Historical Perspective

Leonardo da Vinci's contributions to neuroscience

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Leonardo da Vinci (1452–1519) made far-reaching contributions to many areas of science, technology and art. Leonardo's pioneering research into the brain led him to discoveries in neuroanatomy (such as those of the frontal sinus and meningeal vessels) and neurophysiology (he was the first to pith a frog). His injection of hot wax into the brain of an ox provided a cast of the ventricles, and represents the first known use of a solidifying medium to define the shape and size of an internal body structure. Leonardo developed an original, mechanistic model of sensory physiology. He undertook his research with the broad goal of providing physical explanations of how the brain processes visual and other sensory input, and integrates that information via the soul.

Although Leonardo da Vinci is well known as the creator of some of the world's most famous paintings, such as the 'Mona Lisa' and 'Last Supper', he was accomplished in an astonishingly wide range of disciplines [1–3]. His studies of the brain provide an example of his inspirational drive to understand an extraordinary variety of natural phenomena. His careful observation of nature led to dozens of original discoveries, and his unparalleled draftsmanship made him a pioneer of anatomical illustration. Leonardo's studies of sensory physiology were directed towards establishing a physical basis by which the brain interprets sensory stimuli and through which the mind functions.

The evaluation of Leonardo's accomplishments in any area presents special challenges. His surviving notes are largely disorganized, and are written in his characteristic reversed script – 'mirror-writing' – and peculiar orthography [4]. Although he planned major publications on painting, mechanics and anatomy, these works were not published in his lifetime (with the exception of his illustrations for a mathematics text [5]). His anatomical works were first published in the period 1898–1916 [6–8]. Thus Leonardo exerted only a minor influence on the history of anatomy during the Renaissance.

Leonardo is today seen as one who observed nature directly, making original discoveries because he was shielded from the sterile, neo-Platonist environment of Renaissance Florence. He did not attend university, and only began studying Latin in his early 40s. He wrote: '…my works are the issue of pure and simple experience, who is the one true mistress.' [9] This reliance on experience rather than the printed word contrasted with the prevailing approaches to anatomical research, teaching and illustration [10]. The writings of Galen (129–*c*.199) dominated anatomical teaching from the 2nd to 16th centuries, and reliance on his authority stifled almost all progress. From the 14th century onwards, dissections were encouraged throughout much of Europe, but other than Leonardo's work there was virtually no progress in the field of anatomy from the time of Mondino (*c*.1275–1326) to that of Vesalius (1514–1564) [10]. Nonetheless, Leonardo was a product of his times, and it is important to balance enthusiasm for his originality with an appreciation of the extent to which he was influenced by the authority of ancient and medieval science [11,12]. His personal library contained several anatomical treatises [13,14] including that of Mondino, which remained highly influential for several centuries [15]. His primary Arab medical source was probably the *Canon* of Ibn Sina (who was also known as Avicenna; 980–1037), and late in his life he studied Galen's *On the Usefulness of the Parts*. Leonardo read at least parts of these texts and incorporated their anatomical framework into his thinking.

Leonardo's early neuroanatomical studies: the skull and *senso comune*

Leonardo's anatomical activity began in Milan in the period 1487–1493 [11,12,16–19]. His earliest surviving neuroanatomical studies consist of a series of drawings of the skull that date from *c*.1489. In preparing these compositions, Leonardo was partly motivated as an artist studying surface features of human anatomy, and in them he displayed his unsurpassed draftsmanship. The skull shown in Fig. 1a reveals the first accurate depictions of the anterior and middle meningeal arteries and anterior, middle and posterior cranial fossae [20–22]. Leonardo shows the frontal vein, which was traditionally used by surgeons and barbers in bloodletting to treat head pain and mental conditions. His drawing also includes the optic, auditory and other cranial nerves emerging from the bone. Another drawing shows the proportions of the skull (Fig. 1b), including the pole of the cranium [23,24]. By drawing the center of gravity he identified the axis about which the head rotates. Leonardo shows the skull from the side with the vault bisected; his inclusion of the frontal sinus represents an original discovery.

In most of his drawings of the skull, Leonardo followed medieval tradition in relating the structure of the brain to mental function. The intersecting lines above the pituitary fossa in Figs 1a and 1b are intended to show the position of the *senso comune* (literally 'common sense') or confluence of the senses. This position corresponds approximately to the third ventricle of the brain, and was supposedly the locus of the soul. 'The soul seems to reside in the judgment, and the judgment would seem to be seated in that part where all the senses meet; and this is called the *senso comune*,' Leonardo wrote (*c*.1490). 'The senses are moved by the objects; and these objects send their images to the five senses by which they are transferred to the *imprensiva*, and from this to the *senso comune*. From thence, being judged, they are transmitted to memory, in which according to their power they are retained more or less distinctly.' [25] In a drawing dated by scholars to *c*.1490–1494, Leonardo provided a crude schematic drawing of the three ventricles (Fig. 1c) [26–28].

