Patrik Krieger · Alexander Groh *Editors*

Sensorimotor Integration in the Whisker System

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Chapter 1
Introduction

Alexander Groh and Patrik Krieger

Abstract Sensation in animals and humans is often an active process that involves motion, e.g., moving fingers on a textured surface and eye movements. In this dynamic process, motion and sensation are strongly interdependent: internal motor information is needed to interpret external sensory signals, and sensory information is used to shape appropriate behavior. This book explores the neural mechanisms underlying sensorimotor integration that allow the sensory and motor systems to communicate and coordinate their activity. Studying the rodent whisker system has tremendously advanced our understanding of sensorimotor integration in mammals and is the focus of this book. In ten chapters, written by leading scientists, we present important findings and exciting current directions in the field.

Keywords Sensorimotor integration · Whisker system · Somatosensory barrel cortex · Shrew · Thalamus · Central pattern generator · Whiskered robot · Neuromodulator · Connectivity

Analyzing the neural mechanisms underlying sensorimotor integration requires a model system that allows well-defined sensory stimulation and simple readouts of motor output. The rodent whisker system fulfills these criteria and in addition offers transgenic approaches that can be used, in particular in mice to dissect functional units underlying touch perception. The facial whiskers are tactile organs used to identify and locate objects, similarly to how humans use fingers to explore texture and shape of objects. The chapters in this book describe how animals use tactile sensory organs—whiskers in rodents and shrews—in behavioral tasks and describe how data on whisker kinematics can be used to understand the nature of the sensory data that is collected in order to initiate a motor program. Furthermore, data on the

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role of cortical and sub-cortical brain areas in linking sensory perception and motor control are discussed.

One feature of the whisker system which is often highlighted is the striking one-to-one correspondence between the peripheral whisker pad and corresponding brain areas in the brainstem, thalamus and the somatosensory barrel cortex. The fact that there is a strong link between structural and functional properties—you can "see" the circuit—is experimentally advantageous. However, it is noteworthy that cortical barrel column are not always present in animals with whiskers, e.g., shrews. Understanding tactile information processing should thus be done using a combination of species, each with its peculiar specialization. One such comparison is made in Chap. 2 where tactile exploration is studied in water shrews, star-nosed moles and the eastern mole. Accompanied by outstanding photography the authors take us on a journey into the world of water shrews, which use their whisker to detect prey, and the star-nosed mole, which uses a different type of tactile sensory organ. Like rats and mice, water shrews have an exquisitely specialized whisker system used to explore their environment, but the central representation of whisker input is different in the neocortex. Moles on the other hand don't have whiskers but rely on specialized skin surfaces. Similar to the barrel system, there is a somatotopic map connecting the sensory skin receptors with brain modules. The chapter also touches on a behaviorally relevant integration of touch and smell (further explored in Chap. 7), used by the eastern moles for food localization. Comparing tactile information processing in different species provides different examples of modular brain maps. Furthermore, incorporating the concept of a "sensory fovea" the authors show parallels between somatosensory, visual, and auditory systems. A structure-function subdivision of the whisker system includes the mechanoreceptors in the hair follicles that transmit sensory information to the brainstem, and from the brainstem information is transmitted to the thalamus. Chapter 3 describes the physiological properties of the whisker thalamus, in particular the ventral posterior medial thalamus (VPM). The chapter discusses in detail how thalamic responses are influenced by sensory, cortical, inhibitory (from reticular nucleus of the thalamus) and modulatory (brainstem) afferents. Furthermore, the chapter discusses how low- and high-frequency sensory inputs are differentially processed depending on the operational mode of the thalamic cells, and it is shown how these operating modes are affected by neuromodulators (see also Chap. 11), in particular cholinergic and noradrenergic modulation. The chapter furthermore raises many interesting questions regarding similarities and differences in brainstem versus cortical modulation of thalamic activity.

The somatosensory barrel cortex is the first cortical station for the whisker input. The barrel cortex is a prototypic neocortical area with its vertical columnar organization and its six layers, each layer thought to make different contributions to information processing. The barrel columns are defined based on the visible "barrel" pattern in layer four. The intricate circuitry of the somatosensory barrel cortex has been mapped in great detail using paired/multiple whole cell recordings in the brain slice. This wealth of data is reviewed in Chap. 4, with data on anatomical and functional properties of monosynaptic connections. Although the authors structure their

review on the concept of an easily defined cortical column, they also give evidence that emerging data challenges a too simplified model of how information is transmitted within and between columns. In particular there is a lack of data on inhibitory connections and how the translaminar connectivity fits with the columnar module. The previous chapters presented the thalamocortical circuitry that is underlying the sensory "aspects" of the whisker system. Chapter 5 focuses on mechanisms behind cortical processing of touch and its relation to long-range projections to motor cortex. A further emphasis is on imaging techniques that have tremendously advanced our knowledge about sensory processing in the cortex. The authors also show how the use of genetic tools, including genetically encoded calcium or voltage indicators, can be used to answer key questions in neuroscience. For example, using these methods, in particular using in vivo two-photon calcium imaging, the authors show how somatosensory and motor areas interact. Furthermore, with a focus on studies using two-photon calcium imaging it is shown how the spatial-temporal dynamics of cortical representation whisker information processing. Chapter 6 explores the transformation of tactile information into behaviour via activation of the whisker motor cortex. Evidence is presented showing that the whisker motor cortex can be sub-divided, both structurally and functionally, into modules each having different functions. In addition the authors discuss how whisker movements occur as a result of interactions between cortical command signals with sub-cortical central pattern generators (CPG). Whereas the whisker representation in the somatosensory cortex shows the characteristic barrel pattern, the equivalent topographic representation in the vibrissal motor cortex has not been found. The motor cortex is suggested to contain a motor map rather than a map of the whisker pad, such that more or less complex motion programs are elicited by activity in different areas of the motor cortex. The encoding of whisker deflections is thus rather "diffusely" represented in the motor cortex such that different sensory experiences activate a behaviourally appropriate whisker movement pattern. Chapter 7 summarizes recent evidence for a brainstem central pattern generator (CPG) for rhythmic whisking. Importantly, whisking, breathing, sniffing and possibly locomotion are controlled by this CPG, suggesting a common "master clock" for rhythmic behaviors. From a functional perspective it appears that a coordination of whisking and sniffing, in addition to being advantageous in regard to activating common facial musculatures, can provide a mechanism by which spatial information from the whisker movements can serve as a spatial map. This mechanism in addition to binding the sensory events to one object, can provide information on where in space the odor is coming from.

