1 Introduction to the barrel cortex

1.1 Introduction

The barrel cortex is a remarkable structure. Its form has captured the imagination of researchers for decades and its versatility has ensured that it finds a place in each new wave of neuroscience research. Since its discovery by Woolsey and Van der Loos in the early 1970s, researchers have used barrel cortex to study some of the most pressing questions in neuroscience. How does the cortex develop? How does active touch work? What makes neurons plastic? In each case, the value of the barrel cortex has been to help neuroscientists to relate structure with function through its unique and easily defined form.

In order to understand how these questions are being addressed currently, it is useful to understand some of the basic structural and functional features of the barrel cortex. The first three chapters of this book address some of the fundamental anatomy and physiology of the barrel cortex. For the expert in the field, most of what is written in these chapters will probably be quite familiar but will hopefully still serve as a useful reference to the original studies. While most of the original anatomical studies span the 1970s and 1980s, new neuroanatomical findings are still being described into the current century. Curiously, a review of this anatomical literature has not previously been written. For those less familiar with barrel cortex, the anatomical pathways linking the periphery to barrel cortex are described in Chapter 2 along with the intracortical connections, the study of which, at the time of writing, is still an active area of research. Chapter 3 deals with the cellular and synaptic physiology of the cortex. Many of these features of cortex are presumably common to all cortical areas but have been studied most completely in barrel cortex to date. We begin

here by looking at three questions: What animals have barrels? What are barrels? Why are barrels important for neuroscience research?

1.2 System overview

1.2.1 What animals have barrels?

The barrel cortex is part of the somatosensory cortex. It receives and processes tactile information derived from the whiskers on the contralateral face of the animal. In cross-section, the cortex is a six-layered structure where the main input layer is layer IV (see Figure 1.1C, D; color version in the plate section). The barrels that give the barrel cortex its name are located in layer IV. If a horizontal section is taken through layer IV, the distinctive pattern of the barrels can be seen. The barrel pattern replicates the pattern of whiskers on the face of the animal such that each whisker corresponds to a single barrel. The topological position of the barrel within the barrel cortex is identical to the topological position of its corresponding whisker. Figure 1.1 (Plate 1 in color section) shows a picture of the whiskers on the face of a young rat together with a section through barrel cortex layer IV showing the same pattern in barrels. A pathway comprising just three synapses connects the primary afferents carrying information from the whisker follicle receptors to the cortex and the final link in this pathway is made into layer IV of the cortex to produce the characteristic barrel pattern.

The whiskers are an important tactile sense organ for rodents in the same way as the hands are an important sense organ for humans and other primates. The sensory innervation of each whisker follicle is quite high, reflecting the importance of the information they transmit. In rats, each of the larger follicles receives terminations from approximately 200 trigeminal ganglion cells and the smaller follicles closer to 50. Each muzzle contains about 36 large whiskers, which can be whisked back and forth by muscles in and around the whisker pad, and numerous smaller vibrissae, which do not move and are located around the lip and front of the snout. In total, the muzzle on each side of the face contains approximately 165–210 whiskers depending on the species and strain of animal, which corresponds to the same number of barrels in each hemisphere of the cortex. The area of cortex devoted to the whiskers reflects the high innervation levels of the whisker follicles. In the mouse, the barrel cortex represents approximately 13% of the cortical surface area in total and 69% of the somatosensory cortex (Lee and Erzurumlu, 2005). Figure 1.2 shows a picture of the relative proportions of the body representations for a human and a rodent. The vibrissae are as over-represented in rodents as the hands and lips are in humans. In absolute terms, the barrel field comprises 4.7 to 6.4 mm^2 in the rat and 2.1 to

