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Microscopic anatomy of sensory receptors

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Abstract

Experiences following stimulation of the senses have been recorded for millennia and they could be related to the gross anatomy of the sense organs. Examination of their microanatomy was to await the development of achromatic microscopes in the early 19th century. Among the microscopic structures that were isolated and described were specialized sensory cells, called receptors, and they could be related to the stimuli that excited them. Those located in well-defined sense organs (like eyes, ears, nose and tongue) were named on the basis of their morphology, whereas the receptors in or beneath the surface of the skin were generally named after those who first described them. Illustrations of early representations of sensory receptors are combined with 'perceptual portraits' of the microanatomists who described them.

Keywords senses, receptors, microscopes, microanatomy, histologists, perceptual portraits

Introduction

Experiences related to the senses have always been at the heart of neuroscience. What is seen, heard, smelt, tasted or felt could be related to sense organs and speculations regarding their underlying processes have been entertained since ancient times. Disorders of the senses, particularly blindness and deafness, provided one of the sources for such speculations and another related to the processes serving normal perception (see Crombie, 1964; Finger, 1994). Both were based on the known anatomy of the senses and most attention was directed to the sense of sight. Anatomical knowledge was limited by what could be seen with the naked eye and it improved greatly following the dissections of Andreas Vesalius (1514-1564; 1543) and others after him. The underlying anatomical structures remained unseen until the next century when microscopes were focused on animal matter. One of the early uses of the telescope by Galileo Galilei (1564-1642) in 1610 was his modification of it to observe an insect's eye. It was reported that "he perfectly distinguishes with his telescope the organs of motion and of the senses of the smaller animals, especially in a certain insect, which has each eye covered by a rather thick membrane, which, perforated with seven holes, like the visor of a warrior, allows it sight" (Fahie, 1903, p. 207).

Popular awareness of microscopes and their uses was broadened with the publication of *Micrographia* by Robert Hooke (1635-1703; 1665). In addition to the detailed illustrations, Hooke gave cells their name and identified plant cells. The senses also came under similar early microscopic scrutiny. The application of microscopes to biological specimens was a huge leap assisting understanding, but the microscopes themselves were neither powerful nor free from optical aberrations; the techniques for preparing specimens for observation were also limited (Turner, 1998). Hooke also described a more powerful simple microscope (see Ford, 2007). It was with such a device that Antoni van Leeuwenhoek (1632-1723; 1675) observed a variety of animal cells as well as nerve fibers. During the 18th century

microscopes improved in design and in the quality of lenses within them (see Mayall, 1886 for a survey of early microscopes) but interest in focusing the instruments on sensory receptors was limited.

The microscopic world was transformed by the introduction of powerful achromatic instruments in the 1830s, and rapid advances were made thereafter (Finger, 1994; Harris, 1999; Schickore, 2001, 2007). Among those who combined the achromatic microscope with remarkable observational skills was Jan Purkinje or Purkyně (1787-1869; 1837, Fig. 1). In 1832 Purkinje obtained an achromatic microscope manufactured by Simon Plössl in Vienna (Chvátal, 2017) and directed it at the large cells in the cerebellum, thereby identifying the cells that bear his name. His microscopic observations were made before any adequate staining methods had been developed. Purkinje used alcohol to fix his preparations, and he made thin sections so that they could be examined microscopically. Purkinje's laboratory at Breslau (present day Wroclaw) has been described as the cradle of histology, and it was matched only by that in Berlin (Otis, 2007), established by Johannes Müller (1801-1858). Cell theory was most clearly articulated by Matthias Schleiden (1804-1881; 1838) for plants and Theodor Schwann (1810-1882; 1839) for animals and it is associated with their names. At the end of the century Wilhelm von Waldeyer (1836-1921; 1891) extended the doctrine to nerves. He named the nerve cell body, its fibers and arborizations as a 'Neurone' and supported the doctrine that neurons were the fundamental structural and functional units of the nervous system (see Shepherd, 1991).

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Figure 1 about here

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Illustrations of sensory receptors seen under the microscope were represented in engravings often published in the initial reports describing their structure. In this article the

early illustrations are presented in 'perceptual portraits' (see Wade, 1990, 1995, 2006, 2007c, 2011, 2016, 2017). They generally consist of combining at least two elements – a portrait and some appropriate motif. Here the motifs are early representations of sensory structures which are interwoven with portraits of the microanatomists who described them. The portraits and motifs have themselves been manipulated in a variety of ways, using graphical, photographical, and computer graphical procedures. The original figures of the sensory structures themselves can be found in the references cited.

Senses and receptors

The senses have been separated in many ways. The most obvious is in terms of the organs housing them and the sensations associated with them. These were the sources available to Aristotle (Ross, 1931) and to those who followed him over the next two thousand years: observers could report on their experiences when stimulated, and they could relate them to their body parts. Eyes, ears, nose and tongue could readily be associated with sensations evoked by their stimulation but the experience of touch could not be related to a well-defined organ, only the skin surface itself. Greek speculations regarding the sources of stimulation have long been entertained (Beare, 1906; Finger, 1994; Stratton, 1917; Wade, 2003). Tastes and smells were associated with substances in solution or air-borne that excited locations on the tongue or in the nose; touch was associated with the texture and temperature of objects in contact with the skin; hearing with sounds transmitted through the air; and vision with light, although whether this was generated internally or externally was a matter of debate (Park, 1997).

The situation remained relatively unchanged through the medieval period (Kemp, 1990). Attention was directed principally at interpretations of vision, with much less heed paid to the other senses. Developments did occur in fusing Aristotle's account of the senses

with Galen's pneumatic physiology, and the medical tradition of describing diseases of the senses became more refined. When Galileo Galilei (1623) considered the senses and sensation he did so in the context of this medieval tradition. Nonetheless, he did not share Aristotle's faith in the veracity of the signals provided by the senses, and his approach to sensation can be seen as breaking with the medieval tradition (Piccolino, 2007; Piccolino and Wade, 2008a, 2008b, 2014). He clearly appreciated the indirectness of sensory experiences: "I think that tastes, odors, colors and so on are no more than mere names so far as the object in which we place them is concerned, and that they reside only in the consciousness" (Drake, 1957, p. 274).

From the viewpoint of sensory physiology, Galileo's statement can be taken as a forerunner of Müller's doctrine of specific nerve energies, formulated in the early nineteenth century. Müller (1826) argued that we only have available to us the signals that are sent to the sensorium, and this sentiment is clearly evident in Galileo's writing: "To excite in us tastes, odors and sounds I believe that nothing is required in external bodies except shapes, numbers, and slow or rapid movements. I think that if ears, tongues, and noses were removed, shapes and numbers and motions would remain, but not odors or tastes or sounds" (Drake, 1957, pp. 276-277). In expanding on the relation of stimulus to sensation, Galileo devoted more attention to the senses of hearing, taste, smell and touch than to vision. For touch he stated: "A body which is solid and, so to speak, quite material, when moved in contact with any part of my person produces in me the sensation which we call touch. This, though it exists over my entire body, seems to reside principally in the palms of the hands and in the fingertips, by whose means we sense the most minute differences of texture that are not easily distinguished by other parts of our bodies" (Drake, 1957, p. 275). Note that specialisation within the sense was also described, with greater sensitivity assigned to the fingertips than to other parts of the skin surface. For taste Galileo stated that tiny particles were received by the tongue and their

shapes determined the sensations as they did for smell by striking small protuberances in the nasal passage. With regard to sound, Galileo adopted a similar mechanistic interpretation. Touch, taste, smell and hearing were related to the elements of earth, water, fire and air. The analysis of these four senses was mechanical, both in terms of the stimulus and the response to it. Essentially, Galileo was following the Aristotelian path of treating touch, a patently mechanical sense, as the yardstick against which taste, smell and hearing should be considered. By contrast, Galileo was much more enigmatic in his consideration of vision: "I believe that vision, the sense eminent above all others in the proportion of the finite to the infinite, the temporal to the instantaneous, the quantitative to the indivisible, the illuminated to the obscure – that vision, I say, is related to light itself" (Drake, 1957, p. 277).