In previous chapters "Information processing" is discussed in terms of the evoked spike trains analyzed either directly using electrophysiology or indirectly using imaging techniques to visualize changes in voltage or calcium as readout of cortical spiking activity. In Chap. 8 a more theoretical approach is outlined where the computations underlying the encoding of physical parameters by the mechanoreceptors, the further transmission of this information along the sensory system to cortex, and ultimately the transformation of the tactile information into behavior. An emphasis is on the importance of studying whisker movements and the forces exerted on the whisker follicle when the animal uses the whiskers to touch objects

and explore textured surfaces. The chapter furthermore explores how sensory processing can be understood in terms of concepts such as “adaptive representations”, and “population coding”. In Chap. 9 the whisking system is considered as a “closed-loop” which cannot be strictly divided into exclusive “sensory” or “motor” areas. Building on this concept the authors present a model of object localization that describes the process as an interaction of phase-locked loops. As a complement to the previous chapter, the authors also discuss in more general terms the different coding schemes that are likely employed by the whisker system. Modelling tactile information processing using a robotics’ approach the authors of Chap. 10 show how a biologically inspired robot can mimic relevant aspects of active touch behavior. The authors model several features of tactile information processing, including how interactions between cortex and sub-cortical structures are import for decision-making based on tactile input. The whiskered robot is not only designed to replicate touch behavior, but rather also made such that experimental observations of how the robot behaves, and the constraints put on behavior by the brain architecture, can provide understandings into the biology. Based on such observations the authors discuss, e.g., the hypothesis for how cerebellum is involved in tactile information processing. The chapter thus tries to answer the question: Does our current knowledge about sensorimotor integration suffice to engineer a robot that is capable of tactile based behavior?

Chapter 11 summarizes how the sensorimotor circuitry is modulated by monoaminergic neuromodulators: serotonin, dopamine and norepinephrine. The release of these neuromodulators during embryonic development and early post-natal development are shown to be important for neural circuit development. An abnormal neuromodulation early in development is shown to have long-lasting consequences that can underlie individual differences in the development of the somatosensory circuitry. The projection pathways from brainstem areas to cortex are described and data presented how alterations in specific projection pathways affect the cortical circuitry and ultimately behavior. In an outlook chapter the authors discuss how these differences in neuromodulation could be linked neurodevelopmental disorders.

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Part I
Whisker System in Mammals

Chapter 2
Comparative Studies of Somatosensory Systems and Active Sensing

Kenneth C Catania and Elizabeth H Catania

Abstract Comparative studies of diverse species provide a wealth of information about active touch and corresponding brain specializations in the somatosensory system. Here the results of numerous studies of brain and behavior in shrews and moles are reviewed and discussed. Water shrews have elaborate whiskers and can detect prey based on both texture and movement. In contrast to rodents, shrew whiskers are not reflected by barrels in the cortex, but are reflected in the brainstem by prominent barrelettes. Although shrews have a simpler cortical anatomy than rodents, star-nosed mole's cortices are more complex, with three histologically visible and interconnected cortical maps that reflect the nasal rays on the contralateral star. One ray of the star is used as the tactile fovea, and is greatly over-represented in the neocortex. This finding highlights similarities between specialized somatosensory, visual, and auditory systems—each of which may have a sensory fovea for high resolution sensory processing. Both water shrews and star-nosed moles exhibit the remarkable ability to sniff underwater by exhaling and reinhaling air bubbles as they forage. This allows visualization of sniffing during natural behaviors and provides a unique window into the behavioral integration of touch and smell. Finally, eastern moles have the least specialized set of mechanoreceptors but exhibit remarkable olfactory abilities using stereo nasal cues—in conjunction with touch—to efficiently locate prey. These results highlight the many insights that may be derived from specialized model animals.

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Keywords Tactile · Touch · Olfaction · Smell · Stereo · Mechanosensory · Barrel · Barrelette · Whisker · Brain Evolution · Shrew · Mole · Neocortex · Trigeminal · Behavior

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Introduction

Investigations of sensory and motor specialists have provided many key insights into brain organization, function, and evolution. Perhaps the best-known example of this strategy is Hodgkin and Huxley's landmark studies of the giant axon that mediates escape responses in squid, which revealed the ionic basis of action potential conduction [1, 2]. Some other well know examples include studies of barn owls for understanding the neural basis of auditory localization based on coincidence detection [3–5], the use of electric fish for determining the neural basis of rhythmic signaling, jamming avoidance, and animal communication [6, 7], and the study of songbirds for determining the plasticity of networks mediating social learning [8–10]. In a similar way, the specialized whisker-barrel system of rodents has been particularly useful for understanding the neural basis of touch because rodents have an elaborate somatosensory system and at the same time they share many features in common with other mammals. Most importantly, they have a neocortex with somatosensory areas that are homologous to the somatosensory areas found in nearly all other mammals including humans [11]. This homology from mouse to man allows inferences about basic cortical circuitry to be more confidently extended to a wide range of other mammal species. But the key technical advantage of the rodent system was the discovery of histologically visible units, or barrels, in the primary somatosensory system of mice [12] and subsequently rats [13]. The later discovery of similar barrel-like subdivisions at the thalamic [14] and brainstem [15] level (barreloids and barrelettes, respectively) added another dimension to the system, providing the advantages of "visible" whisker maps in the entire pathway from mechanoreceptors to primary somatosensory cortex. These findings greatly facilitated subsequent investigations of neuronal electrophysiology, connectivity, development, and plasticity. More recently these studies have been integrated with detailed behavioral and biomechanical studies, providing one of the most comprehensive views of brain and behavior for any mammalian species.