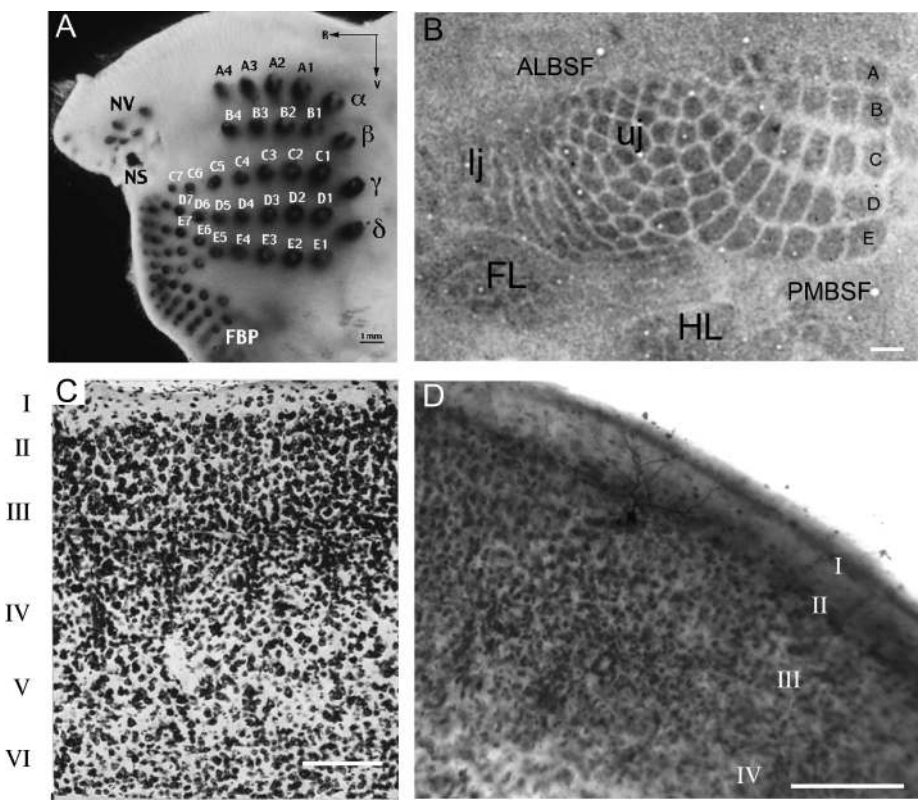

Figure 1.1. Somatotopic organization of the barrel cortex. A. A section through the muzzle of the rat reveals the pattern of vibrissae follicles arranged in five rows labeled A to E. The vibrissae are conventionally numbered from 1 at the back and increasingly higher numbers toward the nose (left). (Reproduced with kind permission of S. Hairdarlui and E. Ahissar.) B. The same pattern is replicated in barrel cortex. This cytochrome oxidase-labeled section through layer IV of the somatosensory cortex reveals barrels organized in five rows. The posterior medial barrel subfield (PMBSF) is on the right and corresponds to the large vibrissae that are actively whisked. The anterior lateral barrel subfield (ALBSF) is to the left and represents the smaller vibrissae around the upper jaw (uj) and nose region and lower jaw (lj). Other components of the body can also be seen such as the forelimb (FL) and hindlimb (HL). (A, B reproduced from http://www. neuro-bio.pitt.edu/barrels/pics.htm.) C. A cross-section through the cortex reveals the six-layer structure and the barrels in layer IV, which appear like staves of a barrel. (Nissl stain adapted from Woolsey and Van der Loos [1970] with kind permission of Elsevier and the authors.) D. Nissl stain through barrel cortex showing the barrels and a pyramidal neuron labeled with biocytin located at the top of layer III. (See color plate section.)

2.8 mm^2 in the mouse (Woolsey and Van der Loos, 1970; Welker and Woolsey, 1974). If the lower jaw, buccal pad and lip areas are included, the rat barrel field is closer to 10 mm^2 (Riddle and Purves, 1995). The absolute dimensions of the barrel cortex can vary from animal to animal (Riddle and Purves, 1995).