Leonardo and the ventricular system

The idea that the ventricles of the brain are responsible for its major functions derives from at least the 4th century BC: the soul resides in the head, but because

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Fig. 1. Drawings of the human skull and brain by Leonardo da Vinci. (a) Drawing of a human skull (Windsor Castle, RL 19058 recto, *c.*1489) [20–22]. Leonardo tried to locate the *senso comune* (site of sensory integration) at the center of the skull. The meningeal arteries and the cranial fossae are shown. Cranial nerves are seen projecting towards the *senso comune*. (b) Two drawings of skulls (Windsor Castle, RL 19057 recto, c. 1489) [23,24]. Leonardo locates the *senso comune* at the geometric center of the brain. The rectangle drawn around the lower skull formed part of Leonardo's studies of the proportions of the human body. (c) Central nervous system and cranial nerves (Windsor Castle, RL 12603 recto, c. 1490) [26,28]. The main drawing shows the layers covering the brain, compared to the layers of an onion. The main drawing and the sketch below show the three cerebral ventricles, following the traditional medieval framework of Ibn Sina and others. (d) Two drawings of the human head (detail of a drawing from the Schlossmuseum, Weimar dated from *c.*1506–1507) [40,41]. Based upon his injection of hot wax into the brain of an ox (not shown), Leonardo obtained a cast of the ventricles. In the upper figure, the three ventricles are labeled *imprensiva* (anterior ventricle, corresponding to the paired lateral ventricles), *senso comune* (third ventricle), and *memoria* (posterior or fourth ventricle). Below the ventricles, seven pairs of cranial nerves are shown. The lower figure shows a human head in an exploded view, with the skull raised over the brain and from the head. (This sheet also includes a figure of the male genitourinary system.) The figures are reproduced with permission (a–c: The Royal Collection © 2001, Her Majesty Queen Elizabeth II; d: Kunstsammlungen zu Weimar). A translation of the text is provided at http://pevsnerlab.kennedykrieger.org/leonardo.htm

the soul is incorporeal, its locus is in the cavities (i.e. fluid-filled ventricles) rather than the surrounding brain tissue [29,30]. The brain was thought to contain an anterior ventricle, usually thought to house the *senso comune*, 'phantasy' and imagination, a second ventricle that mediated cognition, and a posterior ventricle that served memory.

Leonardo's views of the ventricular system were probably based upon his readings of Mondino included in the *Fasciculo di Medicina*, a text attributed to Johannes de Ketham [15,31]. However, Leonardo's approach to the ventricles at this time was notable for two reasons [32]. First, he introduced the term *imprensiva* to describe an anterior cerebral ventricular structure that mediated between sense organs and the *senso comune* (see further information and Ref. [25]). Leonardo is the only anatomist ever to have used this term. 'The *senso comune* is the seat of the soul, memory is its monitor, and the *imprensiva* is its standard of reference', he wrote [33].

A second notable feature of Leonardo's approach is that he described ventricular function in mechanical terms. His physics and engineering studies led him to describe four physical laws of nature: movement, weight, force and percussion [34]. He believed that these four powers behaved in a pyramidal fashion [35]: that is, all powers 'are capable of infinite augmentation or diminution. [Thus] they are pyramidal because they can grow from nothing to infinite greatness by equal degrees.' [36] Leonardo applied his physical laws to both the macrocosm of the earth and the microcosm of the human body.

Vision

In his system of sensory physiology, Leonardo was especially interested in studying vision [3,35,37]: 'The eye, which is termed the window to the soul, is the chief organ whereby the *senso comune* can have the most complete and magnificent view of the infinite works of nature.' [38] He devoted entire notebooks to the study of light and to the physiology of the eye (to study the structure of the eye, Leonardo dissected it, placed it in egg white, then hard-boiled it to aid the sectioning process). A visual image has more clarity or impact based on the size of the pyramidal image extending from the object to the eye; thus it is easier to see near than distant objects. Once a visual stimulus reaches the eye, it causes transduction of a nerve impulse (*sentimento*) down the hollow fibers of the optic nerve by the power of percussion, until reaching the *imprensiva*. The *imprensiva* receives and integrates other sensory input before transmitting the information to the *senso comune* (and hence to the soul and to consciousness).

Role of the spinal cord

During this early phase of Leonardo's interest in neuroanatomy, he became the first scientist to pith a frog. He wrote: 'The frog instantly dies when the medulla of the spine is perforated; and previously it lived without head, without heart or internal [organs] intestines or skin. Here therefore appears to lie the foundation of movement and life.' [39] He labeled the spinal cord 'generative power', reflecting the Platonic view (which he later abandoned) that semen derives from the spinal marrow. Based on his pithing experiments, he also attributed to the spinal cord the 'sense of touch, cause of movement, origin of nerves.' Elsewhere his drawing of the peripheral nervous system includes the comment that 'all the nerves manifestly arise from the spinal cord…and the spinal cord consists of the same substance as the brain from which it is derived.' [40] Leonardo extended his investigation to the problem of how nerves cause muscle contraction. These muscle and nerve membranes, he wrote, are 'almost imperceptible' (*quasi insensibile*) [41]. Whereas the spinal cord mediated life and death, the soul was to him a spiritual force located in the *senso comune*, capable of generating movement (see further information and Ref. [42]).

