Leonardo da Vinci and neuroscience: a theory of everything

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ABSTRACT

Introduction. Leonardo da Vinci represents the archetypal *homo universalis*. A Renaissance icon, he was sponsored by the great patrons of his day. His main obsession was observing nature and the relationship between macrocosm and microcosm (man). Five centuries after his death, the world continues to celebrate him and to recognise his influence on the development of science.

Development. Early in his search to identify the relationship between microcosm and macrocosm, Leonardo recognised the crucial role of the sense of sight and the capacity for integration, located in the brain. His drawings of the cranium and cerebral ventricles are the epitome of this work. In his search for the seat of the soul, he held a neoplatonic cephalocentric view, breaking with medieval tradition. He studied anatomy during his training as an artist, and later performed human dissections, which became a powerful tool enabling him to investigate how the brain controlled movement and the expression of emotions. Leonardo was a pioneer in the study of functional anatomy, and mastered anatomical study and illustration techniques to a level never previously seen. He planned an anatomical treatise that ultimately was never published, and researched the central and peripheral nervous systems, making one of the first drawings of the nervous system as an integrated whole.

Conclusions. Leonardo's main legacy is his search for the unity of man and nature as a single, interdependent system, and the methods he developed to unravel this mystery. He pioneered the scientific method, but his work was diluted after his death, and his neuroscientific legacy was not recovered until much later.

KEYWORDS

Art history, Leonardo da Vinci, neuroanatomy, neuroscience, philosophy of science, Renaissance

Introduction

The year 2019 marked the 500th anniversary of Leonardo da Vinci's death (1452-1519).[1,2] Through his insatiable curiosity, this Florentine polymath, the archetypal *homo universalis* and icon of the Renaissance[2,3] expanded the horizons of knowledge in numerous disciplines. His interests included what we today recognise as neuroscience, and the most noteworthy medical and neurology journals have recently published numerous articles celebrating his legacy.[4-7]

Due to his illegitimate birth (he was the son of Leonardo di ser Piero da Vinci, a wealthy notary from Florence, and Caterina de Meo Lippi, a young orphan from the village of Vinci[8]), da Vinci was unable to access an academic education, and was mainly taught in his home town of Vinci by his paternal grandfather Antonio.[9,10] From a very young age, he showed a great aptitude for drawing; when he reached 14 years old, his father took him to Florence, where he became an apprentice in the workshop of Andrea del Verrocchio (1435-1488).[2,9,10] At the *bottega* (the name given to artisans' workshops

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during the Renaissance[2]), Leonardo delved into learning, studying not only painting and sculpture, but also other complementary disciplines including geometry, surface anatomy, and architecture; this experience left a permanent imprint on the subsequent development of his thought and technique.[2,4,9-11] At Verrocchio's workshop, he coincided with such other painters as Botticelli (1445-1510) and Ghirlandaio (1448-1494).[9,10]

Influenced by such great Quattrocento figures as Leon Battista Alberti (1404-1472), Brunelleschi (1377-1446), and Antonio Pollaiuollo (1429-1498),[9,10] and with the patronage of important Renaissance families including the Medicis, the Sforzas, the Borgias, and King Francis I of France,[3,9,10] Leonardo set off on a long quest, following his obsession with observing nature and understanding how natural processes are related with the functioning of the human body in a single, integrated system.[1,11]

This study addresses Leonardo da Vinci's main observations on the structure and functioning of the nervous system, his motivations, and the impact of his discoveries on the subsequent development of neuroscience.

Development

Macrocosm, microcosm, and the theory of everything

Leonardo quickly surpassed Verrocchio, and understood that no master could give him the answers he sought.[2,9,10] Despite knowing no Greek, and learning no Latin until after the age of 40 years,[12] he undertook to instruct himself in the works of the classical authors. Initially influenced by the ideas explored by Plato (427-347 BCE) in his dialogues *Timaeus* and *Phaedo*,[4] as well as the neoplatonic ideas of Marsilio Ficino (1433-1499), with whom he coincided in the court of Ludovico Sforza in Milan,[9,10] he embraced the concept that the human body is a microcosm created in the image of a macrocosm, and must be governed by the same laws, and that the keys to understanding its structure and function must be found through the observation of nature. For Leonardo, this idea became a search for balance between the earthly and the cosmic.[9]

From another of his peers in Milan, Luca Pacioli (1445-1517), a true master of Leonardo who taught him mathematics,[2,9] he learned about the Fibonacci sequence and the golden ratio,[9,10] which is repeated time and again in nature, for example in the distribution of petals on a flower or in the spiral of a snail's shell. Pacioli referred to this as the *divina proportione* or "divine proportion"; he published a book with this title (completed in 1498), to which Leonardo da Vinci contributed 70 illustrations of complex geometric shapes, which were ultimately the only illustrations he published in his lifetime.[9]

Similarly, as part of his training as a painter, and influenced by the work *De pictura* (1436) by Leon Battista Alberti, Leonardo became interested in studying the anatomical proportions of the human body. His "Vitruvian man" (1490) was an homage to the famous Roman architect Vitruvius and his cannon, the greatest expression of these proportions (Figure 1). As was his nature, Leonardo went a step further. He corrected and expanded the proportions defined by Vitruvius, searching for the precise measurements of perfection and beauty.[2,9] In the drawing, the square, centred on the model's genitalia, represents the earthly, while the circle, centred on the navel, represents the cosmic.[2,9,10] The "Vitruvian man" constitutes a historic milestone in the relationship between art, science, and philosophy, immortalising in a drawing the enduring question of who we are and what our place is in the order of the universe.[9]

Leonardo aimed to achieve a rational understanding of all everyday phenomena and the relationships between them,[11] a true "theory of everything." He understood early on that to achieve this it was necessary to understand how the brain processes sensory stimuli and integrates this information with the soul.[12]

In search of the soul: the influence of Greek culture and early experiments

From the time of Homer (eighth century BCE), Greek culture understood *psyche* ("cold air," the soul) to be the principle of all life.[13] Initially, it was not associated with reason, sentiment, or memory. The first thinker to suggest a mind-body dualism was Heraclitus (540-475 BCE), who attributed the role of "thinking thing" to the *psyche*.[13] In Greek thought, the evolving conception of the soul led to an opposition between two main philosophical currents, which disagreed on the location of the soul in the body: the "cephalocentric" model defended by Plato, and the "cardiocentric" conception developed by his disciple Aristotle (384-322 BCE).[11,13,14]

Plato believed in an anthropological dualism between the (mortal, sensible) body and the (immortal, intelligible) soul; this idea had a great influence on the