At the same time that our understanding of rodents' somatosensory systems have been expanding, advances in the technique of flattening cortex by carefully removing underlying white matter before compressing the cortical hemispheres have provided ever more clear views of the histological patterns in layer 4 cortex in diverse species. This includes the discovery of whisker related barrels in numerous rodents, marsupials, and insectivores. Modules representing alternating electrosensory and mechanosensory inputs have been described in the cortex of the duck-billed platypus [16] and stripes corresponding to nasal appendages have been identified in both S1 and S2 of the star-nosed mole [17, 18]. In the case of primates, myelin-dark modules representing individual fingers have been described in the hand area of area 3B [19, 20]. The latter finding suggests that similar mechanisms may segregate cortical (and subcortical) inputs from discontinuous sensory surfaces into modules during development in diverse species, ranging from rodents to primates.

Clearly there is a rich source of diversity for revealing general principles of brain organization and development by examining a range of different mammalian somatosensory systems. In this chapter we will provide an overview of the brains

and behavior of the water shrew, the star-nosed mole, and the eastern mole. Each of these species is differently specialized in a manner that illuminates a particular facet of sensory biology. Like rats and mice, water shrews have an exquisitely specialized whisker system used to explore their environment. Yet, despite sharing similar mechanoreceptors (whiskers) the central representation of those receptors is strikingly different in the neocortex. Moles on the other hand are also touch specialists, but instead of whiskers they rely on specialized skin surfaces to explore their environment. As in the barrel system, the nasal appendages of star-nosed moles are reflected at cortical and subcortical levels by modules isomorphic with the sensory surface. But in this case, they appear as stripes rather than traditional columns and their sizes reflect the differential behavioral importance of different sensory appendages. This species provides an additional example of modular, visible brain maps and illustrates parallels between high-resolution somatosensory systems, visual systems, and auditory systems. Finally, eastern moles have recently been shown to integrate their somatosensory exploration with the use of bilateral comparisons of olfactory cues (stereo smell) for food localization. Together these insectivores demonstrate a wide range of peripheral mechanoreceptors, diverse cortical representations, and interesting behaviors.

Water Shrews—Variations on a Theme

Figure 2.1 shows a predatory grasshopper mouse (*Onychimys leucogaster*) alongside of a water shrew (*Sorex palustris*). These two species nicely illustrate some of the commonalities and differences in anatomy and brain organization found among mammals. First, we should point out that water shrews are not rodents, they are part of the historical order Insectivora that includes moles, shrews, hedgehogs, and solenodons. Thus, despite appearances, shrews are only very distantly related to rodents. Like all other shrew species, the water shrew is a predator. The grasshopper mouse, on the other hand, is a rodent, albeit it has the distinction of being one of the few predatory rodent species. Both species use their elaborate whiskers in active touch as they identify prey and guide attacks on fast moving and sometimes dangerous invertebrates (grasshopper mice feed on scorpions). Yet despite this similarity in form and function, the cortical representation of the whiskers is very different between these two small mammals.

The flattened juvenile neocortex of the grasshopper mouse (Fig. 2.1c), labeled in this case with the serotonin transporter antibody, appears much like that of other rodent species similarly prepared. It has a patently visible primary somatosensory cortex (S1) containing subdivisions that can be very easily recognized as representing the same body parts that are visible in cortex of laboratory rats and mice. This includes a barrel pattern that clearly reflects the prominent facial whiskers. In contrast, the juvenile water shrew neocortex (in this case processed for the metabolic enzyme cytochrome oxidase (CO)) contains a prominent whisker representation (see [21] for physiological recording data), but no obvious barrels representing the

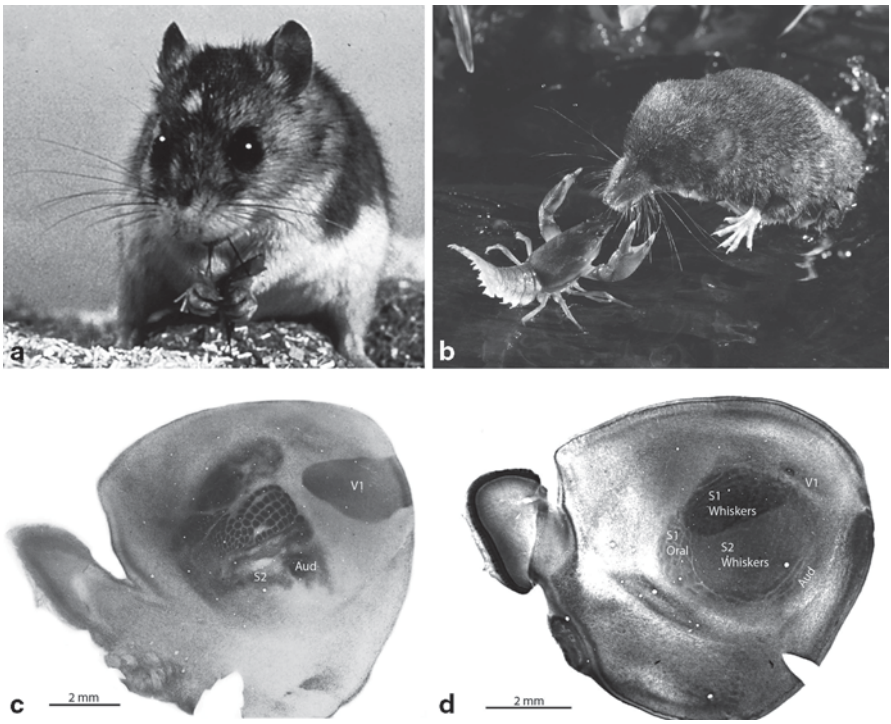

Fig. 2.1 Comparison of a rodent and an insectivore. Although the grasshopper mouse (**a**) and the water shrew (**b**) are both predatory and locate prey using whiskers, they have very different sensory cortices. (**c**) The flattened cortex of the grasshopper mouse shows very prominent cortical barrels (*dark circles* labeled with the serotonin transporter antibody) and large primary visual and auditory areas. (**d**) The flattened cortex of the water shrew shows a large somatosensory cortex with two large whisker representations, but there are no visible barrels. Note also the very small areas of sensory cortex devoted to vision and olfaction in (V1 and Aud, respectively). Data in (**b**) from [61]. Data in (**d**) from [26]. Photo in (**a**) by Jan Decher. (Abbreviations: *Aud* auditory, *V1* primary visual cortex, *Oral* oral). (Published with kind permission of © Kenneth Catania and Jan Dreher 2014)

large facial whiskers (Fig. 2.1d). Why this striking difference in brain organization between physically similar animals with otherwise similar peripheral anatomical features? The answer is not clear, but additional aspects of water shrew behavior may provide some clues.

