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BOOK REVIEW

Geoffrey North and Ralph Greenspan (eds): Invertebrate neurobiology

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Has the molecular revolution, which began in the 1950s, over-skewed biology somewhat? In the foreword to Invertebrate Neurobiology (ISBN 978-0-87969-819-5), Geoffrey North makes clear that the editors share the view that this revolution has tended to foster the impression that the main point of biology is to elucidate molecular mechanisms. They are, however, quick to acknowledge the tremendous insights gained into fundamental processes which stem from this revolution. Indeed, the tremendous contributions made by model organisms are fully acknowledged at the outset. These include the pioneering work of Seymour Benzer and his colleagues on the behavioural genetics of *Drosophila melanogaster* resulting in the identification of genes involved in memory and circadian behaviour. The understanding of the lineage and synaptic wiring diagram of a complete nervous system and the identification of many behavioural mutants of *Caenorhabditis elegans* by Sydney Brenner and colleagues has also transformed Neuroscience. Nevertheless, the editors make the important point that for most biological phenomena, a genuine understanding is a multi-layered process—and nowhere is this more evident than in Neuroscience.

This multi-author volume on Invertebrate Neurobiology is a most welcome addition to the literature. It conveys many aspects of the current excitement in invertebrate neurobiology as well as giving due weight to non-model species. The topics range from biophysical studies on excitability through manipulation of activity in individual neurons and circuits and on to the investigation of behaviour. Appropriate emphasis is placed on the evolutionary aspects of nervous systems. This calls to mind the writings of Theodosius Dobzhansky, a butterfy and beetle collector in his youth in the Ukraine, later a pioneer of modern genetics, who entitled a much-quoted essay ‘Nothing in biology makes sense except in the light of evolution.’ Invertebrate Neurobiology targets graduate students and postdoctoral researchers and the authors have succeeded in making technically complex issues accessible to those new to the field.

It is sometimes said that Invertebrate Neuroscience is undergoing something of a renaissance and those of us working in the field are always pleased to hear such views. But maybe the field has not so much emerged from a ‘dark age’ as simply switched emphasis. As Geoffrey North points out, it is often the case that work on invertebrates is well ahead of similar work in vertebrate neurobiology. This was true in the development of neurophysiology when some key invertebrate preparations helped make major leaps in understanding. Among these preparations were the squid giant axon, so ably exploited by Hodgkin and Huxley (1952). Indeed, as Eve Marder points out in a chapter showing how invertebrate nervous systems can illuminate principles in neuroscience, the Harvard laboratory led by Stephen Kuffler in the 1950s and 1960s solved many fundamental problems using invertebrate preparations. These included the nature of the resting potential in glial cells (Kuffler and Potter 1964; Nicholls and Baylor 1969), the stretch receptor response (Kuffler 1954), electrical synapses (Furshpan and Potter 1959) and the demonstration that GABA is the neurotransmitter used by inhibitory neurons (Otsuka et al. 1966; Otsuka et al. 1967).

Other laboratories also made major advances using invertebrate preparations including the discovery of lateral inhibition (Hartline and Ratliff 1957, 1958), pacemaking mechanisms (Alving 1968). Ted Bullock and Adrian

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Horridge distilled the pioneering anatomy of invertebrate nervous systems and integrated it with current knowledge of function in their comprehensive and inspirational book 'Structure and function in the nervous systems of invertebrates'. Eve Marder's chapter contains some important lessons on the conservation and sometimes lack thereof of signalling across phyla. These subtle differences in pharmacology, at times frustrating, can however be put to excellent use. For example, striking differences have been noted in the sensitivity of insect and vertebrate GABA receptors to steroids, which are important allosteric regulators of GABA receptor function (Rauh et al. 1990, 1993). Recently Alastair Hosie and colleagues have systematically analysed and mutated residues that are candidates to account for these differences and have identified with great precision the hitherto elusive steroid binding site on human GABA receptors (Hosie et al. 2007). This discovery was undoubtedly accelerated by detailed vertebrate-invertebrate comparisons.