Both Aristotle and Galileo felt secure in their analyses of four of the putative five senses, but they were not the same four! Touch posed a problem for Aristotle because of its multiple dimensions, its wide distribution over the skin surface and its primacy as the quintessential contact sense. The other senses were clearly localised to specialised sense organs. Galileo was more concerned with the stimulus than with sensation. Touch, taste, smell and hearing could all be interpreted in terms of the response to mechanical stimulation; vision did not fit easily with this scheme, as little was then known about its physical basis. Accordingly, Galileo did not embrace it in the manner he adopted for the other senses and he wrote very little about the process of vision (Wade, 2007a).

There has been an asymmetry in studies of the senses beyond that of localized sense organs. More attention has been given to vision than to the other senses and this bias was evident in antiquity. In his review of the writings on the senses from Alcmaeon to Aristotle, Beare (1906) devoted 83 pages to vision, 38 to hearing, 28 to smell 20 to taste and 21 to touch. Similar asymmetries have persisted; for example, in the survey of the senses by Charles Bell (1774-1842; 1803), vision was covered in 148 pages, hearing in 80, taste in 5,

smell in 4 and touch in 9. The situation did not change materially over the next hundred years. In the second volume of Schäfer's (1900) *Text-book of Physiology* the chapter on vision was accorded 122 pages, hearing 56, taste 22, smell 10 and the cutaneous senses 37; there was also a chapter on the muscular sense. The difference between Bell and Schäfer was that Schäfer's contributors could provide far more evidence about the structure of receptors than was available to Bell.

The situation regarding the senses was radically revised in the 19th century, with developments in physics, anatomy, and physiology. Senses could be distinguished by the nature of the stimulus that excites the receptors – photoreceptors, mechanoreceptors, chemoreceptors, thermoreceptors and nociceptors. Sherrington (1906) proposed an alternative scheme with three classes of receptors: exteroceptors, interoceptors, and those involved in the monitoring of limb and body position which he called proprioceptors. The criteria that have been applied to separating the senses are the quality of the experience, the nature of the stimulus, the gross and microanatomy of the receptor system, and the pathways to and representation on the cortex (Neff, 1960). The early anatomists who explored the histology of sensory receptors were guided by the gross anatomies of the sense organs.

Among the microscopic structures that were isolated and described after the cell theory had been enunciated were specialized sensory cells, called receptors, and they could be related to the stimuli that excited them. Those located in well-defined sense organs (like eyes, ears, nose and tongue) were named on the basis of their morphology, whereas the receptors in or beneath the surface of the skin were generally named after those who first described them. The isolation of receptors that were specialized to respond to specific forms of environmental energy was adopted as a criterion for defining the senses. The multiplicity of receptors raised problems for determining how many senses there are and cast doubt on the Aristotelian restriction to five. While there has been much debate about the identity of a sixth

sense (Wade, 2003), it is clear that there are many more than five receptor types. They will be examined here with regard to the senses for touch, taste, smell, hearing and vision.

The gross features of the nervous system had been examined with the naked eye, but a new world was exposed by the microscope, and this world was examined by Marcello Malpighi (1628-1694). As a consequence of the many biological structures he examined microscopically (both plant and animal) Malpighi is often regarded as the first histologist. In addition to chick embryos, where he provided one of the first accurate descriptions of development in the nervous system, he examined the brain (including the optic nerve), the skin (which now has a Malpighian layer) and the tongue. His interpretations of physiology were based on the mechanistic concepts derived from the Galileian school; microscopic organization of living tissues was seen as due to the functioning of a multitude of minute machines (Meli, 2011; Piccolino, 1999). The type of microscope Malpighi used is not known (Motta, 1998) unlike Hooke (1665) who gave textual detail and illustrated his compound microscope. We will start the survey of the senses and their receptors with Malpighi's investigations of the papillae in the skin and tongue. He published two monographs in 1665, one on touch and the other on taste; that on touch was not accompanied by illustrations, unlike his longer monograph on taste. Malpighi's portrait is combined with some of the latter illustrations in Figure 2.

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Figure 2 about here

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Touch

Malpighi (1665a) indicated that the numerous conical or filiform papillae on the tongue serve a touch rather than a taste function; similar structures on the skin were described by Malpighi

(1665b). He considered that they were involved in touch because they were more numerous in areas of the skin surface that had greater touch sensitivity (Wilkie, 1969). This view was maintained until the early 19th century. For example, Peter Mark Roget (1779-1869) stated: "It is probable that each papilla contains a separate branch of the nerves of touch, the ultimate ramifications of which are spread over the surface; so that we may consider these papillae, of which the assemblage has been termed the *corpus papillare*, as the principal and immediate organ of touch. This structure is particularly conspicuous on those parts of the skin which are more especially appropriated to this sense, such as the tips of the fingers, the tongue, and the lips: in other parts of the surface, which are endowed with less sensibility, the papillae are scarcely visible, even with the aid of microscope" (1834, p. 378). Within a few years a wide variety of specialized cells in the skin were described and illustrated. In chronological sequence they were published by Pacini (1840), Meissner (1853), Krause (1860), Merkel (1875), Golgi (1880) and Ruffini (1894) and their names continue to be associated with the receptor cells. The anatomists are shown in Figure 3 together with representations of the cells bearing their names.

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Figure 3 about here

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Pacini first observed the onion-shaped cells that bear his name in 1831 during a dissection class as a medical student (Bentivoglio and Pacini, 1995; Henle and Kölliker, 1844) but he did not publish an account of them until 1840 and his illustration was reprinted in Pacini (1889). The cells are large and had been seen as early as 1741 by Abraham Vater (1684-1751) in the skin of human fingertips. He called them 'papillae nerveae' and they were examined in greater detail by his student Johann Gottlob Lehmann (1719-1767) in the same year; they are also referred to as Vater-Pacinian bodies (Neumeister, 1845). Meissner initially

described his microscopic observations of human skin together with his professor at Göttingen (Wagner and Meissner, 1852) and then published them in his own name the following year; they are occasionally called Meissner-Wagner corpuscles (Nafe, 1934). The touch corpuscles were considered to respond to deep pressure. Krause's end-bulbs or corpuscles were described in 1860 and his portrait is combined with an illustration of a touch cell from the conjunctiva of a human eye (Krause, 1861). Merkel (1875) illustrated a variety of specialized skin receptors including the 'touch cell' with which his name became attached three years later. His atlas of the skin and sense organs (Merkel, 1917) contained the schematic diagram of a Merkel cell from a human lip that was used in Figure 3. Golgi (1880) observed two types of cells in the region of the tendon. One was somewhat like the cells described by Pacini and Krause which Golgi referred to it as a 'tactile body'. Vittorio Mazzoni (1880-1940; 1890) showed that they are present in the skin and they are now referred to Golgi-Mazzoni corpuscles. The portrait of Golgi is combined with an illustration of the cells from Merkel (1917). Ruffini is shown in a duplicate and reflection of the representation of cylindrical cells in Ruffini (1894); the publication also drew attention to the Golgi-Mazzoni subcutaneous receptors.

Cutaneous sensory 'spots' specifically responsive to touch (pressure) and pain, as well as warmth and cold, had been described by Johann Wilhelm Ritter (1776-1810; 1801) and were isolated later in the century, using more sensitive and specific apparatus. A division of the skin senses into three separate systems (one to register temperature, a second for pressure, and a third for touch) was proposed by Natanson (1844; see Norrsell, Finger, and Lajonchere, 1999). Three sets of independent studies were reported in the 1880s in support of a separate temperature sense (Blix, 1882, 1884; Goldscheider, 1884, 1885; Donaldson, 1885). Their arguments were implicitly supported by Max von Frey (1852-1932; 1894) who linked the sensations of touch, warmth, cold, and pain to specific skin receptors. Von Frey (1896)

proposed that Meissner corpuscles were involved in touch perception, Ruffini cylinders for warmth, Krause end-bulbs for cold and free nerve endings for pain (Melzack and Wall, 1962).