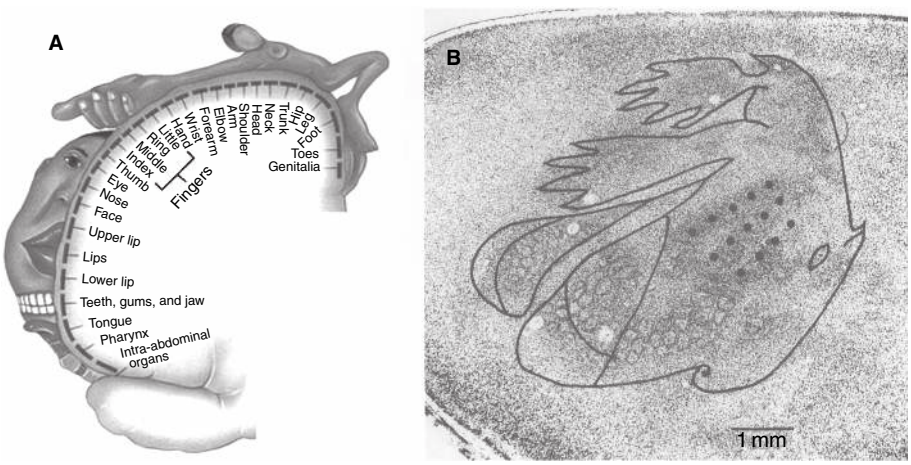

Figure 1.2. Relative magnification of the body surface representation in somatosensory cortex. A. In humans, a large area of cortex is devoted to the face, lips and hand representation compared with the back, even though the surface area of the back is larger than these. This diagram shows a cross-section through the human cortex at the level of the somatosensory representation. The location of areas responding to touch on particular locations of the skin on the contralateral side of the body are labeled and the corresponding distorted map of the body drawn above the cortical surface to depict the homunculus. B. A Nissl-stained section through rat somatosensory cortex shows the location of the barrels. Electrode recordings show that the areas of the body responding to touch correspond to the drawing of the body surface superimposed on the Nissl stain. The rat cortex has an even larger proportion of its cortex devoted to the face than in humans. (Reproduced from Welker [1976], with kind permission of Wiley and the author.)

All animals that have barrels have whiskers of some sort. The whiskers themselves are located in specialized hair follicles that have a follicle sinus, and in this respect they are unlike the hair follicles that give rise to the common fur. When the sinus is pressurized with blood, the individual vibrissa is held more rigidly within the follicle and the receptors are pressed closer to the whisker, thereby increasing the receptor's sensitivity to any mechanical stimuli transmitted via the whisker (see Section 2.1).

A large number of species have whiskers, from rodents through carnivores, insectivores, bats, shrews and marsupials to primates (Table 1.1). Perhaps surprisingly, only a subset of animals with whiskers (or sinus follicles) actually has barrels.

Almost all the rodents that have been studied to date do have barrels (Table 1.1). The beaver is an exception to this rule, and it has been suggested that barrels may be less easy to distinguish the larger the brain (Woolsey *et al.*, 1975a). Squirrels have barrels that are notably less distinct than in rats and mice but none the less present.

Table 1.1. *Comparative analyses of different species that have whiskers; not all have barrels, notably the carnivores, and not all whisk*[a]

Order/suborder or superfamily	Species common name	Barrels	Whisking	Reference
Rodent/Myomorpha	Mouse	Y	Y	Van der Loos and Woolsey, 1973
	Rat	Y	Y	Killackey, 1973
	Hamster	Y	Y	Rice *et al.*, 1985
	Gerbil	Y	Y	Woolsey *et al.*, 1975a
	Muskrat	Y	N	Woolsey *et al.*, 1975a
Rodent/Sciuromorpha	Chipmunk	Y indistinct	N	Woolsey *et al.*, 1975a
	Grey squirrel	Y indistinct	N	Woolsey *et al.*, 1975a
	Prairie dog	Y indistinct	N	Woolsey *et al.*, 1975a
Rodent/Castorimorpha	Beaver	N	N	Woolsey *et al.*, 1975a
Rodent/Cavimorpha	Guinea pig	Y	N	Woolsey *et al.*, 1975a
	Chinchilla	Y	Y	Woolsey *et al.*, 1975a
Rodent/ Hystricomorpha	Porcupine	Y	Y	Woolsey *et al.*, 1975a
Insectivora/Talpidae	Tree shrew	N	N	Woolsey *et al.*, 1975a
Insectivora/Lipotyphla	Mole	Y	N	Catania and Kaas, 1997
Lagomorpha	Rabbit	Y indistinct	N	Rice *et al.*, 1985
Carnivora/Feloidea	Cat	N	N	Rice *et al.*, 1985
Carnivora/Canoidea	Dog	N	N	Woolsey *et al.*, 1975a
	Raccoon	N	N	Woolsey *et al.*, 1975a
Carnivora/Pinipedia	Seal	?	N	
	Walrus	?	N	
	Sea lion	?	N	
Mustelids	Ferret	Y	N	Mosconi and Rice, 1991
Marsupials/ Phalangeroidea	Wallaby	Y	N	Waite *et al.*, 1991
	Australian opossum	Y	N	Weller, 1972
Marsupials/ Didelphoidea	American opossum	N	N	Woolsey *et al.*, 1975a
Primates	Squirrel monkey	N	N	Woolsey *et al.*, 1975a
	Rhesus monkey	N	N	Woolsey *et al.*, 1975a

N, no; Y; yes

[a] Not all species with whiskers are included.

