* sp. (Coleoptera: Ptiliidae), one of the smallest free-living insects. Arth. Struct. Dev. *38*, 247–270.
7. Quesada, R., Triana, E., Vargas, G., Douglass, J.K., Seid, M.A., Niven, J.E., Eberhard, W.G., and Wcislo, W.T. (2011). The allometry of CNS size and consequences of miniaturization on orb-weaving and cleptoparasitic spiders. Arth. Struct. Dev. *40*, 521–529.
8. Seid, M.A., Castillo, A., and Wcislo, W.T. (2011). The allometry of brain miniaturization in ants. Brain Behav. Evol. *77*, 5–13.
9. Roth, G., Rottluff, B., Grunwald, W., Hanken, J., and Linke, R. (1990). Miniaturization in plethodontid salamanders (Caudata: Plethodontidae) and its consequences for the brain and visual system. Biol. J. Linn. Soc. *40*, 165–190.
10. Grebennikov, V.V. (2008). How small you can go: factors limiting body miniaturization in winged insects with a review of the pantropical genus *Discheramocephalus* and description of six new species of the smallest beetles (Pterygota: Coleoptera: Ptiliidae). Eur. J. Ent. *105*, 313–328.
11. Grebennikov, V.V., and Beutel, R.G. (2002). Morphology of the minute larva of *Ptinella tenella*, with special reference to effects of miniaturisation and the systematic position of Ptilldae (Coleoptera: Staphylinoidea). Arth. Struct. Dev. *31*, 157–172.
12. Roth, G., Blanke, J., and Wake, D.B. (1994). Cell size predicts morphological complexity in the brains of frogs and salamanders. Proc. Natl. Acad. Sci. USA *91*, 4796–4800.
13. Roth, G., Rottluff, B., and Linke, R. (1988). Miniaturization, genome size and the origin of functional constraints in the visual system of salamanders. Naturwissenschaften *75*, 297–304.
14. (2011). Oxford English Dictionary Online. (Oxford: OUP).
15. Fauenfelder, M. (2005). The Computer: A History (London: Calton Books Ltd).
16. Sakarya, O., Armstrong, K.A., Adamska, M., Adamski, M., Wang, I.F., Tidor, B., Degnan, B.M., Oakley, T.H., and Kosik, K.S. (2007). A post-synaptic scaffold at the origin of the animal kingdom. PLoS ONE *2*, e506.
17. Richards, G.S., Simionato, E., Perron, M., Adamska, M., Vervoort, M., and Degnan, B.M. (2008). Sponge genes provide new insight into the evolutionary origin of the neurogenic circuit. Curr. Biol. *18*, 1156–1161.
18. Burrows, M. (1996). The Neurobiology of an Insect Brain (Oxford: Oxford University Press).
19. Strausfeld, N.J. (1976). Atlas of an Insect Brain (Berlin: Springer-Verlag).
20. North, G., and Greenspan, R.J. (2007). Invertebrate Neurobiology (Cold Spring Harbor, New York: CSHL).
21. Bullock, T.H., and Horridge, G.A. (1965). Structure and Function in the Nervous Systems of Invertebrates (San Francisco/London: W.H. Freeman and Company).
22. Sengupta, B., Stemmler, M., Laughlin, S.B., and Niven, J.E. (2010). Action potential energy efficiency varies among neuron types in vertebrates and invertebrates. PLoS Comput. Biol. *6*, e1000840.
23. Faisal, A.A., and Laughlin, S.B. (2007). Stochastic simulations on the reliability of action potential propagation in thin axons. PLoS Comput. Biol. *3*, e79.
24. Faisal, A.A., White, J.A., and Laughlin, S.B. (2005). Ion-channel noise places limits on the miniaturization of the brain's wiring. Curr. Biol. *15*, 1143–1149.