Taste

Since the time of Aristotle, there had been a reasonable consensus regarding the qualitative characteristics of taste: salty, sweet, bitter and acidic were the characteristics and they could be related to different parts of the tongue. While there was some debate about additional qualities (see Boring, 1942; Finger, 1994) the involvement of papillae on the tongue in tasting them was widely accepted. Papillae were described by Julius Casserius (1552-1616; 1609) who was a pupil of and successor to Fabricius in Padua (see Riva et al, 2001) and they were examined microscopically by Malpighi (1665a, 1665b). In his illustration (see Fig. 2) Malpighi divided the tongue into five sections and noted the distribution of the papillae, particularly in the posterior section. Albrecht von Haller (1708-1777; 1754) distinguished between different types of papillae and he carried out simple experiments to indicate the specific sensations associated with stimulating the tongue: sugar applied to the papillae resulted in a sweet sensation unlike other parts of the mouth. Bell (1803) localized the sensations of taste more specifically to the papillae at the front and edges of the tongue.

Malpighi's microscopic studies were not ardently pursued by others until better quality microscopes became available. Augustus Waller (1816-1870; Fig. 4) examined the minute structure of taste papillae in frog and in human. He developed an interest in microscopy while a medical student in Paris. He returned to London to practice medicine but continues with his histological investigations. He remarked that the soft tissues of the tongue made microscopic examination of the papillae more difficult in comparison to other senses. His interests were not only in the microscopic structure of the receptors but also in the

pathways of the nerves from them. He stated “I hope to succeed in demonstrating that the organ of taste, far from being the most difficult to examine, is the most accessible, and that the beautiful and simple mechanism of taste may be followed in the depth of the tissues during the continuance of life” (Waller, 1847, p. 277). Initially he investigated the tongue of frog and distinguished between three types of papillae which he called conical, fungiform and lenticular. He also carried out similar studies on human tongue and described conical or filiform papillae and fungiform papillae (Waller, 1849). Later he gave up his medical practice and moved to Germany in order to concentrate on microscopic anatomy (Jay, 2002).

The detailed cellular structure of mammalian taste buds was provided independently by Lovén (1867, 1868) and Schwalbe (1867, 1868). Christian Lovén (1835-1904) received his medical education at the Karolinska Institute in Stockholm and then practiced medicine in Lund, later to become a professor in Stockholm. His initial account of taste papillae was presented in Swedish and this was acknowledged by Gustav Schwalbe (1844-1916) in the following year (Schwalbe, 1868). They both showed that the papillae contained clusters of cells around their sides. Schwalbe called them ‘taste cups’ whereas Lovén referred to them as ‘taste bulbs’ or ‘taste onions’. Titchener (1915) referred to them as ‘taste-buds’ or ‘taste-beakers’. Schwalbe worked with Max Schultze (1825-1874) in Bonn where he investigated taste papillae. His text book on the anatomy of the sense organs (Schwalbe, 1887) contains many detailed illustrations of their microscopic structures and he is shown, together with Lovén, in Figure 4; the representation of a circumvallate papilla is essentially a copy of that in Lovén (1867).

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Figure 4 about here

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Smell

The olfactory bulb was clearly described and illustrated by Antonio Scarpa (1752-1832; 1789) but the detail of the olfactory receptors awaited microscopic investigations (Doty, 2015). The observations and illustrations by Alexander Ecker (1816-1887; 1855, 1857), Conrad Eckhard (1822-1905; 1855) and Schultze (1856, 1862) did much to clarify the structure of olfactory receptors and the pathways of nerves from them (Fig. 6). Eckhard was an anatomist and physiologist at Giessen where he examined the olfactory cells in frogs distinguishing between two types, cylindrical and fusiform. Ecker was an anatomist at Freiburg and studied cells in the olfactory systems of frogs and humans. Both Eckhard (1862) and Ecker (1864, 1869) wrote textbooks on anatomy. Schultze examined the sensory cells within the nose before he investigated those in the eye and his research on olfactory receptors is chronicled by Zippel (1993).

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Figure 5 about here

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Hearing

The location of the inner ear within the bony labyrinth made it difficult to dissect and delayed investigation into its structure. Despite these difficulties, Scarpa (1789) provided detailed diagrams of the cochlear and vestibular system (Fig. 6). This paved the way for his fellow countryman, Alfonso Corti (1822-1876; 1851; Fig. 6), to provide some detail of the microanatomy of the cochlea.

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Figure 6 about here

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Scarpa added greatly to knowledge of the anatomy of the senses as well as of the brain (Grzybowski and Sak, 2013). He made important discoveries on the anatomy of the internal ear and of the vestibular system. His skills as an artist are evident in the anatomical drawings that are printed from copper plates in his books. Scarpa was a friend of the Corti family and as a medical student in Pavia, Corti was greatly influenced by Scarpa's anatomical studies. After graduating in medicine from Vienna, Corti studied histology under Rudolph Albert von Kölliker (1817-1905) in Würzburg where he worked on the retina before turning to the cochlea (Kley, 1986). Corti's involvement in auditory research was restricted to the early 1850s but its impact was immense. He published the illustration (the original of which is colored on a fold-out plate in Corti, 1851) with which his portrait is combined in Figure 6. Corti distinguished between the inner and outer hair cells on the basilar membrane as well as many other anatomical features of the inner ear.

The nerve fibres supplying the inner and outer hair cells were traced by Schultze (1858) but it was his student in Bonn, Otto Deiters (1834-1863; 1859, 1860) who explored the structures of the inner ear in more detail (Fig. 7). He indicated how the inner and outer hair cells were arranged in arcs and he also described the supporting cells for the hair cells, with which his name is associated (see Deiters and Guillery, 2013). Gustaf Retzius (1842-1919; 1884, Fig. 7) provided elegant illustrations of the cell structures on the organ of Corti. Like many anatomists before him, his illustrations were initially produced by an artist but dissatisfaction with this procedure resulted in him making his own drawings. Retzius spent most of his academic life at the Karolinska Institute in Stockholm (Grant, 2011).

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Figure 7 about here

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The inner ear is also comprised of three semicircular canals and two otolith organs (utricle and saccule) the gross anatomies of which were illustrated by Scarpa (1789) and Retzius (1884). They are involved in detecting angular and linear accelerations of the head. The inclusion of the vestibular system in the theatre of the senses came rather late. The anatomy of the semicircular canals was well established (van de Water, 2012) before the functions they served were clarified in the 1870s (Wade, 2003). The accelerations are detected by bending hair cells in the ampullae of the semicircular canals or in the otolith layers of the utricle and saccule.

Vision

When René Descartes (1596-1650; 1637) was discussing the eye he considered that the retina consisted of nerve endings and that their dimensions defined the limits of visual resolution (Wade, 2005). Since these were of a particular size, he argued that no object smaller than a fiber ending could be resolved. When achromatic microscopes were directed towards retinal fibers in the 1830s a greater degree of structure was discerned, but the nature of the receptors was not immediately apparent. Moreover, the previous hypotheses linking visual acuity to the dimensions of retinal elements influenced the initial representations of their structure. Gottfried Reinhold Treviranus (1776-1837, Fig. 8) was a comparative zoologist who did much to establish biology as an independent discipline within Germany, and to provide support for the cell theory. Like Purkinje, Treviranus had the benefit of a Plössl microscope for his studies, and from 1833 he measured the dimensions of many nerves in sensory systems and in the brains of a variety of animals. He considered that the brain was comprised of cylindrical cells arranged in parallel. In his posthumously published volume on the inner structure of the retina, Treviranus (1837) presented drawings based on vertical and horizontal microscopic sections of cells in the visual systems of many species. His diagram of the

crow's retina (Fig. 8) indicated a wider variation in retinal structure than had previously been represented, and the layers within it are clearly shown. Treviranus did, however, make the error of directing the papillae towards the incoming light rather than away from it. In this regard, he was reflecting the earlier ideas (from Descartes onwards) that the terminations of the optic nerves were the receptive elements in the retina, and that they were directed towards the lens. The years following 1840 saw rapid advances in fixing, sectioning, and staining microscopic preparations (see Finger 1994; Harris, 1999; Schickore, 2007). Nonetheless, Treviranus described and illustrated cylindrical cells in the retinas of a variety of animals, and opened the way for others to examine the microscopic structure of the retina in more detail. As Polyak (1957) remarked: "The work of Treviranus, though erroneous in almost every point, was beneficial because it stimulated an immediate series of investigations" (p. 48). The correct anatomical orientation of the retinal elements was described shortly afterwards by Friedrich Bidder (1810-1894; 1839); the terminations of the optic nerve structures were directed towards the choroid rather than the lens.