Barrels can also be seen in animals as diverse as rabbits and marsupials, but not in the common carnivores that have been studied so far. Curiously, the cat has whiskers and barrel-like structures in the brainstem nuclei (barrelettes) but, along with other carnivores, has no detectable barrels in the cortex (Nomura *et al.*, 1986). One of the most spectacular sets of whiskers to be found in the animal kingdom is possessed by another carnivore, the walrus (Figure 1.3; color version in plate section). However, it is not known whether this animal, nor indeed whether pinnipeds in general, has barrels within its somatosensory cortex (Table 1.1).

Most of the suborder of rodents known as myomorphs (which includes rats and mice) both have barrels and "whisk" their whiskers, that is they move their whiskers back and forth rhythmically to sample the space around them. This active tactile behavior is analogous to palpating a surface with the fingers, where the tips of the fingers are rhythmically brought into contact with and retracted from the surface being explored. Animals whisk at very different frequencies; for example, the chinchilla whisks at about 1 Hz while the rat whisks at 7 Hz (Woolsey *et al.*, 1975a). Unfortunately, once again, a simple rule cannot be made between animals that whisk and animals that have barrels, because several animals with barrels do not whisk, including myomophs such as the muskrat (Woolsey *et al.*, 1975a), several other rodents, rabbits, moles, and various marsupials (Table 1.1).

The marsupials are an interesting set of animals with regard to the evolution of the barrels because they represent a primitive mammalian form. Many Australian marsupials have barrels, including the wallaby and opossum. Curiously, the American opossum does not have barrels despite being very closely related to the Australian opossum. It seems likely that they had a common ancestor that had barrels, which were then lost in the American opossum during their separate evolution once the continents drifted apart.

1.2.2 What are barrels?

What exactly is a barrel and what makes it so visible? Whereas the thalamic afferents innervating cortical layer IV usually form a relatively continuous distribution of terminations in primary sensory cortex, in barrel cortex the thalamic afferents form discrete clumps separated on all sides by gaps with sparse thalamocortical afferent branches. The gaps that surround the barrels are known as the septae. The dense clumping of thalamocortical afferents form the center, or core, of each barrel, as can be seen in Figure 1.4. Cells tend to be sparse within the centers of the barrels and denser in the barrel wall, though the difference is greater in mice than rats. The cells in the wall of the barrel tend to project their dendrites in toward the center of the barrel (Simons and