Eve Marder shows how small neuronal networks in invertebrates continue to provide knowledge relevant to the operation of both small and large networks. The evolutionary pressure for computational and escape speed are discussed, as well as the particular advantages in studying neural circuits provided by access to uniquely identified invertebrate neurons. Such identifiable neurons have facilitated the analysis of neuronal development, as a result of which molecules with roles in axon outgrowth have been identified. The author points out that, for many, the key challenge in neuroscience is understanding how behaviour arises from the collective action of identified neurons and their connectivity.

Todd Holmes and colleagues describe recent developments in circuit-breaking and behavioural analysis by molecular genetic manipulation of neural activity in Drosophila. With developments in gene delivery and a new range of genetically encoded sensors it is now possible to systematically modify activity in selected neuronal circuits and monitor physiological and behavioural consequences. Electrical silencing or activation of fly neurons can be achieved by expressing various ion channels. Inducible electrical activation can even be achieved by this means. Rapid electrical excitation and inhibition can also be triggered optically using the remarkable channelrhodopsin molecules. The authors make the point that through the power of reverse genetics and molecular engineering, integrative neuroscience is becoming a science of causality rather than being limited to observational and correlative enquiries. The authors also address the mapping of native channel function using dominant negative mutated channel subunits and RNA interference targeting specific ion channels. The important technical breakthrough utilising the tetanus toxin light chain, which permits controlled, targeted silencing of chemical synapses (Sweeney et al. 1995) is also discussed. Circuit modifications of the kinds described and those anticipated in the near future are likely to make major contributions to neuroscience.

Randolf Menzel has extensively explored honeybees (*Apis mellifera*), social animals with the most sophisticated community structure of all the insects. The author focuses on the electrophysiology and optophysiology of complex brain functions. This chapter deals with intracellular recording and marking, as well as extracellular recordings from multiple units and optical recordings. The author concludes that general rules of brain function can only be derived from comparative studies and shows how the rich variety of ecological adaptations, behavioural repertoires and brain structures in insects offer a unique opportunity to discover principles of brain design. To the very special advantages of behavioural complexity of these organisms (ease of access and capacity for manipulation) can now be added the complete sequencing of the genome (Honeybee Genome Consortium 2006). This will undoubtedly accelerate even further discoveries on these remarkable insects.

Leslie Vosshall provides an authoritative account of olfactory/gustatory information processing. The chemical senses of taste and smell are ancient sensory modalities that allow animals to make adaptive decisions to enhance their survival. The chapter describes olfactory and gustatory organs and compares the chemoreceptor gene families of insects and vertebrates, followed by detailed sections on odorant receptors, taste receptors and pheromone receptors. Gustatory and olfactory coding are also addressed. Interestingly, although the mechanisms that control chemosensory receptor expression and olfactory axon guidance differ between vertebrates and invertebrates, the outcome in both is remarkably similar.

Visual processing of information in insects is considered in two chapters. First, Alexander Borst and Juergen Haag describe optic flow processing in the fly. Dipterans are renowned for their acrobatic manoeuvrability, enabling them, for example, to chase mates at turning velocities of more than 3,000 degrees per second with delay times of less than 30 ms. This remarkable behaviour has triggered considerable research on both its sensory control and on the aerodynamic principles of the flight output. These authors review the current state of knowledge on neural processing of optic flow that represents one sensory component intimately involved in flight control. The work also illustrates how a fly, *Calliphora viscina*, other than Drosophila, can make major contributions to invertebrate neurobiology. Following an introduction to the fly visual system, the authors discuss the mechanisms of directional selectivity and the roles of lobular plate circuitry in optic flow processing.