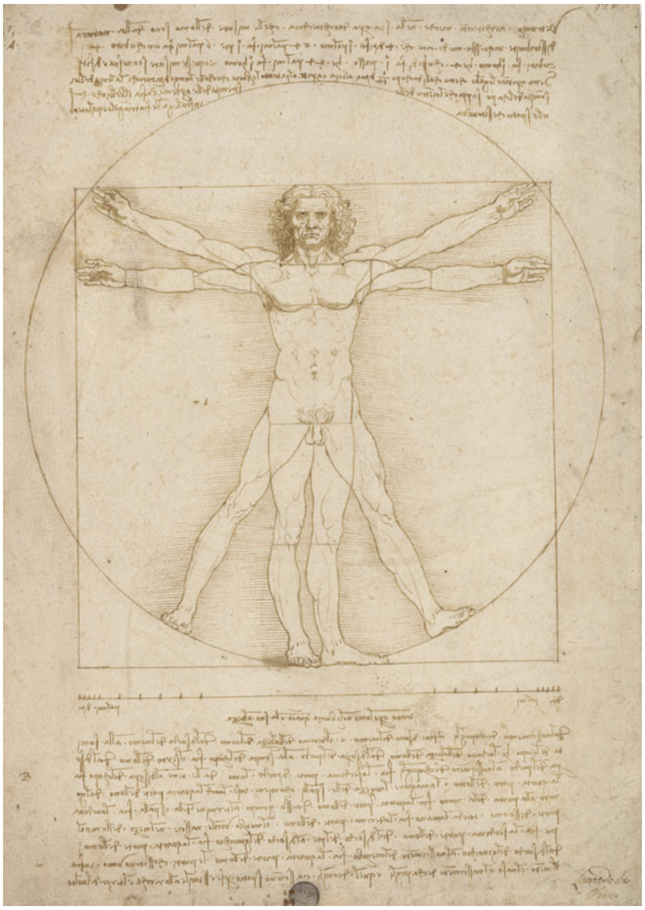


Figure 1. The "Vitruvian man" (1490-1491). This drawing depicts the unity of macrocosm and microcosm, raising the question of who we are and what our place is in the universe. The square, centred on the model's genitalia, represents the earthly, while the circle, centred on the navel, represents the cosmic.[9] © Gallerie dell'Accademia, Venice. Italian Ministry of Cultural Heritage and Activities and Tourism

subsequent development of Christianity, and became a key characteristic of neoplatonic thought during the Renaissance.[13,15] In his *Republic*, Plato divides the soul into three parts, with the most important (*nous* or *logos*; "reason") located in the head, and secondary centres in the heart (*thymos*, or "spirit") and upper abdomen (*epythymia* or "appetite").[13-15] Plato was the first thinker to refer to the *logos* as "mind."[13]

Regarding this cephalocentric conception of the soul, while the brain's ventricles were first described by Herophilos (325-280 BCE), it was his contemporary Erasistratus (310-250 BCE) who revisited the theory of *pneuma*, proposed by Stoic philosophers including Diogenes of Appolonia (fifth century BCE) and Anaximenes (585-524 BCE), establishing that air is the vital principle or "breath of life."[15] According to this theory, air enters the body through respiration and is transformed into *pneuma*, which circulates through the veins and arteries, passing through the heart, and finally takes its place in the cerebral ventricles, where it becomes *pneuma psychikon* (*spiritus animalis*), which governs the mental faculties.[4,15]

For Aristotle, on the contrary, man is a physical union of body and soul; he considers the latter to be an intrinsic principle of the body, and therefore to be mortal.[15,16] In his treatise *On the soul*, he argues for the existence of three types of soul: the vegetative soul (present in plants), the sensitive soul (present in animals and humans), and the rational (or intellectual) soul, which is exclusive to humans.[14,15] In this world view, the centre of psychic life and sensory perception (which Aristotle refers to as *sensus comunis*) is located in the heart[15]; while the intellectual faculties of the soul reside in the cerebral ventricles, this system lacks functions directly involved in the physiology of perception.[15] For Aristotle, the brain was simply a gland with the secondary role of "cooling" the heart.[14,15]

The idea of the *sensus comunis* as the convergence of the senses evolved in the Middle Ages, and was a significant influence in the neurophysiological and philosophical thought of Leonardo da Vinci.[11,14] Similarly, the Aristotelian logic of deductive and inductive reasoning and the importance Aristotle gave to empirical observation constituted the pillars on which Leonardo built his own protoscientific method.[16]

Great classical physicians, including Hippocrates (460-370 BCE) and Galen (129-200 CE), defended Plato's cephalocentric conception. In his work *On the sacred disease*, Hippocrates describes how *pneuma* derived from external air is transported to the brain, inducing the development of intelligence, and is constituted in the seat of the soul.[15] Galen, a major influence on Leonardo's subsequent anatomical research,[17] went even further, asserting that mental functions were located in the "substance" of the brain. Nonetheless, one of his main translators, Nemesius (ca. 390 CE), transferred these functions back to the ventricles.[11,14] With the death of

Galen, the Aristotelian cardiocentric view of the soul took hold in Western thought, almost unopposed, for nearly 2000 years.[14]

The Renaissance saw a renewal of interest in the classical Greek and Roman authors[2,3] and a revival of the philosophical debates on the location of the soul in the human body and the structure and function of the organs composing it, questioning the scholastic tradition of the Middle Ages. In this context, the study of anatomy arose more from philosophical than from medical interest: the limited development of surgery at the time did not require anatomical understanding of structures located deeper in the body.[18,19]

These ideas had a significant impact on Leonardo, signalling a means of understanding and disentangling the laws governing man's relationship with nature. In 1847, when he was very young, he performed an experiment with frogs in an attempt to locate the soul. He observed that using a stiletto to pierce the spinal cord at its junction with the cranium (known today as "pithing") caused immediate death of the animal, while the frog was able to survive for several minutes after removal of the heart and organs (Figure 2).[4,11,12,14] This is the first record of a neurophysiological experiment since the time of Galen[14]; for Leonardo, it resolved the problem of the location of the soul as the principle of life. In his notes, he recorded that: "… here therefore, it appears, lies the foundation of movement and life…"[4,11,12,14] Leonardo never killed another animal and converted to what we refer to today as veganism.[3,10]

Satisfied with this conceptualisation of the location of the soul, Leonardo dedicated his efforts to clarifying the location of the soul within the brain itself.[14]