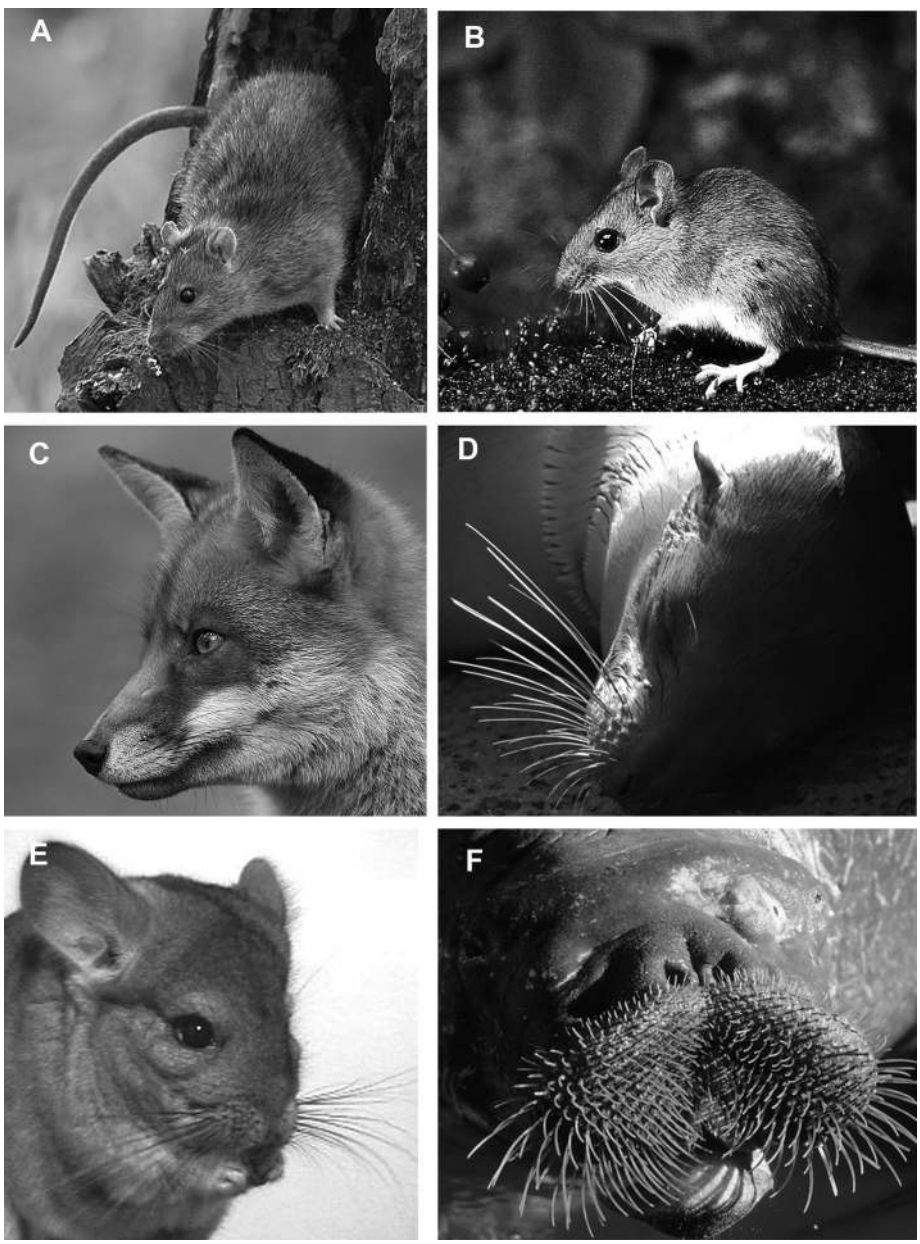

Figure 1.3. Many species of animals have whiskers. A. The rat is a common laboratory species for studying barrel cortex (*Ratus norvegicus*). (Courtesy of Stephen Round, reproduced with kind permission.) B. The mouse is a valuable laboratory species that can be genetically manipulated and is frequently used to study barrel cortex (pictured is the common wood or field mouse *Apodemus sylvaticus* a cousin of the laboratory mouse, which is derived from the house mouse *Mus musculus*). C,D. Foxes (C) along with other carnivores such as sea lions (D) have whiskers but are unlikely to have barrels because other carnivores such as cats do not. E. The chinchilla has whiskers and barrels. F. The walrus has an impressive set of whiskers but it is not known whether this species has barrels. (See color plate section.)