Water Shrew Senses

Water shrews are adept predators that forage primarily at night along the sides of streams and ponds in North America. It seems remarkable that these animals, the world's smallest mammalian divers, can make a living and avoid predators using

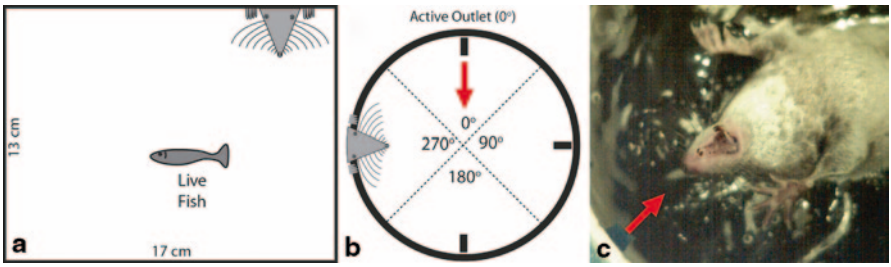

Fig. 2.2 Water shrews detect motion and can capture prey in water without the use of vision. **a** Schematic illustration of the chamber used to examine the foraging efficiency of water shrews capturing live fish under either full spectrum lighting or infrared lighting. Shrews were filmed with a high-speed camera. Shrews were equally efficient under both lighting conditions. **b** Schematic illustration of the chamber used to test responses to brief water pulses simulating escaping fish. Shrews attacked the water motion with a short latency. **c** Frame captured from high-speed video showing a shrew attacking the water motion in the absence of prey. (Published with kind permission of © Kenneth Catania 2014

this foraging strategy, and it is natural to wonder about the relative contribution of their different senses to this activity. Figure 2.1 (c and d) provides an important and obvious clue to the sensory priorities of this species. In contrast to the grasshopper mouse, water shrews have tiny eyes. This anatomical feature is in turn reflected in their neocortex. Water shrews have a very small primary visual area (V1) compressed to the far caudal and dorsal aspect of the hemisphere. Somatosensory cortex appears to have "taken over" much of the cortical territory. Though this last interpretation is almost certainly backwards. Because shrews resemble ancestral mammals in many respects [22], it is more likely that visual cortex in rodents has "taken over" territory that was once somatosensory during the course of evolution. In any case, visual cortex is very small in water shrews, and the same is true for auditory cortex at the more caudal and lateral extreme of the hemisphere (see [21] for shrew electrophysiology). The latter observation is of interest because it has been suggested that some shrews may echolocate [23, 24]. This would be surprising in the case of water shrews, as auditory cortex is very small. Indeed, experiments show water shrews do not use echolocation [25]. In concordance with these observations, counts of cranial nerve number in water shrews reveal a tiny optic nerve (6000 fibers) and an equally small auditory nerve (7000 fibers). In contrast, the trigeminal nerve carrying information from the whiskers contains 27,500 fibers—similar in size to that of laboratory mice [26].

To investigate water shrew behavior and the possible contribution of vision in foraging, shrews were offered live fish in a small chamber under either full spectrum lighting or infrared lighting (Fig. 2.2a). Shrews were very efficient and equally fast at capturing fish under both conditions, demonstrating that vision was not required for this behavior. Many fish were captured in less than one second from the time the shrew entered the water [25]. Slow motion analysis of water shrews capturing fish suggested that water motion generated by fish escape responses might be an important cue used to identify the location of prey. To further investigate this possibility,

water shrews were presented with very brief, periodic pulses of water in the absence of prey and filmed with high speed video. This paradigm was designed to simulate the brief water disturbance caused by an escaping fish. The results clearly showed that water shrew attacks were triggered by brief water movements (Fig. 2.2b, c). In addition to illustrating that water shrews may use prey escape responses for localization, the experiments further highlight their reliance on somatosensation, rather than vision, as the water movements were not visible [25]. Finally, water shrews were incredibly fast, attacking the stimulus with a latency of only 20 milliseconds (from stimulus to initiation of attack).

The experiments described above highlight the strategy shrews use to locate active prey, but shrews also feed on many immobile invertebrates. To investigate their responses to shapes and textures, rather than just movement, water shrews were presented with simulated, highly detailed caste silicone fish, along with a series of rectangular and spherical shapes as distractors (Fig. 2.3a). Even in the absence of visual or olfactory information the shrews were dramatically successful at choos-