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Figure 8 about here

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The authorities on retinal structure were Kölliker (1850, 1854) and Schulze (1866); their portraits are combined with their diagrams of retinal cells in Fig. 9. The numerical ordering of the layers in the retina was reversed between the representations. For Kölliker's diagram the sequence started with the rod and cone layer; for Schultze's the number of layers was extended to ten, and the sequence terminated with the choroid (see Wade, 2007b, Fig. 12). Schultze (1866) also examined the complement of rods and cones in a variety of animals, and suggested that rods and cones function under different levels of illumination – which became known as duplicity theory.

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Figure 9 about here

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Schultze's (1866) suggestion of different functions for rods and cones instigated a search for differences in the chemical compositions that could account for them (see Wade, 2008a, 2008b). Heinrich Müller (1820-1864; 1851) observed the red color of the retinas of frogs and Franz Boll (1849-1879; 1877/1977) initially referred to the color of the dark-adapted retina as 'intense purple-red' but he revised this to 'red'. Boll provided convincing evidence that *Sehrot* (visual red) reflected the color of the rod pigment and that it was bleached by light. Willy Kühne (1837-1900; 1879/1977), not only appreciated the significance of Boll's research but also reported extensions of it. Kühne extracted rhodopsin from the rods of frogs and rabbits and showed that the rate of bleaching was dependent not only on the intensity of light but also on its wavelength. The visual purple was confined to rods and was not seen in the foveas of humans. Most significantly, Kühne established a 'visual cycle': visual purple in the rods is bleached by light to form visual yellow which in turn is transformed to visual white.

Kinesthesis

As noted in the introduction, Schäfer (1900) included a chapter on the muscular sense (written by Sherrington) in his textbook, although relatively little was said about the receptors involved. Touch and kinaesthesis are often considered in combination (see Rose and Mountcastle, 1959): coordinated behavior is based upon the integration of sensory information from on the skin surface and beneath it. The principal receptors were considered to be in the muscles or their tendons which respond to the stretching of muscles or the tension in tendons as well as in the joint capsules. Arthur Hill Hassall (1817-1894; 1851) illustrated

muscle spindles but they were described in greater detail by Ruffini (1898) who distinguished between three different types. Specialised receptors were also found in the tendons by Golgi (1880) and they continue to be known as Golgi tendon organs. The joint receptors are considered to be of four types: free nerve endings, Golgi endings, Ruffini cylinders and Pacinian corpuscles. The muscle and tendon receptors are shown in Figure 10 together with their discoverers.

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Figure 10 about here

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Hassall (1849), a general practitioner from London, published one of the first books devoted to microscopic anatomy; it consisted of two volumes that were lavishly illustrated with many of the figures in color. It was translated into German (Hassall, 1852) and an American edition was published in 1851. Additional plates of illustrations were produced for the latter and it was one of these that contained the initial indications of muscle spindles; the original English edition and its German translation did not contain the figure. Ruffini (1898) acknowledged that Hassall's (1851) "description and interpretation, although brief, show clearly he had before him 'muscle-spindles'" (p. 190). August Weismann (1834-1914; 1861) provided more detail of the organization of the muscle spindles within the 'Weismann bundles' and Kühne (1863) gave them the name 'muscle spindles'. When Golgi (1880) investigated the receptors in the tendons that bear his name he was able to use his revolutionary silver staining method (see Mazzarello, 2010).

Discussion

Silver staining was introduced by Golgi (1873; Fig. 11) and it transformed the histology of the nervous system (see Mazzarello, 1999; Wade and Piccolino, 2006). His novel technique

for staining nervous tissue consisted of hardening the preparation in potassium bichromate and then impregnating it with silver nitrate. The subsequent black reaction exposed the networks of nerves in grey matter in a manner that had not been possible previously. Among other novel histological techniques introduced thereafter was the stain invented by Franz Nissl (1860-1919; 1894, Fig. 11). Nissl discovered the effects of the stain as a medical student in 1884 and provided a published account a decade later (Kreutzberg, 1984). It involved aniline dye which resulted in a bluish appearance of brain cell nuclei.

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Figure 11 about here

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The Golgi technique was applied to sensory cells and a beautiful illustration of retinal structure was provided by one of his students, Ferruccio Tartuferi (1852-1925; 1887, Fig. 12). The horizontal and amacrine cells are clearly represented, as are the rods, cones and bipolar cells. Santiago Ramón y Cajal (1852-1934; 1889) employed the silver staining method to map many of the nerve pathways in the brain, including those from the senses. He is shown in Figure 12 within the structure of the inner ear. His artistry in depicting neural structures has been made more accessible in two recent books in English (Schoonover, 2010; Swanson et al., 2017) which reproduce many of Cajal's drawings. Cajal displayed skills at drawing from an early age and wished to develop them as an artist but he was persuaded by his father to study medicine at the University of Saragossa. He obtained his degree in medicine from the University of Madrid in 1877 and later occupied chairs of anatomy and histology at the universities of Valencia, Barcelona, and Madrid. Despite sharing the Nobel Prize in Physiology or Medicine in 1906, Golgi and Cajal expressed opposing views of the basic organization of the nervous system. Where Golgi saw an intricate network connecting the axonal arborizations of a variety of nerve cells, Cajal identified specific and well organized

intercellular contacts between individual cells allowing for a circumscribed and unidirectional flow of the nervous signal (Shepherd, 1991; Wade and Piccolino, 2006).

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Figure 12 about here

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Conclusions

The detailed structures of the specialised cells responding to external stimulation were bared to achromatic microscopes in the 19th century. The historical asymmetries of attention devoted to the senses were maintained during this period but the range of receptors reversed this bias. Touch furnished a wider variety of receptors than the other senses and they are known by the names of those who described them rather than by their morphology. Most of the observations were made before the Golgi and Nissl staining methods were available; these were subsequently applied in tracing the pathways from the receptors to the brain.

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Figure legends

Figure 1. *Purkinje's microscopic cells* by Nicholas Wade. Purkinje is portrayed peering down a Plössl microscope in a background comprised of the cerebellar cells he illustrated in 1837.

Figure 2. *Malpighi's tongue* by Nicholas Wade. Marcello Malpighi is shown with his illustrations of the papillae on the bovine tongue (derived from Malpighi, 1665a). He divided the tongue into five sections and noted the distribution of the papillae, particularly in the posterior section. His diagram of the microscopic features of the tongue is inset at the upper left and right.

Figure 3. *Explorers of the skin* by Nicholas Wade. From upper left to right, Filippo Pacini (1812-1883), Georg Meissner (1829-1905), Wilhelm Krause (1833-1910); lower left to right, Friedrich Merkel (1845-1919), Camillo Golgi (1843-1926) and Angelo Ruffini (1864-1929) combined with illustrations of their eponymous cells.

Figure 4. *The taste papillae of Waller, Lovén and Schwalbe* by Nicholas Wade. Left, Waller is shown within his illustration of a fungiform papilla from a frog (derived from Waller, 1847). Right, the diagram of a circumvallate papilla (from Schwalbe, 1887) is based on an earlier engraving by Lovén (1867). Lovén is embedded on the left and Schwalbe is on the right.

Figure 5. *The olfactory cilia of Ecker, Eckhard and Schultze* by Nicholas Wade. Left, a portrait of Ecker is combined with a diagram of epithelial and ciliary olfactory cells of the

frog (derived from Ecker, 1864). Centre, Eckhard is shown with olfactory cells of humans (derived from Eckhard, 1862). Right, Schultze with olfactory cells from owl, pike, frog and human (derived from Schultze, 1856).