In the following chapter, Eric Warrant and colleagues describe ommatidial adaptations for spectral, spatial and polarisation vision in arthropods. The authors note that 'compound eyes are the most numerous and widespread eye design on the planet', so the earth is viewed in large part through compound eyes. The authors give an account of apposition compound eyes and ommatidia, followed by photoreceptor adaptations for optimising the visual signal. Adaptations for spatial vision, effects of dark and light adaptation and colour vision are all discussed. The authors go on to show that rhabdomeric photoreceptors are intrinsically polarisation sensitive. It emerges that compound eyes are highly adaptive organs whose ommatidia have been shaped by multitudinous evolutionary pressures that arthropods experienced during their radiation into almost every conceivable habitat. Arthropods undoubtedly have a rich visual impression of their world, one that is evolutionarily matched to their ecological needs.

Daniel Robert and Ron Hoy show how, with respect to auditory systems, insects "are marvels of evolutionary engineering". They describe form and function in insect hearing which is used in tasks such as finding mates and hosts and avoiding predators. They point out that although the literature is strong on the structure, neurobiology and molecular genetics of insect hearing, our understanding of the mechanical characterisation process remains more sketchy. Indeed, insect hearing involves mechanoreception at very low energy levels: its threshold is thought to be near the level of thermal noise. This exquisite mechanical sensitivity has made the study of audition extremely challenging. The authors describe the structural diversity of insect ears and show how, as is the case in vertebrates, insect ears need to detect and encode one or a combination of three fundamental physical parameters: frequency, intensity and direction of propagation. They show how directional hearing presents particular challenges for very small animals. Active mechanisms in insect hearing are also discussed. The important contributions of Drosophila mutants are acknowledged and the authors describe in some detail the mechanical response of the antennal receiver of the mosquito, *Taxorhynchites brevipalpis*. The authors conclude that insects have an unmatched ability to make complex things happen at the small end of the biometric scale along with an awe-inspiring diversity in form and function which is providing new insights into mechanisms of hearing.

Dawn Blitz and Michael Nusbaum describe mechanosensory regulation of invertebrate motor systems. Mechanoreceptors can transduce touch, pressure sound waves from the external environment as well as internal changes such as vascular pressure, muscle stretch, muscle tension and joint position inside the body. Invertebrate model systems have made a major contribution to understanding mechanosensory regulation because they often provide better access to analysis at the level of individual identified neurones and synapses. The authors describe the ion channels that transduce mechanical energy and the neuronal coding of external space. Neuronal coding of muscle tension and length and mechanosensory regulation of motor circuits and behaviour are discussed in detail. Throughout, the authors emphasise the accessibility of invertebrate systems which provide insights ranging from subcellular events, through the cellular, circuit and behavioural levels. Although much remains to be learnt, the authors conclude that mechanosensory systems are finely tuned and extensively regulated, thereby maximising their ability to provide information to the CNS, although they make it clear that the flow of information between mechanosensory neurones and their CNS targets is not unidirectional.

Mark Frye describes the neuromechanics of fly flight control, prefacing his account by reminding us of Santiago Ramon y Cajal's observation that the insect visual system was the most magnificent and complex of the myriad systems he had seen (Cajal and Sanchez 1915). The author shows how fly flight is regulated by a massive sensory-to-motor convergence, has the highest energy requirement of any animal locomotion and supercedes even the most sophisticated human-engineered robots.

Roy Ritzmann and Ansgar Büschges note that insects are among the most agile animals on the face of the earth and show how the adaptive nature of their walking systems has contributed to their success. Insects can walk either on a tripod or by means of metachronal gait, or by using an intermediate gait between these extremes. The authors discuss local control circuits for walking pattern generation and howthe basic pattern can be modified to generate more complex movements. Changes in local circuit activity and the involvement of higher circuits are discussed along with the implications for robotics.

Paul Katz and Scott Hooper describe invertebrate central pattern generators (CPGs). The neural control for almost all neuronal movements originate in neuronal circuits called CPGs. In these, rhythmic neural outputs are produced autonomously without sensory feedback or patterned input. The authors describe CPG circuits and point out the problems associated with moving from behaviour to neural circuits and back. There are in fact very few examples of well-characterised CPG circuits. Mechanisms underlying endogenous rhythmicity, endogenous burster neurones and network oscillators are discussed. Mechanisms underlying phase relationships of complex motor patterns are examined along with the roles of synaptic properties in pattern generation. Great progress has been made in describing CPG neuron composition and synaptic connectivity, neuronal and active properties and the conductances underlying these properties in several systems. However, for no CPG has the final step of linking motorneuron activity to movement been accomplished and this represents an exciting challenge for future research.