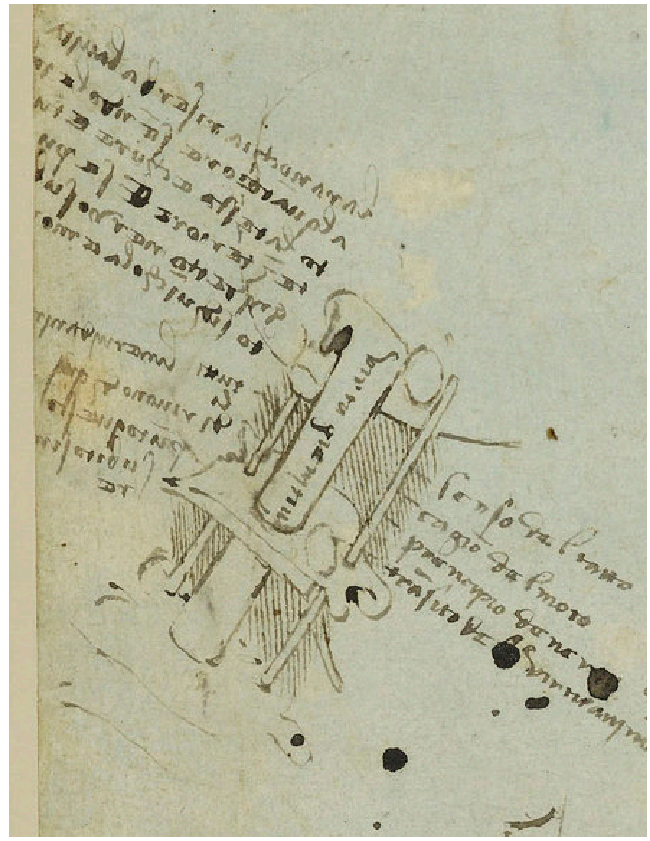
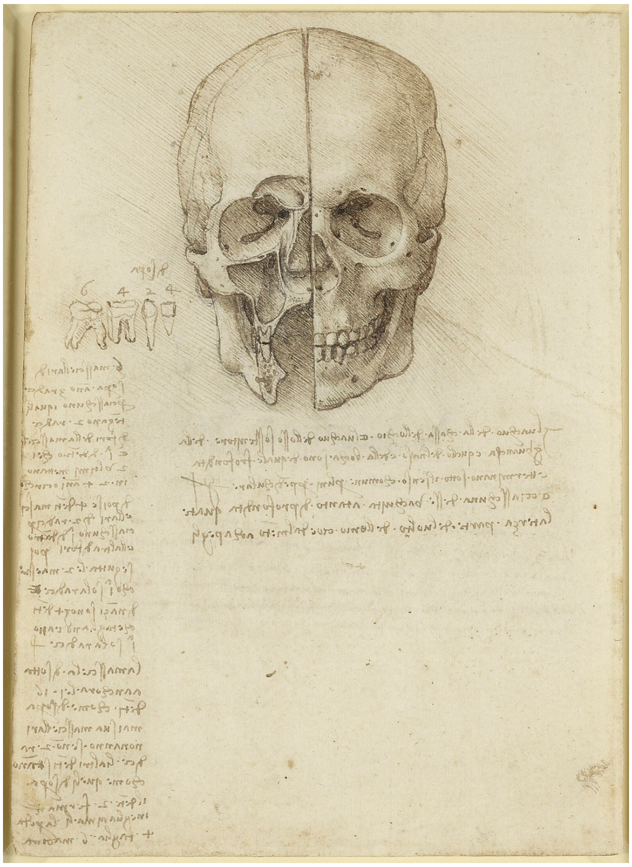


Figure 2. Experiment with piercing (pithing) the frog spinal cord (1487). Using a stiletto to pierce the spinal cord at its junction with the cranium caused the immediate death of the animal, while the frog was able to survive for several minutes after removal of the heart and organs. In his notes, he recorded that: "… here therefore, it appears, lies the foundation of movement and life…"[4,12,20] RCIN 912613v. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

In search of the soul: the senses, *senso comune*, and the cerebral ventricles

Da Vinci's early anatomical work was motivated by the need to perfect his technique as a painter and draughtsman, and was based on the study of surface anatomy and comparative anatomy.[20,21] However, he had always been interested in studying the cranium to learn about how the eyes and sense of sight were related with the brain and soul.[11,12,14,21]

There, it is no coincidence that the earliest records of his anatomical studies correspond to a series of drawings of skulls, dating from 1489.[4,12,20,21] In analysing these drawings, it is essential to note the influence of Leonardo's knowledge of architecture and his relationship with the architect Francesco di Giorgio Martini (1439-1501), which equipped him to manage the geometrisation of space and to use transparencies to show internal structures without resorting to three-dimensional models.[14] Leonardo applied these concepts to anatomical study and illustration, developing novel techniques such as the use of different planes and axes for anatomical sections.[14,21] Figure 3 shows a study of a cranium with a coronal hemisection, with the first description of the maxillary and frontal sinuses. Figure 4 shows the cranium sectioned on two planes, displaying the interior of the cranial vault. The drawing shows the



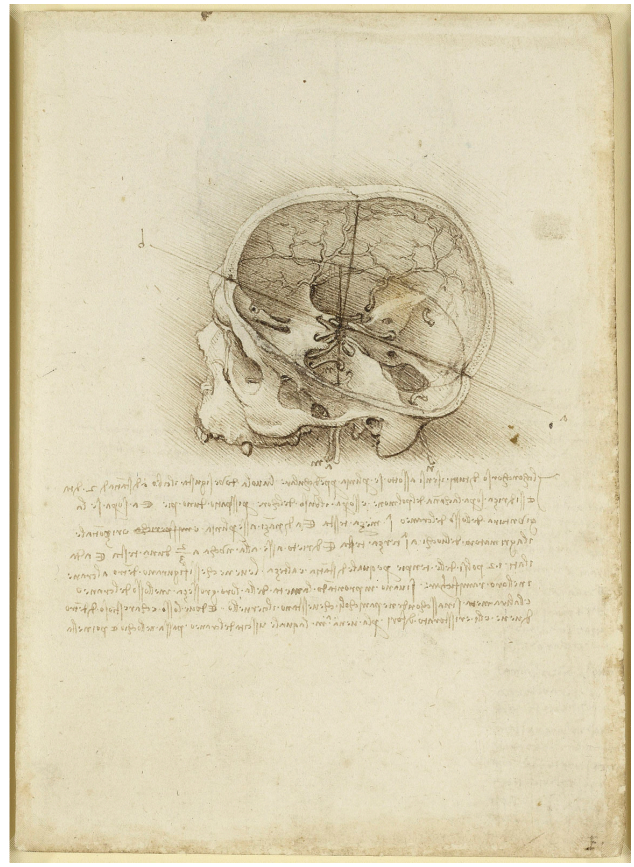


Figure 3 (left). Skull studies (1489): coronal hemisection. The drawing shows a frontal view of the cranium with a coronal hemisection, with the frontal and maxillary sinuses shown on the right side.[4,20,21] RCIN 919058r. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

Figure 4 (right). Skull studies (1489): section on two planes. A cranium is shown in three dimensions, with a lateral section of the skull cap showing the three cranial fossae and the impression of the anterior and middle meningeal arteries. The intersection of the lines over the optic chiasm signals the location of the *senso comune* (the convergence of the senses), the seat of the soul.[12,20,21] RCIN 919058v. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

impressions of the middle and anterior meningeal arteries on the inner table, and includes the first description of the anterior, middle, and posterior cranial fossae, although no name is given to them.[12,21] Beyond these milestones, Leonardo's drawings of the cranium cannot be compared with any known anatomical texts from the time[21]; some authors consider that his anatomical drawings remain unsurpassed in terms of beauty and naturalism.[2,12,19,22]

Nonetheless, the drawing of the cranium shown in Figure 4 was intended to demonstrate the location where the senses converge, known by the Greek philosophers as *sensus comunis*.[14,21] The lines, like a system of coordinates, intersect immediately over the optic chiasm, in the anterior part of the third ventricle, indicating the location of the *sensus comunis*.[14,21]