Figure 6. *The inner ears of Scarpa and Corti* by Nicholas Wade. Left, Scarpa produced detailed grey-scale representations of the cochlea and vestibular apparatus as well as outline drawings, both of which are shown (derived from Scarpa, 1789). Right, Corti can be seen within his illustration of the structure and hair cells of the basilar membrane of the cochlea (derived from Corti, 1851).

Figure 7. *The hair cells of Deiters and of Retzius* by Nicholas Wade. Left, Deiters is shown together with his diagram of the cells (*f* in the illustration) supporting the hair cells (derived from Deiters, 1859). Right, one of the diagrams by Retzius (1884) of the structure of the organ of Corti together with a portrait of Retzius.

Figure 8. *The retina of Treviranus* by Nicholas Wade. The portrait of Treviranus is combined with his diagram of the crow's retina (from Treviranus, 1837).

Figure 9. *The retinas of Kölliker and Schultze* by Nicholas Wade. Left, Kölliker can be seen in his representation of the retina (derived from Kölliker, 1854). Right, Schultze's portrait is embedded in his illustration of retinal structure, flanked by his diagrams of an isolated rod and cone (derived from Schultze, 1866).

Figure 10. *Kinaesthetes* by Nicholas Wade. Left, Hassall in an illustration of muscle spindles in the tongue (derived from Hassall, 1851). Centre, Ruffini in his representation of muscle

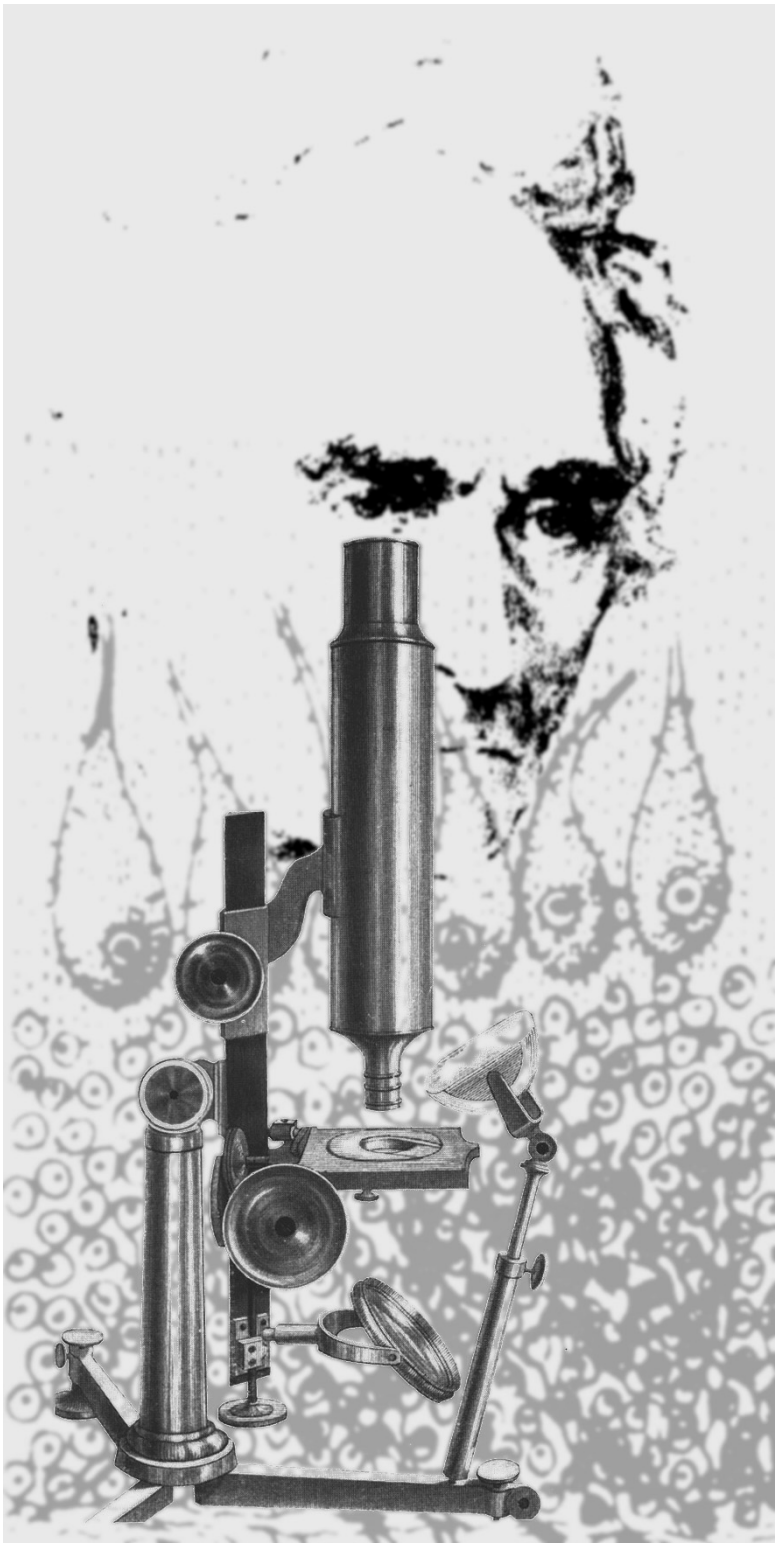
spindles (Ruffini, 1898). Right, Golgi combined with his illustration of nerves supplying tendon organs (derived from Golgi, 1880).

Figure 11. *Nerve cell stainers* by Nicholas Wade. Left, Golgi can be dimly discerned in the arborizations of a Purkinje cell stained by the black reaction. Right, the portrait of Nissl is combined with brain tissue stained by his aniline method.

Figure 12. *Tartuferi's retina and Cajal's inner ear* by Nicholas Wade. Left, Tartuferi was an ophthalmologist who first applied the silver staining method to the retina; his portrait is combined with the figure from Tartuferi (1887). Right, a portrait of Cajal is presented within his depiction of the receptors and nerves of the inner ear.

Figures

Figure 1. *Purkinje's microscopic cells* by Nicholas Wade. Purkinje is portrayed peering down a Plössl microscope in a background comprised of the cerebellar cells he illustrated in 1837.