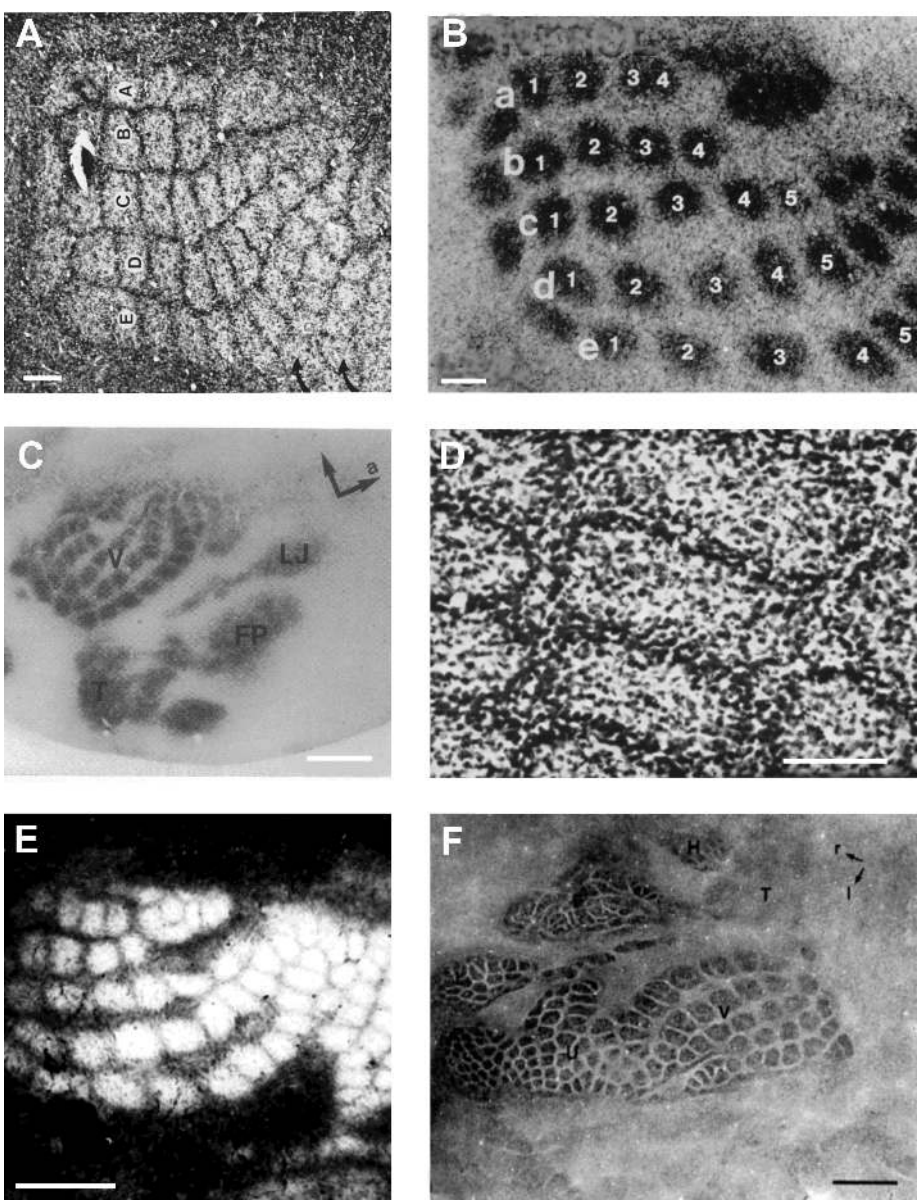

Figure 1.4. Barrels can be seen by a variety of methods. A. A stain for tenascin, which is an extracellular matrix molecule, labels the areas outside the mouse barrel cortex in a fenestrated pattern. (Reproduced from Cooper and Steindler [1986] with kind permission of the authors and Wiley.) B. Acetylcholinesterase is located on presynaptic terminals of the thalamocortical afferents at young ages and so labels barrel field in rats. (Reproduced from Schlaggar *et al.* [1993] with kind permission of the authors and Macmillan Publishing.) C. Similarly, the 5-hydroxytryptamine 1b receptor labels thalamocortical afferents at young ages in rats. (Reproduced from

Woolsey, 1984), again sparing the surrounding septal area between the barrels, where they pick up synaptic contacts from the thalamocortical afferents (Figure 1.4). The simple spatial separation of cells in the walls and thalamic afferents in the center of the barrel is sufficient to see barrels under a microscope in an unstained slice, presumably owing to the small difference in refractive index between the myelinated axons and the (unmyelinated) cells.

The barrel itself is most often visualized using cytochome oxidase (CO). This enzyme is present in mitochondria, which are particularly dense at synapses. Since the synapses are far denser in the barrel centers than either the walls of the barrel or the septal areas, so too is the CO. Staining for CO, therefore, shows up the barrels rather well, but only shows the inside of the barrel up to the inside edge of the barrel wall (Land and Simons, 1985). Other mitochondrial enzymes can also be used to the same effect, for example succinate dehydrogenase (Belford and Killackey, 1979).