Linking the sense of sight with a bridge between nature and the soul, and emphasising the supremacy of sight over the other senses, Leonardo's descriptions of the visual pathway highlighted the optic chiasm and its anatomical relationship with the olfactory nerve and cavernous sinus (Figure 5). At the same time, he performed studies on optics and on the physiology of visual perception,[23] concluding that we see objects because the eyes are able to receive light; this stands in opposition to the ideas of classical thinkers such as Plato, Galen, and Roger Bacon (1214-1294), who asserted that

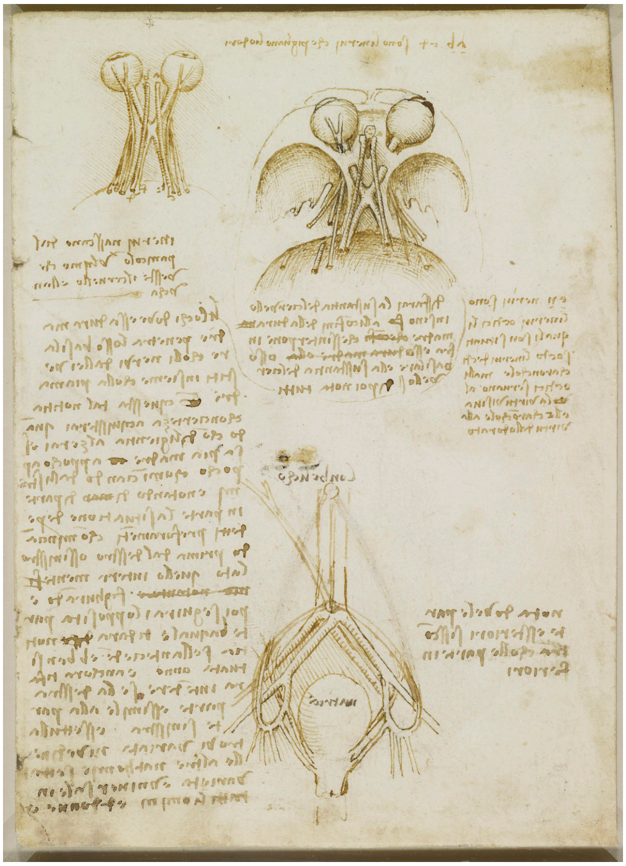


Figure 5 (left). Optic nerves, optic chiasm, and cranial nerves (1508). The drawing shows the close relationship between the optic nerves, optic chiasm, olfactory nerves, and olfactory bulb. It also includes a dissection of the lateral wall of both cavernous sinuses, exposing the oculomotor nerves, abducens nerve, and the ophthalmic branches of both trigeminal nerves.[4,12] RCIN 919052. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

Figure 6 (right). The layers of an onion and the brain's ventricles according to medieval tradition (1489). The drawing shows Leonardo's bewilderment at the challenge of establishing the location of the soul within the brain and the importance of the sense of vision in answering this question. In accordance with medieval tradition, he likens the different layers covering the brain to the layers of an onion, and includes a diagram of the three cerebral ventricles: anterior (*sensus comunis*), middle (reasoning), and posterior (memory).[11,14,27] RCIN 912603r. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

the power of sight emanated out from the eyes, enabling objects to be perceived.[12]

According to da Vinci's notes, "the eye, the window of the soul, is the chief means whereby the understanding can most fully and abundantly appreciate the infinite works of Nature."[24]

The notes in Figure 5 also include a precise description of the olfactory bulb; Leonardo was the first to consider this structure as a cranial nerve.[12]

Regarding the anatomy of the brain, he was initially influenced by the medieval tradition of Albertus Magnus (1193-1280)[25] and believed that the ventricles were responsible for the functions of the brain: Leonardo likened the superficial layers of the brain and cranium to an onion, initially defending the widely accepted model of three cerebral cavities: the anterior (*sensus comunis*), middle (reasoning), and posterior (memory).[14,20,21] In turn, Albertus Magnus, heir to the Galenic tradition, was inspired by the vision of Avicenna (908-1037) and Maimonides (1138-1204); like them, he considered the soul to be located in the *sensus comunis*.[11,25]

Figure 6 represents da Vinci's bewilderment with the immensity of the challenge he faced. The drawing