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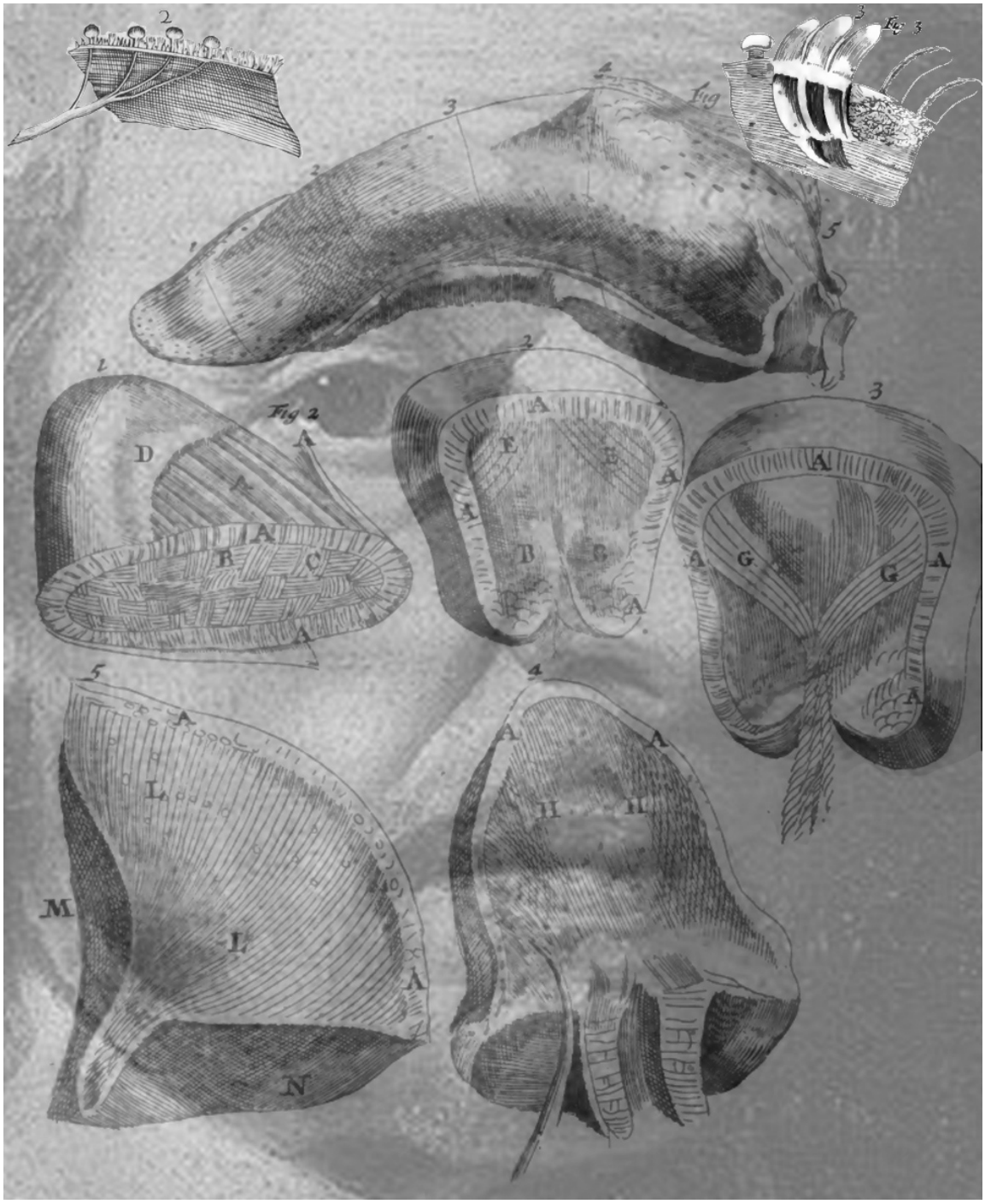


Figure 3. *Explorers of the skin* by Nicholas Wade. From upper left to right, Filippo Pacini (1812-1883), Georg Meissner (1829-1905), Wilhelm Krause (1833-1910); lower left to right, Friedrich Merkel (1845-1919), Camillo Golgi (1843-1926) and Angelo Ruffini (1864-1929) combined with illustrations of their eponymous cells.

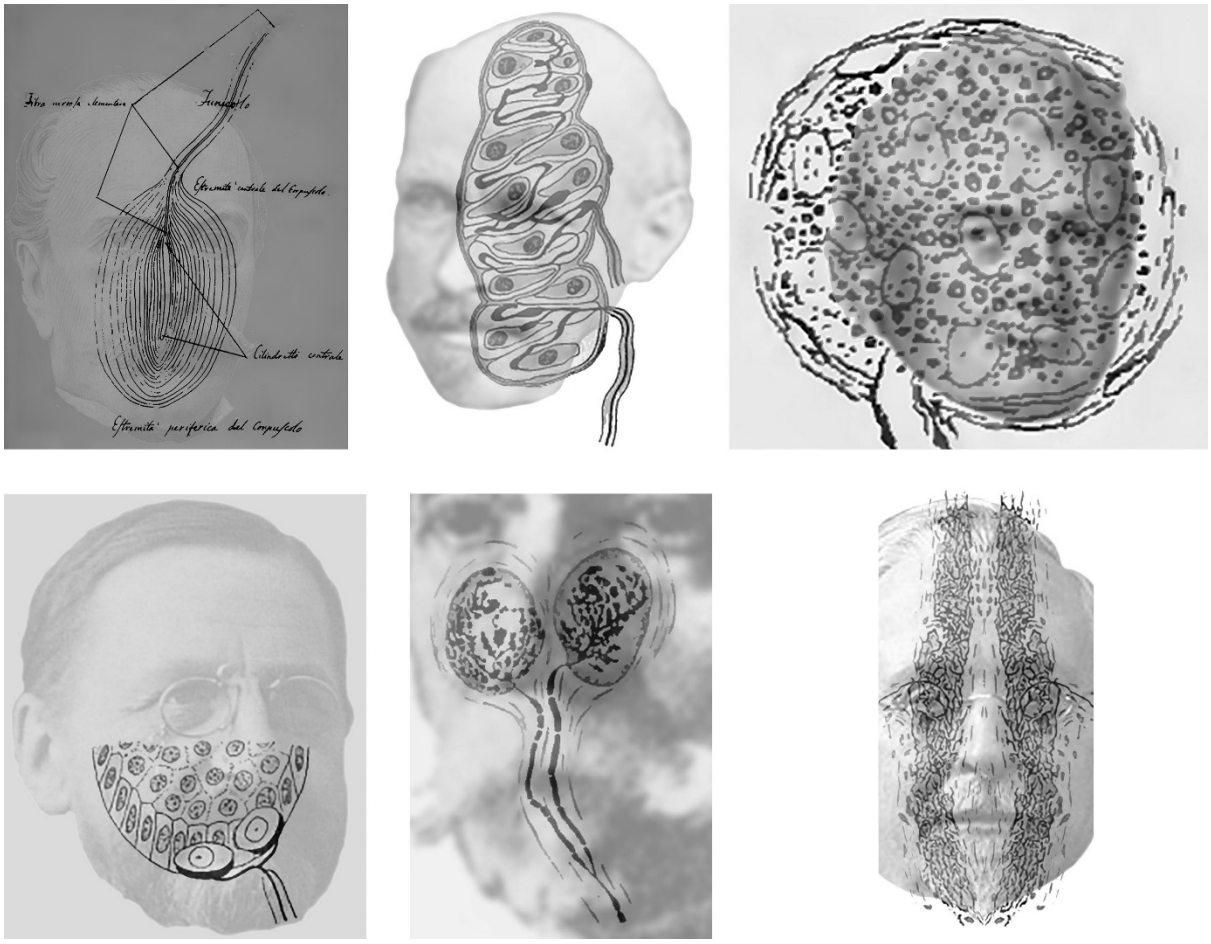


Figure 4. *The taste papillae of Waller, Lovén and Schwalbe* by Nicholas Wade. Left, Waller is shown within his illustration of a fungiform papilla from a frog (derived from Waller, 1847). Right, the diagram of a circumvallate papilla (from Schwalbe, 1887) is based on an earlier engraving by Lovén (1867). Lovén is embedded on the left and Schwalbe is on the right.

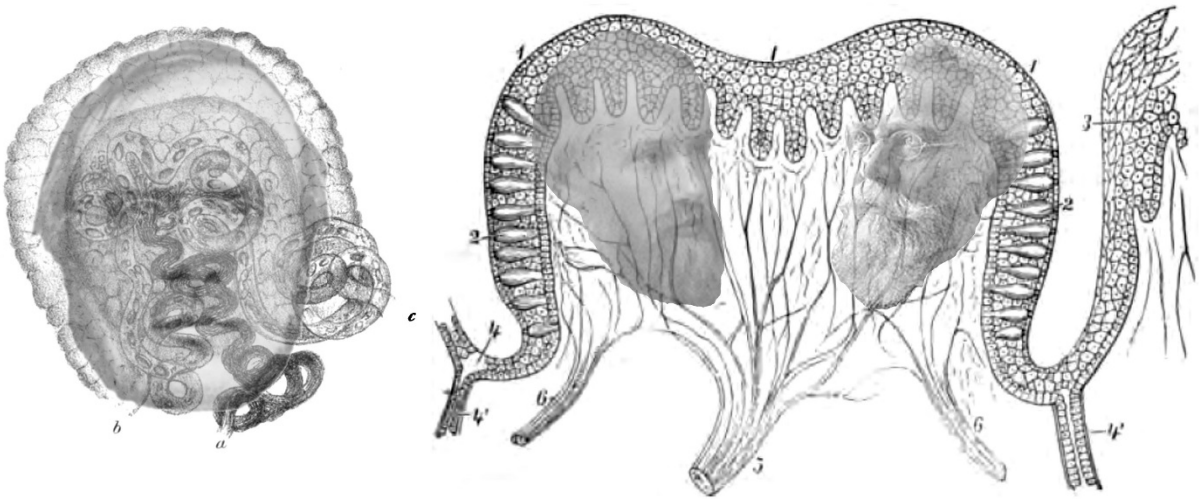


Figure 5. *The olfactory cilia of Ecker, Eckhard and Schultze* by Nicholas Wade. Left, a portrait of Ecker is combined with a diagram of epithelial and ciliary olfactory cells of the frog (derived from Ecker, 1864). Centre, Eckhard is shown with olfactory cells of humans (derived from Eckhard, 1862). Right, Schultze with olfactory cells from owl, pike, frog and human (derived from Schultze, 1856).