The other major method for visualizing barrels is a Nissl stain. The Nissl stain shows where the barrels are located by showing up the differences in cell density. Differences in cell density across barrels are greater in mice than rats and, on a practical note, it can be difficult to see barrels using Nissl stains in rats older than about one week of age. Since the major cell density difference occurs between the edge and the center of the barrel, Nissl stains most readily show the barrels if a horizontal section is taken through the barrel field. However, it is possible to see the walls of the barrels in a coronal or transverse section through the layers of the cortex, where they form curved structures reminiscent of barrel staves (Figure 1.4). This is the resemblance that prompted Woolsey and Van der Loos to name this part of the somatosensory cortex "barrel" cortex.

Other methods can be used to see the barrel pattern, most notably staining for various receptors and enzymes such as nicotinic receptors, serotonin

Caption for Figure 1.4 (cont.)

Bennett-Clarke *et al.* [1993] with kind permission of the authors and the National Academy of Science.) D. A Nissl stain shows up the variation in cell density across the barrels, which appears relatively cell sparse in the middle and denser at the cell wall surrounding the barrel in the mouse. (Reproduced from Woolsey and Van der Loos [1970], with kind permission of the authors and Elsevier.) E. 1,1′-Dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI) is a lipophilic dye that can be used to label fixed tissue. Here the thalamocortical afferents have been labeled in layer IV of the rat barrel cortex in this fluorescent micrograph. (Reproduced from Boylan *et al.* [2000], with kind permission of the authors and Wiley.) F. One of the earliest stains to be used for studying barrel cortex was succinic dehydrogenase, a mitochondrial enzyme, present at synapses and hence particularly dense in the barrels. (Reproduced from Koralek *et al.* [1990), with kind permission of the authors and Wiley.)

(5-hydroxytryptamine [5HT] receptors, such as $5HT_{1B}$ and acetylcholinesterase (Bennett-Clark *et al.*, 1993; Schlaggar *et al.*, 1993; Bina *et al.*, 1995). These methods rely on the differential distribution of the molecule involved on the thalamocortical afferents rather than the neurons. However, the general usefulness of these receptors for viewing barrels is limited to the first couple of weeks of postnatal life because their expression is developmentally downregulated (see Chapter 4). Finally, elements of the extracellular matrix such as tenascin are particularly dense in the septal areas surrounding the barrel and can, therefore, be used to see a negative or fenestrated picture of the barrels by marking where the barrels are not (Cooper and Steindler, 1986).

The essential elements of a barrel are, therefore, a core of thalamic axons and a barrel wall of two to three cell layers in thickness. The middle of the barrel has a lower cell density than the outer wall but nevertheless does contain cells. In the mouse and rat, the larger barrels are located at the posterior medial part of the barrel field (Figure 1.1), which is, therefore, known as the posterior medial barrel subfield, and the smaller barrels are at the anterior lateral part. In both species, the barrels are arranged in five rows conventionally labeled from A to E (Figure 1.1). Rows A and B contain just four barrels while the other three rows contain approximately 8–10 barrels within the posterior medial subfield. The pattern accurately reflects the pattern of whiskers on the face of the animal; for example the gerbil, which has seven rather than five rows of whiskers, also has seven rather than five rows of barrels in the cortex (Woolsey *et al.*, 1975a).

The barrels in the mouse tend to be narrower in the dimension along the rows than in the orthogonal direction along the arcs. The larger barrels are about 200 μm in width and about 100 μm along the axis of the row. Each large barrel contains approximately 2000 neurons (Pasternak and Woolsey, 1975). Of the neurons present, about 75% are excitatory and 25% inhibitory (Ren *et al.*, 1992). The cells within layer IV principally project to layers above and below them. A strong projection is sent vertically to layers II/III and a smaller but important projection to layer Va directly below. Both these projections tend to preserve the topography of the barrels because they do not spread appreciably into surrounding barrels. In addition, layer IV projects to cells in layer VI.

The cells in the septal regions surrounding the barrels have a different set of major inputs and outputs, which make it probable that they form a partly separated interdigitated circuit within the barrel cortex. Whereas cells located within a barrel tend to connect with other cells within that barrel, cells in the septal regions form a wide mesh of connections with septal regions several barrels apart. They tend not to receive as great a thalamic input from the ventroposterior medial thalamic nucleus (VPm) as the barrel cells but do receive callosal input from the barrel field in the other hemisphere unlike the barrel