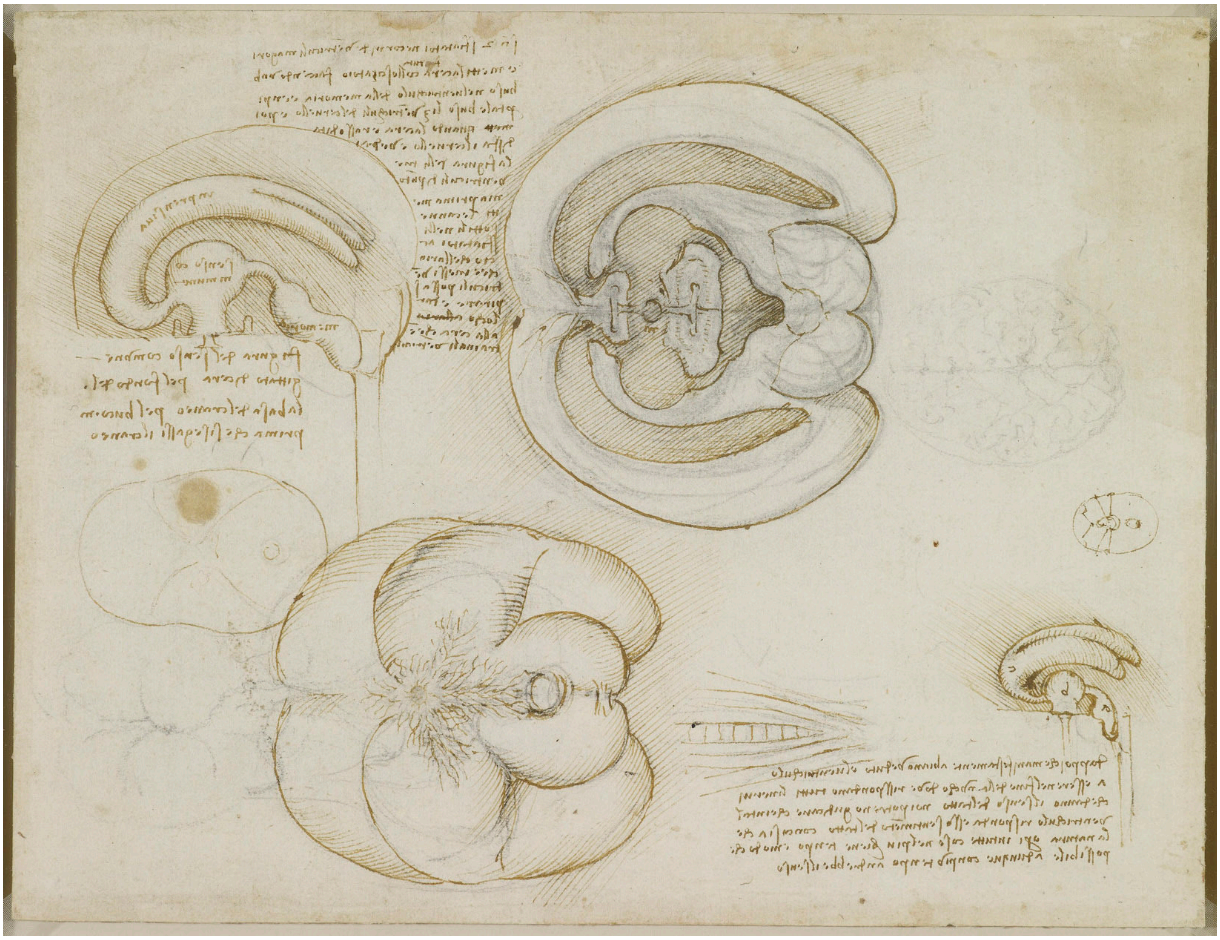


Figure 7. Wax cast of the ventricles of the brain of an ox (1508). The drawings show the results of Leonardo's experiments and his reinterpretation of the anatomy of the cerebral ventricles. They are described as *imprensiva* (anterior), *senso comune* (middle), and *memoria* (posterior); the first includes a division, corresponding to the lateral ventricles. We also observe the communication between the *imprensiva* and *senso comune* (foramen of Monro) and between the *senso comune* and *memoria* (aqueduct of Sylvius).[11,14,27] RCIN 919127. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

raises more questions than it answers, and the diagram indicating the location of the ventricular system, with the three cavities inside the brain, is based not on empirical knowledge but on medical writings from the time. We may imagine how unsatisfied Leonardo would have been with this model.

To advance in his research and improve his understanding of the brain, he had to begin learning dissection techniques. Once more, lacking medical training, he had to teach himself, studying Galen, Avicenna, and Mondino de Luzzi (1270-1326),[4,11,14,17,21] although it is likely that a friend, the anatomist Marcantonio della Torre (1481-1511), would have taught him some techniques years later.[26] He began with animals, and later continued with human dissections. Acting on the margin of legality, he dissected approximately 30 corpses over his lifetime, both during his time in Florence and Milan and in Rome, enduring extremely poor sanitation and using very rudimentary tools.[20,21]

Between 1506 and 1508, Leonardo felt himself prepared for the challenge and, employing his knowledge of the use of moulds for producing bronze sculptures, invented a new technique for studying brain anatomy by injecting molten wax into the brains of oxen to create casts, which enabled him to better understand the structure of the brain in three dimensions.[4,11,12,14,20,27] To perform the experiment (the evidence indicates that he must have performed several, and that he had dissected oxen previously), he made perforations in the frontal lobe to act as air outlets, then injected the molten wax into the fourth ventricle. The wax solidified upon cooling, taking the shape of the container. He subsequently dissected away the brain tissue, obtaining a perfect cast of the bovine ventricular system. The cast showed him that the first ventricle is not a single structure, but rather is composed of two lateral bodies; he also wrote the first description of what later came to be known as the foramen of Monro (1700-1757).[4,12,21,27] Figure 7 shows the results of his technical experiments with ox brains and how his understanding of brain anatomy changed with respect to the initial conception demonstrated in Figure 6.

Leonardo's experiment with injecting wax into the cerebral ventricles is considered one of the most inspiring demonstrations of the empirical nature of the modern scientific method.[27]

Figure 8, known as the "Weimar anatomical sheet," includes two drawings of the nervous system and another of the anatomy of the genitourinary system.[28] The main drawing shows the evolution of Leonardo's anatomical conception of the ventricular system, which is considerably more accurate and bears a greater resemblance to today's understanding. The drawing shows how the optic nerves converge at the base of the third ventricle and not in the anterior horns of the lateral ventricles; as a result, Leonardo places the *sensus comunis* in this cavity, coinciding exactly with the geometrical analysis he had conducted in the series of drawings of crania from 1489.[11,14] Furthermore, this extraordinary document includes a second drawing, which represents a novel method of anatomical illustration, developed by Leonardo himself: the different parts of the head are shown separately in what we would today call an "exploded view," with the upper part (corresponding to the skull cap) removed to show the contents of the cranial vault, the central part showing the brain and its connections, and the lower part depicting the skull base, showing the folds in the dura mater (Figure 8).[28]

With all this knowledge, acquired this time through direct observation and experimentation, Leonardo broke away from the prevailing dogma and redefined the functions of the three ventricular cavities. He calls the first cavity and its lateral horns the *imprensiva*, and relates it with judgement and intellect (not greatly dissimilar to the cognitive functions of the frontal lobe); the second is called the *senso comune* (inspired by the *sensus comunis* of the Greek thinkers), and serves as the convergence of the senses as well as controlling movement, thereby highlighting the integrating function of the brain; and the third (*memoria*), located in the posterior fossa, is characterised as the place in which memories are stored.[11,14] Therefore, Leonardo was a pioneer in the localisation of cerebral functions.

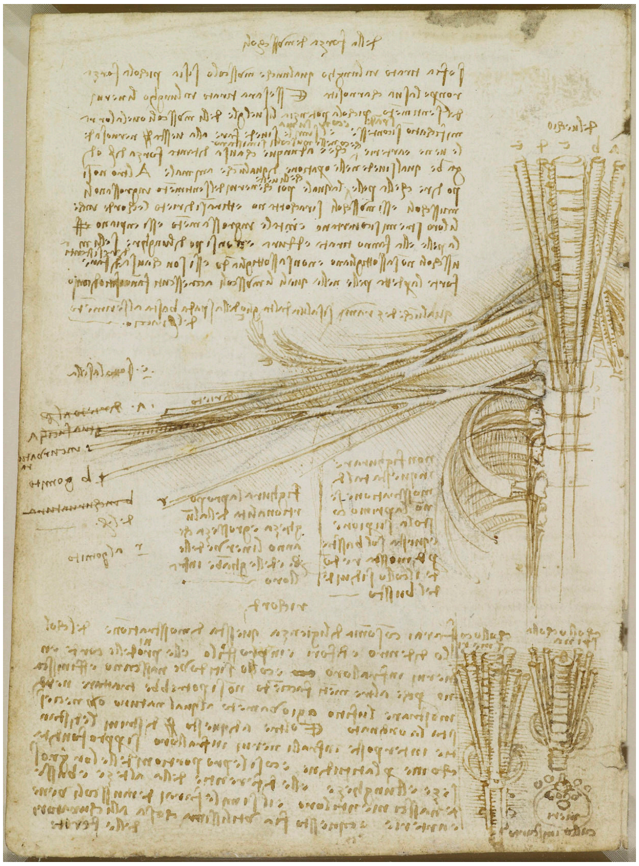
Leonardo produced no further anatomical illustrations of the brain after 1508,[20,21] which would appear to show either that he was satisfied with his conclusions on the location of the soul,[14] or that he faced insurmountable technical limitations preventing further progress in this research, and continued pursuing his multiple other interests.