Later neuroanatomical studies

Imaging the ventricles

After pursuing other interests, from painting the 'Last Supper' to inventing ball bearings, Leonardo resumed his anatomical studies in around 1506. He used his expertise as a sculptor to perform a brilliantly original experiment to define the shape of the cerebral ventricles. 'Make two vent-holes in the horns of the greater ventricles, and insert melted wax with a syringe, making a hole in the ventricle of memory; and through such a hole fill the three ventricles of the brain. Then when the wax has set, take apart the brain, and you will see the shape of the ventricles exactly.' [43,44] The technique of using solidifying masses to determine structure would not be applied to biology again until the work of Fredrik Ruysch (1638–1731). In independent studies, Leonardo also made glass models of the aorta and casts of the ventricles of the heart to study their function.

Leonardo thus visualized the cerebral ventricles, which he presumed to contain the *imprensiva*, *senso comune*, and *memoria*. His drawings show clearly the interventricular foramen of Monro (named after Alexander Monro, 1733–1817). Having performed his initial studies on an ox, he translated his findings to the human brain (Fig. 1d) [45,46]. This astonishing sheet of drawings shows the skull, brain and cranial nerves in an exploded view. In this and other drawings he includes what are probably the earliest naturalistic depictions of the optic chiasm.

The sense of smell

Another of the many examples of Leonardo's interest in neuroscience is his research into the sense of smell. He was the first to define the olfactory nerve as one of the cranial nerves [47], as it had been omitted by Galen and later anatomists [10]. He was probably the first to propose an olfactory psychophysical experiment: after designing an experiment to test the color of paints flowing from two separate containers through a common funnel, he wrote 'also repeat this experiment with the winds of different odors.' [48] In considering the mechanism of olfaction, he commented that the olfactory bulb of the lion is particularly suitable for study because of its large size [49]. In the Middle Ages, this principle of using advantageous experimental systems and of studying comparative anatomy was not unheard of but was unusual, whereas it is taken for granted today. Leonardo described the potency of musk which is carried through air '…a thousand miles…without any diminution of itself.' [50] Finally, he compared the senses, arguing that 'the sense of smell resembles music' [51], an analogy used commonly by perfumers today.

Conclusions

Leonardo's fame as an artist was enormous in his own lifetime, and in many ways has grown over time. By contrast, his specific accomplishments in science have always been harder to appreciate. This is in large part because his notes were not all transcribed, translated, published and interpreted until the 20th century. It is also difficult for today's scientists to comprehend Leonardo's background of medieval science and technology. For example, after reading the literature of optics and then performing original experiments, Leonardo struggled to the conclusion that we see objects because the eye receives light [35,37]. This position opposed the prevailing view of Plato, Euclid, Ptolemy, Galen and Roger Bacon, that visual power emanated from the eye outward to allow an object to be perceived.

Through his studies of the brain, Leonardo provides us with a fascinating view of the intersection of his art and science. Today we see these as activities in separate domains, but to him painting *was* a science, and to see was to know. Leonardo created a theory of sensory perception from the input of sensory stimuli to their processing in the brain. Using his extraordinary visual faculty and his experimental creativity he made a series of original discoveries. To the historian of science, Leonardo's contributions to neuroscience also show what could be known five centuries ago, and how research problems could be approached. It is unfortunate that Leonardo's contributions to anatomy had only a modest influence historically, but that does not diminish the significance of his accomplishments.

Which areas of neuroscience would interest Leonardo today, and what meanings does he hold for us? One imagines that he would have a particular interest in current neuroimaging technologies, such as structural and functional magnetic resonance imaging, that allow us to localize the sources of behaviors to particular brain areas. He naturally would have been fascinated by modern approaches to the visual system, from the basic principles of light reception to microscopic images of the retina.

We are fascinated by Leonardo today because his curiosity was unparalleled, and the breadth of his accomplishments is inspirational. Leonardo's experimental success was often limited, he failed to publish his anatomical works, and he never synthesized his theories and observations into a coherent treatise on anatomy. Nonetheless, we can appreciate that he tried to understand seemingly all aspects of the brain from structure to function. His speculations ranged from sensory perception to the function of dreaming, from how we sneeze to the ability of a mother's mental state to influence the health of her unborn child. He was concerned with the relation of the senses to the soul. Our present climate in neuroscience is distinctly different; most of us are specialists and reductionists. We have made great progress in understanding brain structures, brain circuitry and molecular events. We probably are still no closer to understanding the human soul than was Leonardo, or his intellectual predecessors from Aristotle to Albertus Magnus. But scientists today are less inclined even to approach such a subject.

Further information

Supplementary information, including additional figures and translations of Leonardo's writings on the brain, can be found at http://pevsnerlab.kennedykrieger.org/leonardo.htm

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