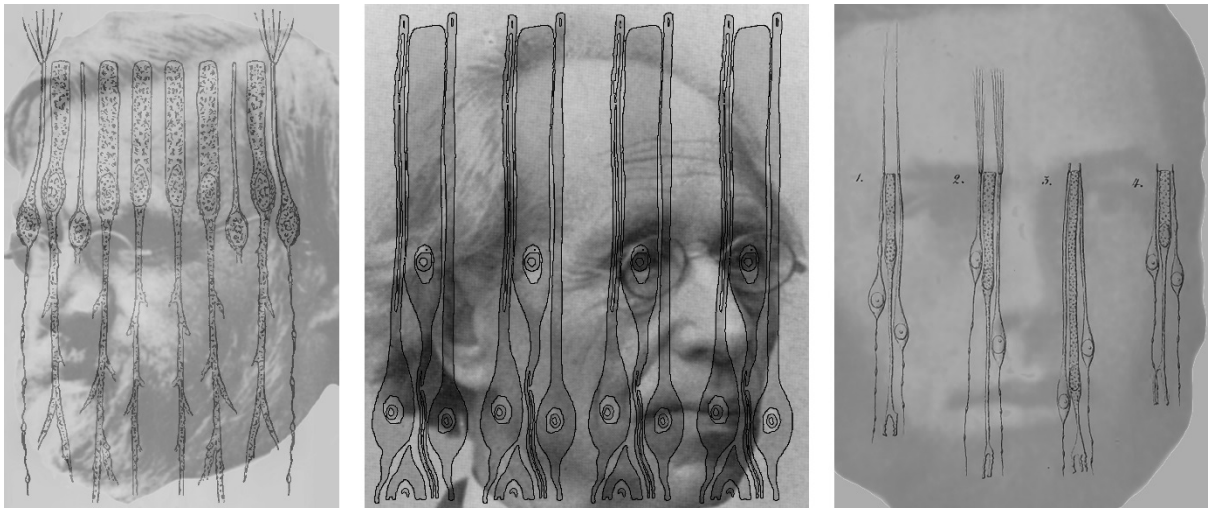


Figure 6. *The inner ears of Scarpa and Corti* by Nicholas Wade. Left, Scarpa produced detailed grey-scale representations of the cochlea and vestibular apparatus as well as outline drawings, both of which are shown (derived from Scarpa, 1789). Right, Corti can be seen within his illustration of the structure and hair cells of the basilar membrane of the cochlea (derived from Corti, 1851).

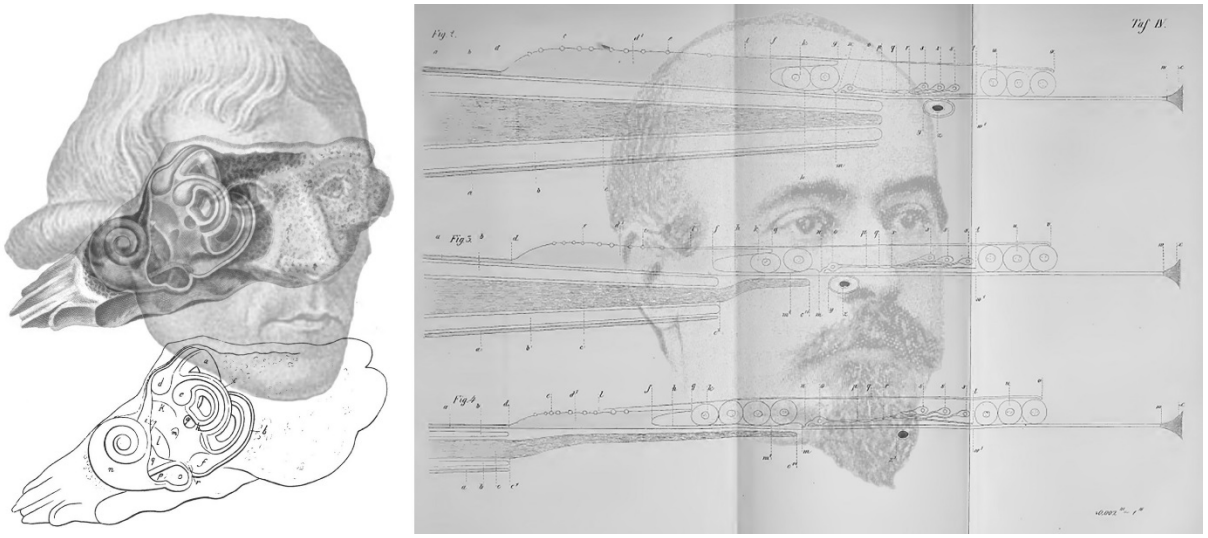


Figure 7. *The hair cells of Deiters and of Retzius* by Nicholas Wade. Left, Deiters is shown together with his diagram of the cells (*f* in the illustration) supporting the hair cells (derived from Deiters, 1859). Right, one of the diagrams by Retzius (1884) of the structure of the organ of Corti together with a portrait of Retzius.

Figure 8. *The retina of Treviranus* by Nicholas Wade. The portrait of Treviranus is combined with his diagram of the crow's retina (from Treviranus, 1837).