25. White, J.A., Rubinstein, J.T., and Kay, A.R. (2000). Channel noise in neurons. Trends Neurosci. *23*, 131–137.
26. Faisal, A.A., Selen, L.P.J., and Wolpert, D.M. (2008). Noise in the nervous system. Nat. Rev. Neurosci. *9*, 294–303.
27. Laughlin, S.B., and Lillywhite, P.G. (1982). Intrinsic noise in locust photoreceptors. J. Physiol. *332*, 25–45.
28. Perge, J.A., Niven, J.E., Mugnaini, E., Balasubramanian, V., and Sterling, P. (2012). Why do axons differ in diameter? J. Neurosci. *32*, 626–638.
29. Niven, J.E., Anderson, J.C., and Laughlin, S.B. (2007). Fly photoreceptors demonstrate energy-information trade-offs in neural coding. PLoS Biol. *5*, 828–840.
30. Niven, J.E., and Laughlin, S.B. (2008). Energy limitation as a selective pressure on the evolution of sensory systems. J. Exp. Biol. *211*, 1792–1804.
31. Attwell, D., and Laughlin, S.B. (2001). An energy budget for signaling in the grey matter of the brain. J. Cereb. Blood Flow Metab. *21*, 1133–1145.
32. Cherniak, C. (1994). Component placement optimization in the brain. J. Neurosci. *14*, 2418–2427.
33. Laughlin, S.B., van Steveninck, R.R.D., and Anderson, J.C. (1998). The metabolic cost of neural information. Nat. Neurosci. *1*, 36–41.
34. Laughlin, S. (1981). A simple coding procedure enhances a neurons information capacity. Z. Naturfor. *36*, 910–912.
35. Hanken, J. (1983). Miniaturization and its effects on cranial morphology in plethodontid salamanders, Genus *Thorius* (Amphibia, Plethodontidae): II. The fate of the brain and sense organs and their role in skull morphogenesis and evolution. J. Morphol. *177*, 255–268.
36. Kemp, T.S. (2009). The endocranial cavity of a nonmammalian eucynodont, *Chiniquodon theotenicus*, and its implications for the origin of the mammalian brain. J. Vert. Paleontol. *29*, 1188–1198.
37. Beutel, R.G., Pohl, H., and Hünefeld, F. (2005). Strepsipteran brains and effects of miniaturization (Insecta). Arth. Struct. Dev. *34*, 301–313.
38. Hanken, J. (1984). Miniaturization and its effects on cranial morphology in plethodontid salamanders, genus *Thorius* (Amphibia: Plethodontidae). I. Osteological variation. Biol. J. Linn. Soc. *23*, 55–75.
39. Yeh, J. (2002). The effect of miniaturized body size on skeletal morphology in frogs. Evolution *56*, 628–641.
40. Beutel, R.G., and Haas, A. (1998). Larval head morphology of *Hydroscapha natans* (Coleoptera, Myxophaga) with reference to miniaturization and the systematic position of the Hydroscaphidae. Zoomorphology *118*, 103–116.
41. Polilov, A.A. (2008). Anatomy of the smallest Coleoptera, featherwing beetles of the tribe Nanosellini (Coleoptera, Ptiliidae), and limits of insect miniaturization. Entomol. Rev. *88*, 26–33.
42. Polilov, A.A., and Beutel, R.G. (2010). Developmental stages of the hooded beetle *Sericoderus lateralis* (Coleoptera: Corylophidae) with comments on the phylogenetic position and effects of miniaturization. Arth. Struct. Dev. *39*, 52–69.
43. Maglia, A.M., Pugener, L.A., and Mueller, J.M. (2007). Skeletal morphology and postmetamorphic ontogeny of *Acris crepitans* (Anura: Hylidae): a case of miniaturization in frogs. J. Morphol. *268*, 194–223.
44. Schmidt, A., and Wake, M.H. (1997). Cellular migration and morphological complexity in the caecilian brain. J. Morphol. *231*, 11–27.