Emotion, control of movement, and the peripheral nervous system

During his days at Verrocchio's *bottega*, Leonardo wrote in his notes that "… the secret of movement and the expression of human emotion, so vital to the artist, lies in the nerves and muscles of the body…"[20,21] In his eagerness to understand the relationship between emotions, facial expression, and the neurological control of these phenomena, he performed studies on the cranial nerves and their close links with the brain and soul.[20,21] In the famous Weimar anatomical sheet (Figure 8), he drew the cranial nerves in pairs, identifying them with letters rather than numbers.[28] Here, he is mistaken about the apparent origin of the nerves, as he does not identify the brainstem as an intracranial structure; however, he does correctly establish the anatomical relationship between the optic and olfactory nerves, as well as the long course of the vagus nerve. This sheet also includes a text that clarifies his intentions: "draw the nerves which move the eyes in any direction, and its muscles; and do the same with their eyelids, and with the eyebrows, nostrils, cheeks and lips, and everything that moves in a man's face."[21]

Figure 5 shows the relationship between the optic nerves, olfactory nerves, and optic chiasm with greater detail and precision. As mentioned above, Leonardo was the first to consider the olfactory nerve as a cranial nerve.[12] The figure also includes a dissection of the lateral wall

Figure 8. The "Weimar anatomical sheet" (1508). The progression of Leonardo's understanding of the anatomy of the brain. The *imprensiva*, *senso comune*, and *memoria* are shown. The optic nerves converge in the base of the third ventricle, not in the first ventricle. The bottom right drawing shows an "exploded view" of the different parts of the head and brain. The cranial nerves are shown in pairs, and identified with letters.[20,21,28] KK6287v. Reproduced with permission from Kunstsammlungen zu Weimar, Weimar, Germany



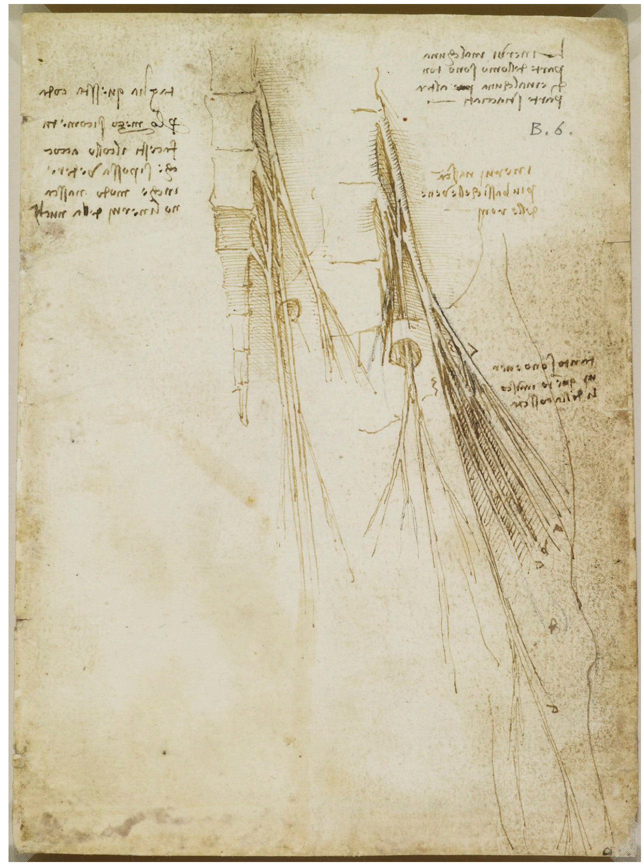


Figure 9 (left). Brachial plexus (1508). Illustration of the brachial plexus, showing the superior, middle, and inferior trunks in detail. The anatomical relationship between the divisions and cords is less precise, although the representation of the terminal branches is more accurate.[20,21] RCIN 919020v. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

Figure 10 (right). Lumbosacral plexus (1508). Dissection of the lumbosacral plexus, including the femoral nerve and its multiple branches in the thigh, the obturator nerve, and (in what was a systematic error) a duplicated sciatic nerve.[20,21] RCIN 919023r. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

of both cavernous sinuses, exposing the oculomotor nerves, abducens nerve, and the ophthalmic branches of both trigeminal nerves.[14]

Leonardo also studied the peripheral nervous system and its involvement in controlling movement. On this subject, we must be aware of the limitations affecting this work: as no fixing or preservation techniques had yet been developed, nerve fibres would begin to soften and decompose after several hours.[21] This made nerves particularly difficult to dissect, and they were frequently mistaken for tendons.[4] Da Vinci referred to the fine nerve fibres innervating muscles as "nervous membranes," describing them as *quasi insensibile* ("almost imperceptible").[12]

Figure 9 is the final result of a series of drawings of the brachial plexus, in which he refined his technique until he was able to precisely describe the superior, middle, and inferior trunks.[21,29] While the depiction of cords and divisions is less precise, other studies of the innervation of the arm clearly display the terminal branches and the radial, ulnar, and median nerves.[20,21,29] Once more, Leonardo did not have merely a passive interest in the anatomical structure; rather, he wanted to know how it was related with movement and with life itself. In this respect, his observations on the brachial plexus are based not only on dissections, but also on lesionology: he described how the sensation and function of the arm were affected differently by lesions to specific areas.[21,29] Therefore, da Vinci was also a pioneer in the study of functional anatomy.

Fewer studies exist of the lumbosacral plexus; however, there is clear evidence that Leonardo developed dissection techniques to unravel the complex labyrinth of this pelvic structure. According to his notes, "there are as many nerves as muscles in the thigh."[21,30] Figure 10 shows one of his finest drawings of the lumbosacral plexus and the nerves of the leg, including the femoral nerve and its multiple branches in the thigh, the obturator nerve, and (in what was a systematic error) a duplicated sciatic nerve.[20,21,30] Regarding the functional anatomy of the lower limbs, Leonardo makes some interesting observations on the action of agonist and antagonist muscles and their mutual dependency and need for coordination, several centuries before the work of Sherrington (1857-1952).[21]

Finally, in a little-known drawing (Figure 11), da Vinci presents one of the first known representations of the central and peripheral nervous systems as an integrated whole, describing the spinal cord as the "tree of all the nerves,"[21] once more recognising its fundamental role. In his notes, he writes 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."[4,20,21] From his experiments with frogs, in which he found that perforating the spinal cord at its junction with the brain caused the immediate death of the animal, he deduced that the spinal cord was responsible for the sense of touch and the origin of all movement.[11,21,31] Nonetheless, he also mistakenly followed Plato and Hippocrates in the belief that the spinal cord was also responsible for the *virtu gientjtiua* ("generative power") of life, the production of semen.[11,14]

The drawing in Figure 11 depicts the body in movement and, therefore, the functional role of the nervous system in movement. Once more, the long trajectory of the vagus nerve is noteworthy.[20,21]

Leonardo continued studying functional anatomy, addressing practically all systems of the body,[20] and focused particularly on the cardiovascular system,[32,33] applying his knowledge of mechanics and hydraulics to understand the physiology of the heart's valves.[34]

The frustrated anatomical treatise, the "man without letters," and the birth of the codices