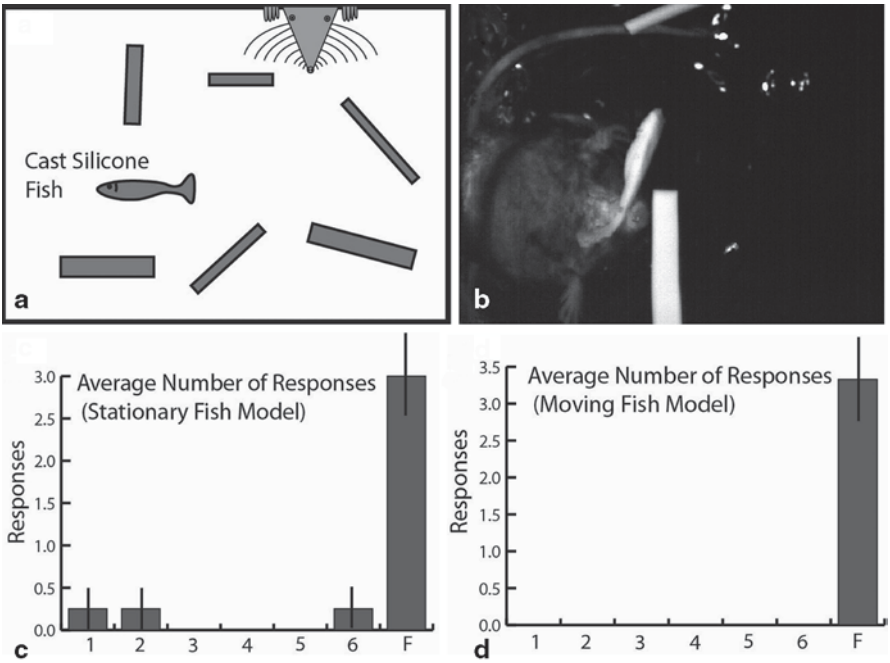

Fig. 2.3 Water shrews use their whiskers to detect texture/shape of objects. **a** Schematic illustration of the chamber used to test water shrews' ability to detect an object without olfactory or visual cues. Three silicone rectangles and three silicone cylinders were placed in the chamber, along with a silicone model fish. **b** A water shrew attacks and grabs a silicone fish under infrared lighting. Shrews often took the model fish back to their home cages. **c** Graph showing the average number of times over 4 trials that each of 4 shrews bit either a distractor object (1–6) or the model fish "F". **d** Graph showing the average number of attacks (retrieving, biting or lunging with open mouth) for each moving object for 3 shrews over 4 trials. Objects were moved with a magnet under the chamber. (Published with kind permission of © Kenneth Catania 2014)

ing the silicone fish over the similarly sized silicone shape models (Fig. 2.3c). This demonstrated that water shrews cannot only detect movements, but they can also use their whiskers to identify objects via shape and texture. As might be expected, with no reward for retrieving inedible silicone fish, the shrews soon stopped capturing these imposters. But if caste fish were made to move (by placing a small piece of metal in them and moving them with a magnet) the water shrews' responses were resurrected and they again attacked the silicone fish in preference to the other objects. Together these results show the value of both movement and shape in eliciting attacks (Fig. 2.3d). This seems appropriate, given that small prey hidden in the shallow water along streams and ponds would be expected to exhibit distinctive shapes and textures and some would also be likely to move (e.g. escape responses of fish and crayfish, for example). Other shrews have also been shown to use prey shape as an important criterion for predatory attack [27].

Underwater Sniffing

As suggested by their anatomy, behavioral experiments indicate that water shrews depend heavily on their whiskers to locate prey while foraging. Yet their speed and efficiency raise the possibility that other senses might be involved. As described previously, there was no evidence for the use of echolocation or sonar. In addition, we tested for the ability to detect electric fields, both in terms of behavioral responses and by surveying the skin surface of the head to detect potential electroreceptive organs. There was no evidence for electroreception in terms of behavior or peripheral anatomy. However, water shrews were able to use olfaction in a very unique way. When searching for prey while submerged, they emitted air bubbles from their nostrils that spread over objects they were exploring and then re-inhaled the same air (Fig. 2.4).

This behavior was remarkable, because it had all the characteristics of sniffing, but occurred underwater (the behavior was first observed in semi-aquatic star-nosed moles, see later section). To investigate this further, shrews were trained to follow a scent trail underwater in a two choice test. They were very proficient at following the trail as long as the emitted air bubbles could make direct contact with the scent trail they were following [28]. When the air bubbles were blocked with a stainless steel grid, the shrews' performances dropped to chance, despite the close proximity of the scent trail. This form of underwater sniffing seems to require direct contact of the air with odorants to provide relevant information.

Water Shrew Brainstem—Barrelettes without Barrels

When first investigating the neocortex of shrews [21] one of our interests was determining whether this lineage of mammals exhibited cortical barrels. Five different shrew species (including water shrews) were examined using eletrophysiological

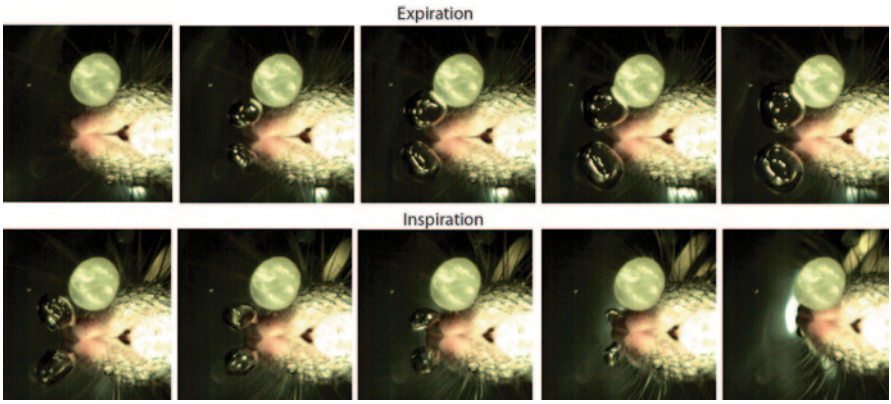

Fig. 2.4 Ten frames taken from high-speed video showing a single underwater sniff by a water shrew. In this case the shrew is sniffing a small piece of wax. The animal has paused during its movements and expires air (*upper row*) that comes in direct contact with the object. This air is then re-inhaled (*lower row*). Using this strategy, water shrews can follow a submerged scent trail. (Published with kind permission of © Kenneth Catania 2014)

mapping with dense microelectrode penetrations combined with subsequent analysis of flattened cortical sections processed for CO. The primary (S1) and secondary (S2) somatosensory areas were both identified. S2 was larger in shrews compared to most other mammal species that have been investigated, taking up roughly the same amount of neocortex as S1 and being characterized by neurons with relatively small receptive fields. As expected from shrew behavior and the cranial nerve counts described above, both S1 and S2 were dominated by large representations of the whiskers from the contralateral side of the face. The S1 representation of the whiskers was visible by a CO dark wedge of tissue in most species. The S1 whisker representation was most obvious in the smallest shrew species (the masked shrew, Sorex cinereus) [21]. But in no case, for any species, were cortical barrels apparent.