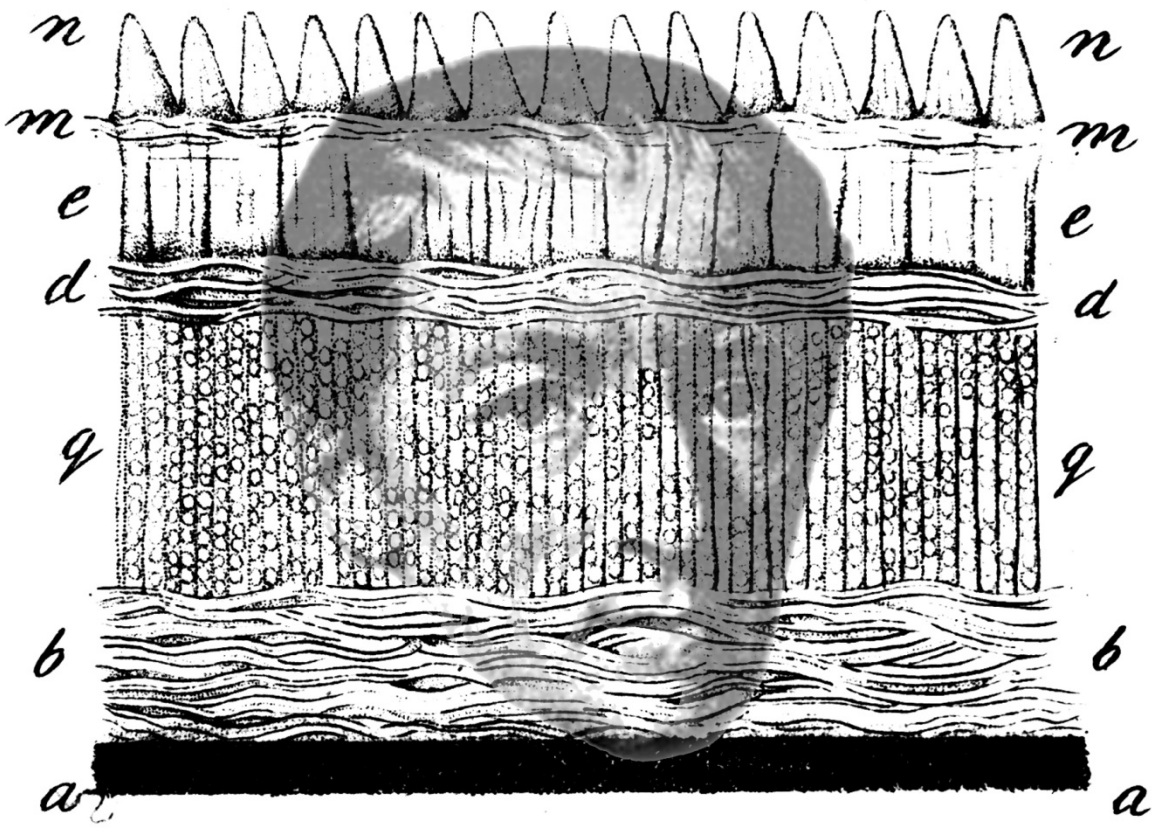


Figure 9. *The retinas of Kölliker and Schultze* by Nicholas Wade. Left, Kölliker can be seen in his representation of the retina (derived from Kölliker, 1854). Right, Schultze's portrait is embedded in his illustration of retinal structure, flanked by his diagrams of an isolated rod and cone (derived from Schultze, 1866).

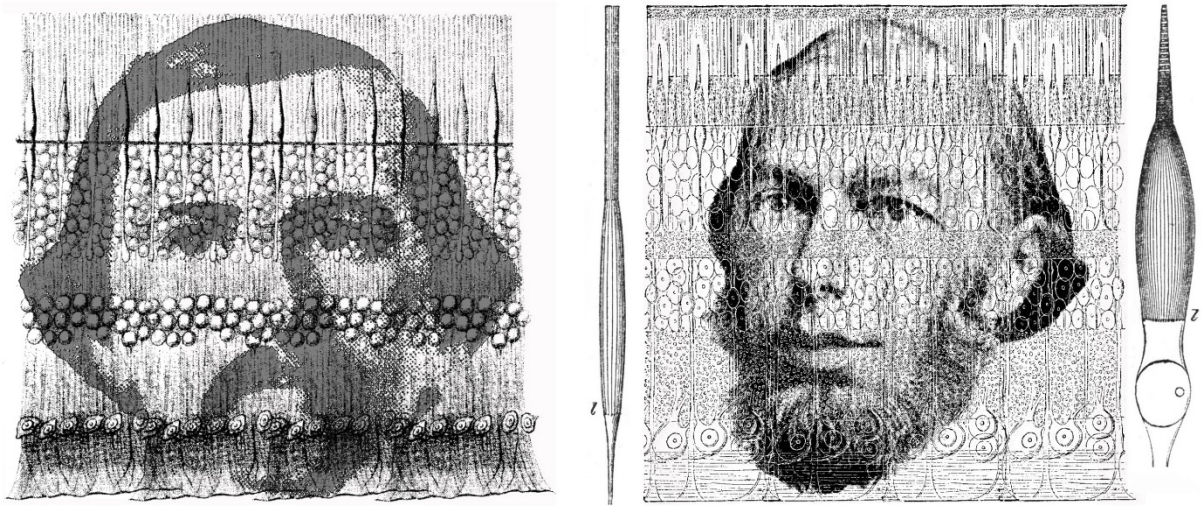
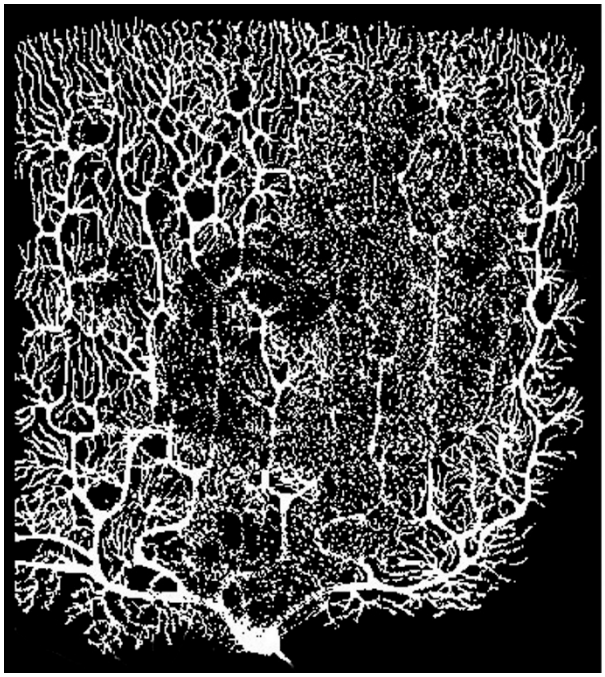


Figure 10. *Kinaesthetes* by Nicholas Wade. Left, Hassall in an illustration of muscle spindles in the tongue (derived from Hassall, 1851). Centre, Ruffini in his representation of muscle spindles (Ruffini, 1898). Right, Golgi combined with his illustration of nerves supplying tendon organs (derived from Golgi, 1880).

Figure 11. *Nerve cell stainers* by Nicholas Wade. Left, Golgi can be dimly discerned in the arborizations of a Purkinje cell stained by the black reaction. Right, the portrait of Nissl is combined with brain tissue stained by his aniline method.



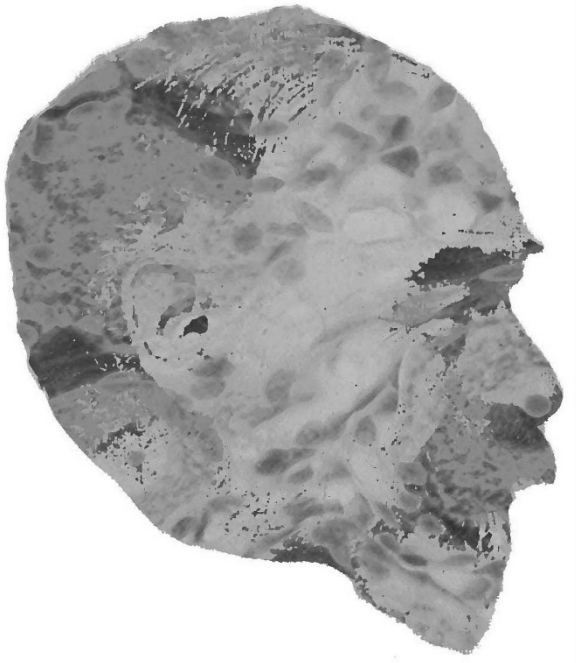
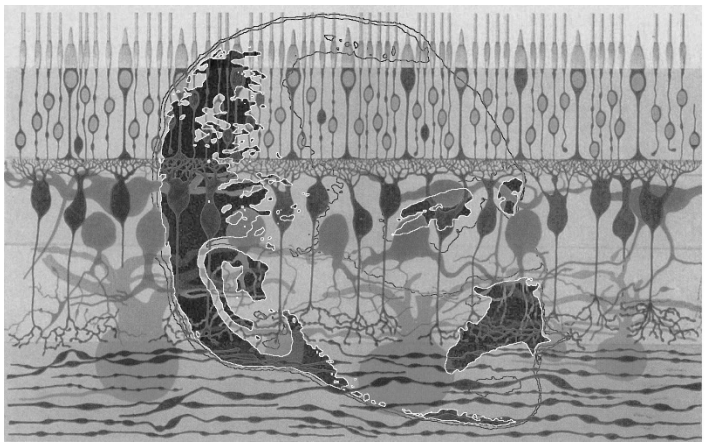



Figure 12. *Tartuferi's retina and Cajal's inner ear* by Nicholas Wade. Left, Tartuferi was an ophthalmologist who first applied the silver staining method to the retina; his portrait is combined with the figure from Tartuferi (1887). Right, a portrait of Cajal is presented within his depiction of the receptors and nerves of the inner ear.