In 1489, during the first period he spent in Milan, Leonardo wrote in his notes that he was considering writing a comprehensive study of the human body, including the "veins, nerves, muscles, and bones." He would call the work *On the human figure*.[11,14] The "Vitruvian man" (1490) would have been part of this project. The book never came to be published. Famous for never completing anything,[9,10] and after years of anatomical research, during his second stay in Milan Leonardo considered collecting everything he had learned in an anatomical treatise, to be developed with his friend Marcantonio della Torre, an anatomist from the University of Pavia, with whom he worked intensely between 1509 and 1511.[26] Unfortunately, della Torre died of plague in 1511,[20,26] and yet another of Leonardo's works remained unfinished.[19,20] Had it been published, Leonardo would have preceded Andreas Vesalius (1514-1564) by 30 years; Vesalius' book *De humanis corporis fabrica* (1543), featuring illustrations by Titian's disciple Jan Stefan van Calcar (1499-1546), is considered the first treatise on modern anatomy.[19,21,35]

Leonardo worked at the margins of science.[36] His extraordinary discoveries, so beautifully illustrated in his drawings, were never published and were forgotten after his death.[11,18,20,37] His assistant, Francesco Melzi of Milan, spent 50 years at his villa in Vaprio d'Adda, in Bellagio, organising working groups to order and classify the more than 7200 pages of texts and drawings that Leonardo bequeathed him.[9,14,20] When Melzi died in 1570, the manuscripts were forever dispersed, giving rise to the "codices" (25 in total). Most of these documents are named for the place where they are stored or the families that acquired them (eg, *Codex Madrid I and II*, or the *Codex Leicester*).[2,9,20]

The manuscripts preserved today are thought to account for only 25% of the documents that Leonardo left to Melzi.[9]

Pompeo Leoni (1533-1608), King Philip II's favourite sculptor,[2] who frequently travelled between Spain and Italy, was interested in Leonardo's manuscripts and drawings and compiled a series of documents that included the anatomical drawings.[9,20,21] The Weimar anatomical sheet (Figure 8) also belonged to the collection bound by Leoni, but the page was removed

Figure 11. An integrated view of the central and peripheral nervous systems (1508). The drawing depicts the integration of the central and peripheral nervous systems and the role of both in controlling movement, as suggested by the small man shown in the centre. The long course of the vagus nerve is also noteworthy.[21] RCIN 919034v. Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020

centuries later at the Kunstsammlungen in Weimar, where it was included in Goethe's collection of art by the Italian masters.[28] When Leoni died, the anatomical drawings were passed to the collector Thomas Howard, 21st Earl of Arundel, who took them to England. It is unclear how they came to be included in the Royal Collection, but it has been suggested that they were acquired during the reign of Charles II, between 1660 and 1665.[20] According to the available records, in 1690 they appeared in the catalogue of Kensington Palace during the reign of William III,[20] and were later stored in the archives of Windsor Palace.[2,20,21] They remained there, forgotten, for nearly a century. In 1773 they were rediscovered by the Scottish anatomist William Hunter, who recognised their extraordinary merit and beauty.[2,20] The *Codex Windsor* was born. Hunter had planned to publish the drawings, but died in 1781, once more delaying their dissemination.[2,20] In 1883, Jean Paul Richter translated and published Leonardo's notebooks, but copies of only some of the anatomical drawings were published, between 1898 and 1916.[20] Finally, a complete edition of the work was published for the first time between 1978 and 1980.[20,38]

Leonardo today: his legacy and the fusion of art and science

With the exception of *A treatise on painting*, published in 1651, Leonardo kept his extraordinary discoveries secret. As he was not involved in the academic world of the time, his work was marginalised in history. According to the science historian Desiderio Papp, "… his true influence on the development of science was less, in many ways, than that of some other souls who were mediocre compared to him."[36] Some authors even question whether Leonardo can truly be considered an anatomist.[2,19,35] As mentioned above, he had no medical training, did not publish any of his work, and most importantly, he had radically different motivation. While he revolutionised the study of anatomy, his research was motivated less by an interest in morphology than by a need to develop a philosophical view of the unity of man and nature, the relationship between microcosm and macrocosm, as described by Plato.[1,20] In such a view, it is fundamental to understand how each component (living beings or inert matter) fits perfectly into a single harmonious system that functions according to a handful of mathematical laws,[19] none other than "the mystery of creation," in the words of Kenneth Clark.[39]

Given his lack of formal training and his limited knowledge of Latin, Leonardo described himself as a "disciple of experience" or *omo sanza lettere*, a "man without letters."[2,3,9,10,24] He stood out for his mirrored writing, written in Tuscan dialect, and his poor spelling.[40] In fact, one of his main biographers, Walter Isaacson, highlights an interesting irony: for Leonardo, the lack of an academic education actually represented an advantage, as it allowed him to develop his own worldview and granted the freedom to generate knowledge based on experience, moving away from the classical tradition.[9,35]

However, Leonardo was already greatly admired during his lifetime, not only for the quality of his artistic work, but also for his multiple talents and abilities.[2,41] According to Carmen Bambach, it cannot be overstated that the paedagogical dimension of Leonardo's artistic activity would be a lasting influence.[2] Da Vinci is depicted as Plato (carrying the *Timaeus* in his left hand) at the centre of the *School of Athens* fresco in the Vatican by Raphael, an admirer of his,[2,9] and the king of France himself, Francis I, invited him to live at the palace in Clos-Lucé, near his own residence, the Château d'Amboise, so that he may have the time, freedom, and resources to continue developing his projects and, in so doing, bring the Renaissance to France.[42] Due to Leonardo's fame, many made the pilgrimage after his death to see with their own eyes the wealth of manuscripts and drawings kept by Melzi in Vaprio d'Adda.[14,20] Many copies were made of his drawings and his ideas were plagiarised, and he was rarely cited or acknowledged.[14] For such authors as Charles Gross, Leonardo's fame in northern Italy as an artist/anatomist and the naturalistic techniques he developed for anatomical illustration represented the starting point for the birth of modern anatomy, facilitating the subsequent work of Vesalius.[43]

It is very difficult to establish the true magnitude of Leonardo's impact on the subsequent development of the arts and sciences in Western culture.

However, if anybody was influenced by his research and anatomical studies, it was Leonardo himself.[11] During his long journey of discovery, he drew many studies of facial physiognomy and the relationship between muscles, movement, and the expression of emotion. It is impossible not to think of the gazes and facial expressions in Leonardo's paintings and how he was able to give his paintings soul as he improved his understanding of the unity of brain and body, and the relationship between the body and nature.