As is familiar to most investigators of small mammal cortical histology, cyto- and chemoarchitectural borders and modules such as barrels are usually more apparent in juvenile animals than in adults. When water shrews fortuitously gave birth in the lab, we once again examined somatosensory cortex, this time in juveniles [26]. The goal was to specify borders between areas in greater detail for these unique species and to search once more for cortical barrels that might be evident at early stages of development but later obscured. We were successful at more clearly delineating borders of sensory areas and even numerous subdivisions representing body parts, especially the large, S1 whisker representation marked by the wedge of CO dark tissue. But, once again, we concluded there were no cortical barrels apparent even at juvenile stages of cortical development [26].

With these previous investigations in mind, we were surprised to later discover in the juvenile water shrew brainstem [29] perhaps the clearest and most prominent barrelettes yet observed in a mammal (Fig. 2.5b, c, d). Barrelettes were apparent in the principle nucleus (PrV), the interpolar spinal trigeminal nucleus (SpI), and the

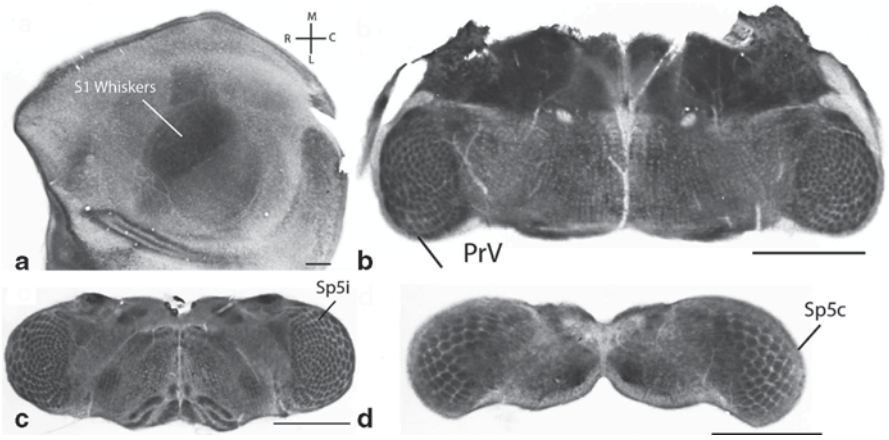

Fig. 2.5 Water shrews have barrelettes without barrels. (**a**) Flattened juvenile water shrew cortex processed for cytochrome oxidase and showing the large whisker representation devoid of barrels. (**b**–**d**) Prominent barrelettes are visible in trigeminal sensory nuclei: (**b**) the principle trigeminal nuclei (PrV), (**c**) the interpolar spinal trigeminal nucleus (SpI) and (**c**) the caudal spinal trigeminal nucleus (SpC) of juvenile water shrews. Scale = 0.5 mm. (Published with kind permission of © Kenneth Catania 2014)

caudal spinal trigeminal nucleus (SpC). Barrelettes were apparent in adult water shrew brainstem as well, though (as is the case for rodents) they were slightly less clear than in juveniles. Injection of anatomical tracers into the adult water shrew whisker pad indicated that barrelettes in shrews, as in rodents, reflect the selective aggregation of afferent terminals from the whiskerpad [29].

These findings highlight the different ways that whiskers can be represented in diverse mammals. In rodents, cortical barrels representing the whiskers are the most obvious, whereas trigeminal barrelettes and thalamic barreloids are much less clear. In contrast, trigeminal barrelettes in water shrews are strikingly clear despite the absence of barrels at the cortical level.

Star-Nosed Moles

Olfaction might be the first thing that comes to mind when one considers a star-nosed mole (*Condylura cristata*). In fact, recent studies show that star-nosed moles and their relatives have impressive olfactory abilities, but the star is a tactile organ, not a chemoreceptor. It consists of 22 epidermal appendages that ring the nostrils in 11 symmetric pairs (Fig. 2.6a). Each appendage, or "ray" is covered with many hundreds of small epidermal domes called Eimer's organs (Fig. 2.6b). Together they are innervated by over 100,000 myelinated nerve fibers, giving this skin surface, which is only about a centimeter across, the highest innervation density of any known skin surface. Eimer's organs are a characteristic feature of mole nasal epidermis

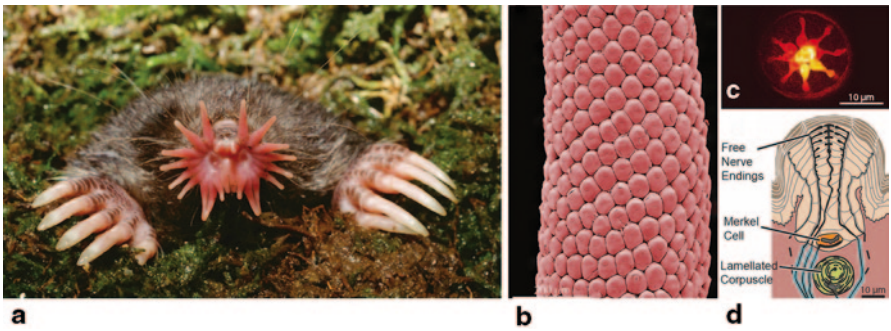

Fig. 2.6 Anatomy of the star. **a** Star-nosed moles have an impressive epidermal specialization on their nose consisting of 22 appendages (rays) that surround their nostrils. **b** Each ray is covered with small domes called Eimer's organs that are densely innervated. **c** Top view of nerve endings in a single Eimer's organ visualized with DiI. The star has the highest innervation density of any known skin surface. **d** Each Eimer's organ contains a Merkel cell-neurite complex, a lamellated corpuscle, and free nerve endings. (Published with kind permission of © Kenneth Catania 2014)

and are found on the skin of almost all of the nearly 30 different mole species [30]. But only the star-nosed mole has evolved nasal rays that increase the surface area of the sensory epithelium providing room for 25,000 Eimer's organs. Evolution of this delicate structure could probably only occur in the star-nosed mole's wetland environment, a unique habitat for moles, and this at least partially explains why no other mole has such an elaborate and fragile snout. Because the star is essentially made of Eimer's organs, knowing the function of these structures is fundamental for understanding the star.