45. Kelber, C., Rössler, W., and Kleineidam, C.J. (2009). Phenotypic plasticity in number of glomeruli and sensory innervation of the antennal lobe in leaf-cutting ant workers (*A. vollenweideri*). Dev. Neurobiol. *70*, 222–234.
46. Gibson, G.A.P., Herarty, J.M., and Woolley, J.B. (1999). Phylogenetics and classification of Chalcidoidea and Mymarommatoidea - a review of current concepts (Hymenoptera, Apocrita). Zool. Scripta *28*, 87–124.
47. Farris, S.M., and Schulmeister, S. (2011). Parasitoidism, not sociality, is associated with the evolution of elaborate mushroom bodies in the brains of hymenopteran insects. Proc. R. Soc. B *278*, 940–951.
48. Strausfeld, N., and Meinertzhagen, I. (1998). The insect neuron: types, morphologies, fine structure, and relationship to the architectonics of the insect nervous system. In Microscopic Anatomy of Invertebrates, Volume 11B, Insecta, F. Harrison and M. Locke, eds. (Hoboken, N.J: Wiley-Liss, Inc.), pp. 487–538.
49. Niven, J.E., Graham, C.M., and Burrows, M. (2008). Diversity and evolution of the insect ventral nerve cord. Annu. Rev. Entomol. *53*, 253–271.
50. Roberts, A., and Bush, B.M.H., eds. (1981). Neurones Without Impulses (Cambridge: Cambridge University Press).
51. Niven, J.E., and Chittka, L. (2010). Re-use of neurons in the development, evolution and function of neural circuits in invertebrate nervous systems. Behav. Brain Sci. *33*, 285.
52. Laurent, G., and Burrows, M. (1989). Intersegmental interneurons can control the gain of reflexes in adjacent segments of the locust by their action on nonspiking local interneurons. J. Neurosci. *9*, 3030–3039.
53. Niven, J.E., and Burrows, M. (2003). Spike width reduction modifes the dynamics of short-term depression at a central synapse. J. Neurosci. *23*, 7461–7469.
54. Hall, D.H., Lints, R., and Altun, Z. (2006). Nematode neurons: anatomy and anatomical methods in *Caenorhabditis elegans*. Int. Rev. Neurobiol. *69*, 1–35.
55. Chittka, L., and Niven, J.E. (2009). Are bigger brains better? Curr. Biol. *19*, R995–R1008.
56. Eberhard, W.G. (2011). Are smaller animals behaviorally limited? Lack of clear constraints in miniature spiders. Anim. Behav. *81*, 813–823.
57. Eberhard, W.G. (2007). Miniaturized orb weaving spiders: behavioral precision is not limited by small size. Proc. Roy. Soc. B *274*, 2203–2209.

58. Seid, M.A., Scheffrahn, R.H., and Niven, J.E. (2008). The rapid mandible strike of a termite soldier. Curr. Biol. *18*, R1049–R1050.
59. Sutton, G.P., and Burrows, M. (2011). Biomechanics of jumping in the flea. J. Exp. Biol. *214*, 836–847.
60. Wehner, R. (1987). 'Matched filters' - neural models of the external world. J. Comp. Physiol. A *161*, 511–531.
61. Collett, T.S., and Land, M.F. (1978). How hoverflies compute interception courses. J. Comp. Physiol. A *125*, 191–204.
62. Mallon, E.B., and Franks, N.R. (2000). Ants estimate area using Buffon's needle. Proc. Roy. Soc. B *267*, 765–770.
63. Rundell, R.J., and Leander, B.S. (2010). Masters of miniaturization: convergent evolution among interstitial eukaryotes. Bioessays *32*, 430–437.
64. Chen, C.-P., and Chao, C.-M. (1997). Reduction of growth rate as the major process in the miniaturization of the sand dollar *Sinaechinocyamus mai*. Biol. Bull. *193*, 90–96.