Martin Giurfa discusses current progress in invertebrate cognition with particular reference to non-elemental learning beyond simple conditioning. He emphasises the enormous richness of invertebrate behaviour with its high flexibility and shows how invertebrates can go beyond simple forms of associative learning. Indeed, many invertebrate species have been found to solve non-linear discriminations and some can even extract rules from particular sequences of experience and transfer these rules to other sensory domains. Research addressing behavioural complexity and its underlying neural substrates is necessary to characterise the real potential of invertebrate learning and memory.

In a fascinating chapter by Catharine Rankin and Josh Dubnau, the memories of worms and flies are explored from the level of genes to behaviour. The relative advantages and limitations of the models are carefully described along with the important genes identified by the use of these model invertebrate organisms. The authors identify three major obstacles to progress in this field. First, progress is required beyond the identification of individual genes to the understanding of gene networks producing the phenotype of memory. The second obstacle is the complexity of neural circuitry, in other words understanding which genes are acting in particular neurons contributing to features of the phenotype. Finally, the greatest weakness to date has been the challenge presented by the difficulties of electrophysiology in these genetic model organisms, although recent advances in the application of this technology and the use of genetically-targeted optical probes may be fruitful.

David Glanzman in an excellent and comprehensive chapter, "Simple minds: the neurobiology of invertebrate learning and memory", points out that it has been formally recognised since the end of the nineteenth century that invertebrates can learn (Romanes 1895). He shows how a wealth of studies, mostly commencing in the 1960s, focussed on simple forms of non-associative learning, such as habituation and sensitisation. By the 1980s, associative learning, particularly classical conditioning, had been described in several invertebrate systems. The author shows that that learning and memory in the sea slug, Aplysia, depend strongly on NDMA-receptor dependent LTP and modulation of post-synaptic AMPA receptor trafficking. Results from learning studies in Aplysia therefore complement the molecular and genetic data from investigations on Drosophila and *C. elegans*. The prospect that a general molecular model for invertebrate learning and memory may soon be at hand is very exciting.

Jochen Zeil and colleagues address the ecology of visual information processing. They point out that we do not fully understand how behaviourally relevant information is processed to guide behaviour. Much of what we know about the neural basis of visual processing comes from experiments using well-defined, simple patterns. The authors make excellent use of examples based on wasp navigation and burrow surveillance in fiddler crabs. They point out that this work illustrates the benefits of "going wild" with neurobiology.

Jean-Francois Ferveur describes in detail the elements of courtship behaviour in *Drosophila*. To fully understand this process it is necessary to take into account the mutual and dynamic exchange of multiple sensory stimuli (visual, acoustic, pheromonal signals) between the two partners, both perceiving and processing these signals through nervous systems that have been shaped by their respective genotype and experience.

Mario de Bono and Marla Sokolowski provide an overview of foraging in the insect *D. melanogaster* and the nematode *C. elegans*. *C. elegans* is at the forefront of research of sensory inputs that affect foraging-related movement patterns. The fly model is also well established, encompassing behavioural and evolutionary investigations, although the neurobiology of foraging in the fly is at an early stage. Diverse molecules play roles in foraging behaviours: these include neuropeptides, molecules involved in cGMP and insulin signalling as well as molecules involved in carbohydrate and lipid detection and metabolism. A role for a cyclic guanosine monophosphate (cGMP)-dependent protein kinase (PKG) in foraging in worm, fly and honeybee suggests a degree of conservation in genes regulating this complex behaviour.