Function of Eimer's Organs

Eimer's organs were first described in the 1800s by Theodor Eimer in the European mole [31] and they were subsequently found on each mole species that was investigated with the exception of the eastern mole (*Scalopus aquaticus*) [32]. Most investigators concluded that Eimer's organs must have a mechanoreceptive function based on their anatomy and mole behavior. Each organ is associated with Merkel cell-neurite complexes, lamellated corpuscles, and free nerve endings (Fig. 2.6c, d) [33–35]. In addition, moles repeatedly touch the skin surface containing Eimer's organs to objects or prey as they explore their environment and search for food. More direct evidence for a mechanosensory function comes from electrophysiological recordings from the somatosensory cortex [17, 18], from afferents supplying Eimer's organs [36], and from findings in the principle trigeminal sensory nucleus (PrV) [37].

The first direct evidence of Eimer's organ responses came from electrophysiology recordings in the somatosensory cortex of star-nosed moles [17, 38]. Multi-unit

receptive fields were extremely small and often had to be defined with the aid of a microscope. Even so, the lower limit of receptive field size was probably not determined given the limitations of manual stimulation of the skin surface. Nevertheless receptive fields on the star were well under a millimeter in diameter in some areas. Even at this early stage of investigations, there was an evident trend in relative receptive field size with the smallest receptive fields located on the midline and ventral parts of the star and larger receptive fields found for the more lateral parts of the star (see next section for correlations with behavior). Single unit analysis revealed that roughly half of cortical neurons were inhibited when areas just outside their excitatory receptive fields were stimulated—i.e. they demonstrated surround inhibition.

Later recordings from primary afferents in both star-nosed moles and coast moles provide additional evidence for Eimer's organ function [36]. Three different response classes were evident in both species using either a dedicated Chubbuck mechanosensory stimulator [39] or a piezo bending element stimulator. These responses consisted of a Merkel-like response with sustained volleys of action potentials having variable interspike intervals, a Pacinian like response that was evident only at the onset and offset of skin depression (stimulation), and a rapidly adapting response that was directionally sensitive to a sweeping motion across the skin surface [36]. These responses were consistent with the three receptor classes associated with each Eimer's organ. The most interesting response was the directionally sensitive afferents that suggest a roll for Eimer's organs in detecting minute surface features on objects and prey items in the moles' environments [36].

Stars and Stripes in the Brain

When considered in light of the whisker-barrel system of rodents, the anatomy of the star -with its separate appendages, dense innervation, and high concentration of mechanoreceptors—raised the possibility of corresponding cortical modules that separately represent each appendage. To investigate this possibility, star-nosed mole neocortex was mapped using dense microelectrode penetrations followed by anatomical analysis of layer 4 cortex processed for CO [18]. In addition to providing the initial evidence for Eimer's organ function described above, the results of electrophysiological recordings revealed the layout of the star appendages and other body parts in neocortical maps. Three separate representations of the star were identified in lateral cortex, corresponding to the expected location of the face representation in mammals generally (Fig. 2.7a). When the neocortex was flattened and sectioned tangentially, in the same manner that reveals barrels in rodents, each of the three maps of the star was visible as a pinwheel of CO dark stripes (Fig. 2.7c). Not only did this result represent an additional example of distinctive modules in primary somatosensory cortex reflecting the distribution of mechanoreceptors on the face, but it was also the first (and only) demonstration of multiple visible maps representing the same sensory surface. Subsequent investigation of these areas us-

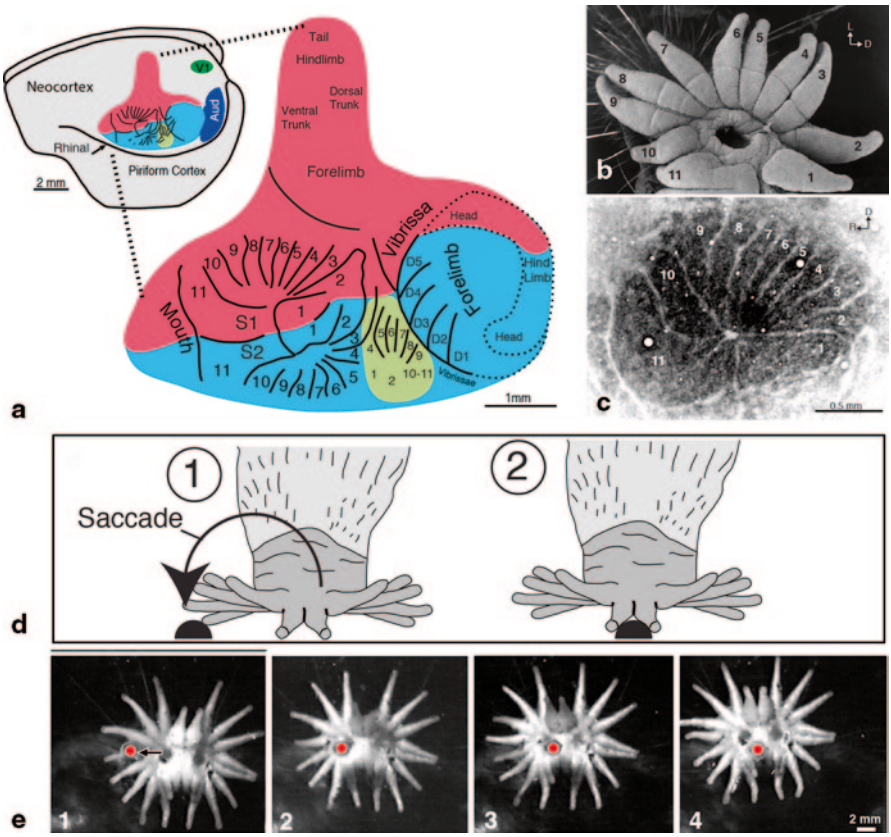

Fig. 2.7 Cortical organization and behavior in the star-nosed mole. **a** Three maps of the contralateral star exist in somatosensory cortex (S1, S2, and S3). The S2 map of the star-nosed mole is comparatively large compared to most other mammals. The S3 representation is not found in other moles or shrews, and thus arose independently. **b** Half of the star under a scanning electron microscope with the 11 rays labeled. **c** The star representation can be seen in flattened cortex processed for cytochrome oxidase. Although ray 11 is small compared to the other rays (b) it has the largest representation in S1. This reflects its use as the somatosensory fovea. **d** Schematic of a star-nosed mole saccade used to move the 11th appendage over an object being explored. **e** Frames from high-speed video showing a star saccade relative to a small prey item (*red circle*). (Published with kind permission of © Kenneth Catania 2014)

ing neuroanatomical tracers [40] revealed that the maps are topographically interconnected to form a cortical processing network.