In *Portrait of Ginevra de' Benci* (1474) (Figure 12), Leonardo's first portrait, which precedes his anatomical studies, the subject's gaze is empty and inexpressive, lacking soul,[11] whereas in the famous *Mona Lisa* (1503-1509) (Figure 13), which he painted after having performed dissections, we observe a profound, evocative gaze that reflects the complexity of the soul. The *Mona Lisa*'s gaze represents the convergence of his studies into optics, visual perception, the expression of emotion, and their relationship with the *senso comune*.[8,11] The "uncatchable smile," as some have described the enigmatic expression used in many of Leonardo's portraits, is another example of this.[44,45] Recent studies suggest that the *Mona Lisa* only smiles with the bottom left part of her face, as in a feigned smile.[46] It has been speculated that Leonardo was aware of this effect, which seems relatively likely given his knowledge of physiognomy and his understanding of the innervation of the muscles of the face.[46]

To achieve these effects, and in order to capture his philosophical thought and anatomical knowledge in his art, Leonardo continued to perfect and to develop his technique: he experimented with different types of pigments and surfaces, played with optics and perspective, worked with *chiaroscuro*, and invented *sfumato*.[2,9,10]

To achieve a *sfumato* effect, multiple layers of paint (up to 20 or 30) are applied, with a thickness of 2 µm in the thinnest areas and 30 µm in the thickest[47]; this gives shapes imprecise outlines and achieves a barely-perceptible transition between colours. Light and shadow are superposed like smoke, giving the composition an appearance of oldness, distance, and perspective.[47] In the words of Gombrich, "the blurred outline and mellowed colours […] allow one form to merge with another and always leave something to our imagination."[9,48] Using this technique, Leonardo was able to achieve a unity between the human figure and nature, fusing his subjects almost imperceptibly with their setting.[45,47]

Leonardo, a unique and unclassifiable genius, makes it clear that he saw no difference between art and science in his approach to an understanding of nature and in his epistemic vision of the creative process.[1,2,19,49] The line between the two is blurred and confused, and his global view of knowledge presupposes the search for beauty, both in aesthetic and conceptual terms. He writes in his notes that "to develop a complete mind: study the science of art. Study the art of science. Develop your senses—especially learn how to see. Realise that everything connects to everything else."[24]

Figure 12. *Portrait of Ginevra de' Benci* (1474). Leonardo's first portrait, painted prior to his anatomical dissections. The subject's gaze is empty, inexpressive, and lacking soul.[2,11] National Art Gallery, Washington, DC

Today, Fritjof Capra recognises in Leonardo what he terms "systems thinking," treating knowledge as a holistic understanding, integrating the whole and its processes.[50] Once more, the concept of microcosm and macrocosm takes a central role.

Therefore, Leonardo da Vinci's legacy goes far beyond his paintings, his countless first descriptions of anatomical structures, and his extraordinary machines: it fundamentally consists of the methods he used, his integral concept of knowledge, and his vision of the unity of man and nature as an integrated, indivisible, interdependent system.[1,19]

Today, Leonardo continues to be a relevant, immeasurable figure. His work has been studied exhaustively, with frequent new readings, reviews, and rediscoveries.[2,9]

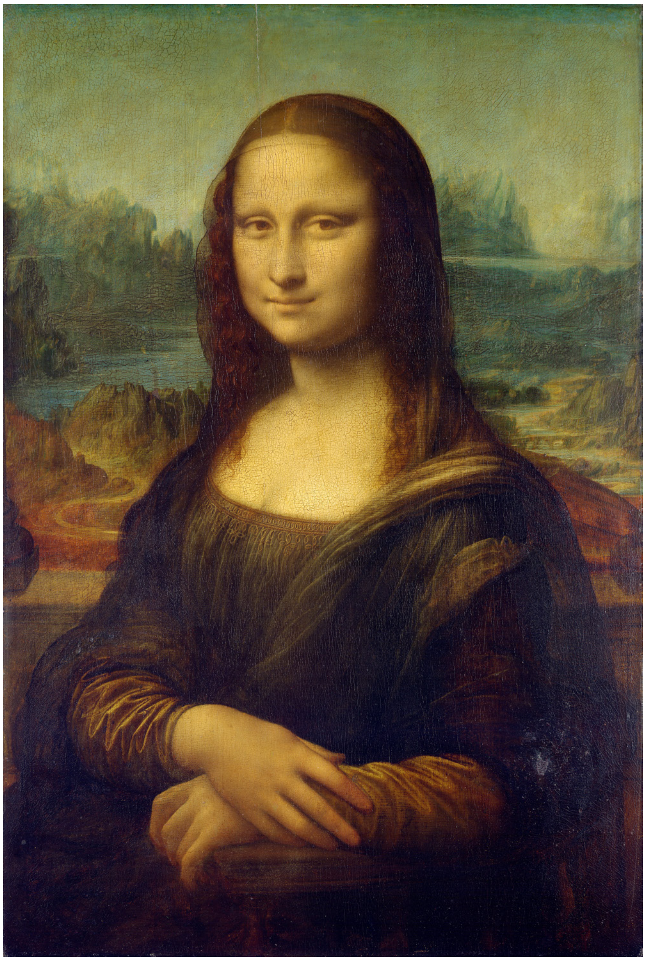


Figure 13. *The Mona Lisa* (1503-1509). Painted after Leonardo had started performing dissections; the subject's gaze is profound and evocative, reflecting the complexity of the soul. It represents the convergence of his studies into visual perception, the expression of emotion, and their relationship with the *senso comune*. Her "uncatchable smile" and the use of *sfumato* are another example.[8,43] The Louvre, Paris

Recently, a previously unknown reflection from the *Codex Atlanticus* has emerged that addresses the importance of medical humanities:

> Medicines when well used restore health to the sick: they will be well used when the doctor together with his understanding of their nature shall understand also what man is, what life is, and what constitution and health are.[51]

For some authors, 500 years after Leonardo's death, we are no closer than he was to unravelling the mystery of the soul and its relationship with the brain.[12] Leonardo ceased his research into the nervous system in 1508, partly due to a lack of technical means to further advance his anatomical and physiological studies (Janssen invented the microscope in 1590).[52] In this way, Leonardo may in the present day have been a neuroscientist, continuing to research the functioning of the nervous system. Just as he applied mechanics and hydraulics to better understand the functioning of the human body, and like Cajal did in his own time, he would apply the available technology, perfecting it, in order to unravel the impenetrable mystery of the human brain, the most complex structure to have evolved and a true bridge between microcosm and macrocosm.

Conclusions

In his search for the relationship between microcosm and macrocosm, and the seat of the soul, Leonardo took inspiration from Plato's cephalocentric theory, becoming fascinated first with the cranium and subsequently with the nervous system itself, revolutionising anatomical study and illustration. A pioneer in the study of functional anatomy and the localisation of cerebral functions, he made significant discoveries on the anatomy and physiology of the nervous system. However, Leonardo da Vinci's legacy in medicine in general and in neuroscience in particular was lost for centuries. Lacking access to formal academic circles, his extraordinary discoveries, so wonderfully recorded in his anatomical drawings, had no significant influence on the subsequent development of neuroscience, unlike his impact on painting and drawing. Nonetheless, and despite his fame during his lifetime, Leonardo's legacy goes far beyond the contents and concepts of his work, and fundamentally consists of his methods and his vision of the unity of man and nature in an integrated system. Through our own limitations, we attempt to categorise him according to contemporary paradigms, but Leonardo did not distinguish art from science; therefore, he approached the understanding of nature and its processes from a global perspective, searching for a rational, unifying explanation for everything. For Leonardo, the sense organs and the integrating capacity of the brain played a central role in this truly "systems thinking." Leonardo was a pioneer in the scientific method, and through careful observation of nature he left a world (and man) different to that previously known.

Conflicts of interest

The author has no conflicts of interest to declare.

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