Spatial aspects of foraging in ants and bees are described by Matthew and Thomas Collett. Ants, bees and many species of wasps are central-place foragers, exploring a home range surrounding a nest and returning with finds for communal use. By and large, the greater the reliance on social over individual preferences, the more the movement patterns of the individual mirror those of the whole colony. The authors conclude that the particular balance of navigational strategies found within a species seems suited to its ecological requirements. Efficient foraging arising from a flexible range of navigational strategies, both individual and communal, is part of the reason why social insects have enjoyed evolutionary success with diverse ecological niches.

Circadian rhythms and sleep is an exciting topic with considerable interest for human as well as invertebrate biology. Circadian behaviour is now one of the best-understood behaviours and the fruit fly Drosophila has led the way in elucidating mechanisms that drive human circadian rhythms; this forms the substance of a chapter by Amita Seghal and Ravi Allada. Exciting developments for the future include understanding how signals from the molecular clock are translated to produce rhythmic behaviour. With respect to sleep, the fly model is yielding important insights.

Bill Kristan and Rhanor Gillette discuss behavioural choice and the neural mechanisms involved in making such choices. They show that the network mechanisms for choosing one particular behaviour over another in sea-slugs and leeches are surprisingly similar. Interestingly, the simplest circuit mechanism—inhibition among command neurons—is not the one used. Instead, neurons used in two or more behaviours are activated to produce different behaviours.

John Ewer describes the neuroendocrinology of eclosion. This is the process of adult emergence, in which the insect sheds the remains of the old exoskeleton from the previous immature stage and commences its adult life. The underlying physiological changes are caused by a number of interacting neuropeptides, the release of which is triggered by the ecdysis triggering hormone (ETH). The author identifies opportunities for future studies involving RNA interference to address the roles of peptides such as eclosion hormone (EH) and crustacean cardioactive peptide (CCAP) in ecdysis.

Robert Meech and George Mackie address the evolution of excitability in lower metazoans. They examine the different manifestations of excitability shown by the Metazoa and illustrate how elements present in bacteria come together in the Protozoa, Porifera, Cnidaria and Ctenophora to form patterns of excitability known as behaviour. The excitability exhibited by the lower Metazoa seems to originate in the graded electrical signals of the protozoa and the all-or-nothing propagated action potentials in the non-nervous glass sponges. Calcium channel inactivation, already present in the Protozoa to prevent overload, stops a propagating impulse going back on itself. With the appearance in the Cnidaria of excitable epithelial canals and specialised nerve axons, impulse propagation changes from a non-directional spread of excitation to a direct point-to-point transmission of information. Calcium-dependent impulses largely give way to sodium-dependent action potentials, whose sole function is to transmit information at the greatest speed. Fascinatingly, the lower metazoans provide many model organisms in which the integrative processing that goes on deep within the vertebrate central nervous system is carried out in the periphery, where the links between molecular evens and whole-animal behaviour are direct and accessible.

Finally, Rodolfo Costa and colleagues address evolution of behavioural genes with a particular focus on genes involved in sex and circadian rhythms. The authors discuss homologues, orthologs and paralogs in the circadian clock, protein predictions and clock evolution as well as the 'evo-devo' of the clock. Functional genetic variation within species is also discussed. The authors conclude that Drosophila will play a key role in our understanding of the molecular basis of evolutionary change in behavioural phenotypes. They also express optimism that future studies on insects such as bees, silkworm and monarch butterflies may soon begin to contribute to our understanding of how genes, whose roles are understood in fly behavioural phenotypes, have been recruited during the evolution of more complex phenotypes .

The 'afterword' by Ralph Greenspan considers universality and brain mechanisms and the important opportunities still offered by research on invertebrate studies. The transition from a wave of key studies taking advantage of 'ideal' physiological preparations, through the era focusing on the worm and fly genetic model organisms is noted. The potential liberating effect of the advent of many new genome sequences making molecular analysis and manipulation applicable to a much wider range of organisms is noted. This coincides with an expanding repertoire of new physiological and imaging techniques and together they are likely to open the door to a fascinating new era of exploration. Overall this is an excellent and timely volume and one the targeted audience should enjoy immensely.

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