Several features of this processing network differ substantially from the condition in rodents. For example, in addition to containing modules representing the individual rays, the secondary somatosensory cortex is much larger than would be predicted based on studies in rodents and most other mammals. S2 is usually much smaller than S1 and is characterized by large receptive fields. In contrast star-nosed mole S2 has proportions similar to S1 and is characterized by small receptive fields

on both the star and other body parts. Interestingly, a large S2 is found in shrews as well (see previous section on water shrews) and may be a general feature of shrews and moles rather than a specialization in star-nosed moles.

Despite sharing some features in common with other moles and shrews (a large S2) comparisons across species indicate that the extra, third map of the nose in lateral and caudal cortex is unique to star-nosed moles. This means that it arose independently in star-nosed moles and was most likely not in the common ancestor to shrews and moles. This is a very interesting finding because the addition of cortical areas is often hypothesized to be one of the substrates for more complex sensory processing and behavioral abilities. In most cases, such comparisons involve distantly related species that differ substantially in brain size. But moles are closely related species of similar brain and body size. The obvious difference between star-nosed moles and other mole species is the elaboration of the sensory surface and corresponding behaviors (see next section). This suggests that star-nosed moles added a cortical area to handle large amounts of complex sensory information from the star, perhaps depending on parallel processing of some aspects of touch.

An additional interesting and obvious characteristic of the star-nosed mole's somatosensory cortex is the overrepresentation of the 11th appendage. Despite the small size of this nasal ray and the relatively few Eimer's organs on its surface, its representation takes up 25% of the S1 star map (Fig. 2.7b, c). In addition, although the 11th appendage is more densely innervated then the rest of the star, only approximately 10% of the afferents supplying the star serve this appendage. Its greater innervation density stems from its small size and few sensory organs compared to the number of innervating afferents, rather than the number of afferents in total. Put another way, the innervation density of ray 11 is high as a ratio of nerve fibers to sensory organs (or skin surface).

When afferent numbers supplying the star are compared to their representations in primary somatosensory cortex, the sizes of the ray representations are not proportional to the number of nerve fibers supplying each ray [41, 42]. This can be contrasted to the situation in rodents, where the size of each cortical barrel has been found to be proportional to the number of nerve fibers supplying each whisker on the face [43]. Investigation of star-nosed mole behavior provides an explanation for the dramatic mismatch between the anatomy of the star and its representation in cortex.

Somatosensory Fovea

Star-nosed moles use the star to explore their environment with a series of high-speed touches. They may touch 10–13 different places every second as they search for food and navigate their tunnels. As was the case for water shrews, detailed investigations required the use of high-speed video recordings [44]. These revealed the explanation for the differential magnification of nasal appendages in the cortical representation; star-nosed moles have a somatosensory fovea at the center of the

star. The 11th, midline pair of appendages is used for detailed investigations of objects of interest (usually food). Most objects encountered as the mole searches its environment are first contacted by the large array of Eimer's organs that cover rays 1–10, as these make up most of the surface area of the star. For detailed investigation, moles make sudden movements of the star to reposition the 11th rays on an object for multiple touches (Fig. 2.7d, e). These nose movements are remarkably similar in their form and time-course to saccadic eye movements in primates [44].

Underwater Sniffing

Star-nosed moles are semi-aquatic and occasionally dive for food, much like water shrews. This raised the question of whether tactile cues used for detecting prey with the star would be degraded in water as a result of its greater viscosity than air. It seemed possible, for example, that movements would be slower underwater. There was no obvious indication of different use of the star underwater for mechanosensory investigation, but a different and unanticipated behavior was observed. This was under-water sniffing—as already described for water shrews, but first discovered in star-nosed moles [28]. Star-nosed moles exhaled air bubbles over objects of interest and then re-inhaled the same air. As was the case for water shrews, they could follow a scent trail laid underwater. In the case of star-nosed moles, a stainless steel grid with large openings was placed over the scent trail at all times. This prevented contact of the star to the scent trail, but allowed for air to be exhaled through the grid and then re-inhaled with each sniff. When the coarse grid was replaced by a fine grid that did not admit air bubbles the moles' performances deteriorated to chance levels.

Measurement of the timing of sniffs and the volume of air expired and re-inhaled showed that underwater sniffing is very similar to sniffing behavior exhibited on land by other small mammals. It is important to keep in mind that small mammal sniffing consists of repeated cycles of small expirations of air paired with small inspirations of air. In contrast to human sniffing, which generally consists of repeated short inspirations, small mammal sniffing on land is essentially the same as underwater sniffing in star-nosed moles and water shrews. That is, expiring air as a part of the sniffing process is not an innovation restricted to the aquatic medium. It is worth noting in this regard, that the terrestrial small mammals (e.g. short-tailed shrews) tested did not exhibit underwater sniffing when trained to retrieve food from a shallow enclosure [45]. Despite the close similarity between terrestrial sniffing and underwater sniffing, this does not appear to be a general feature of small mammal behavior, but rather a specialization of semiaquatic mammals.

That underwater sniffing happens at all is perhaps the most surprising conclusion from these studies. But this behavior also provides an obvious and very informative window into sniffing behavior; you can see the sniffs. Because each sniff is visible as an air bubble that emerges from the nostrils and is then re-inhaled, it is possible to clearly note the timing of sniffs relative to other behaviors using high-speed video.