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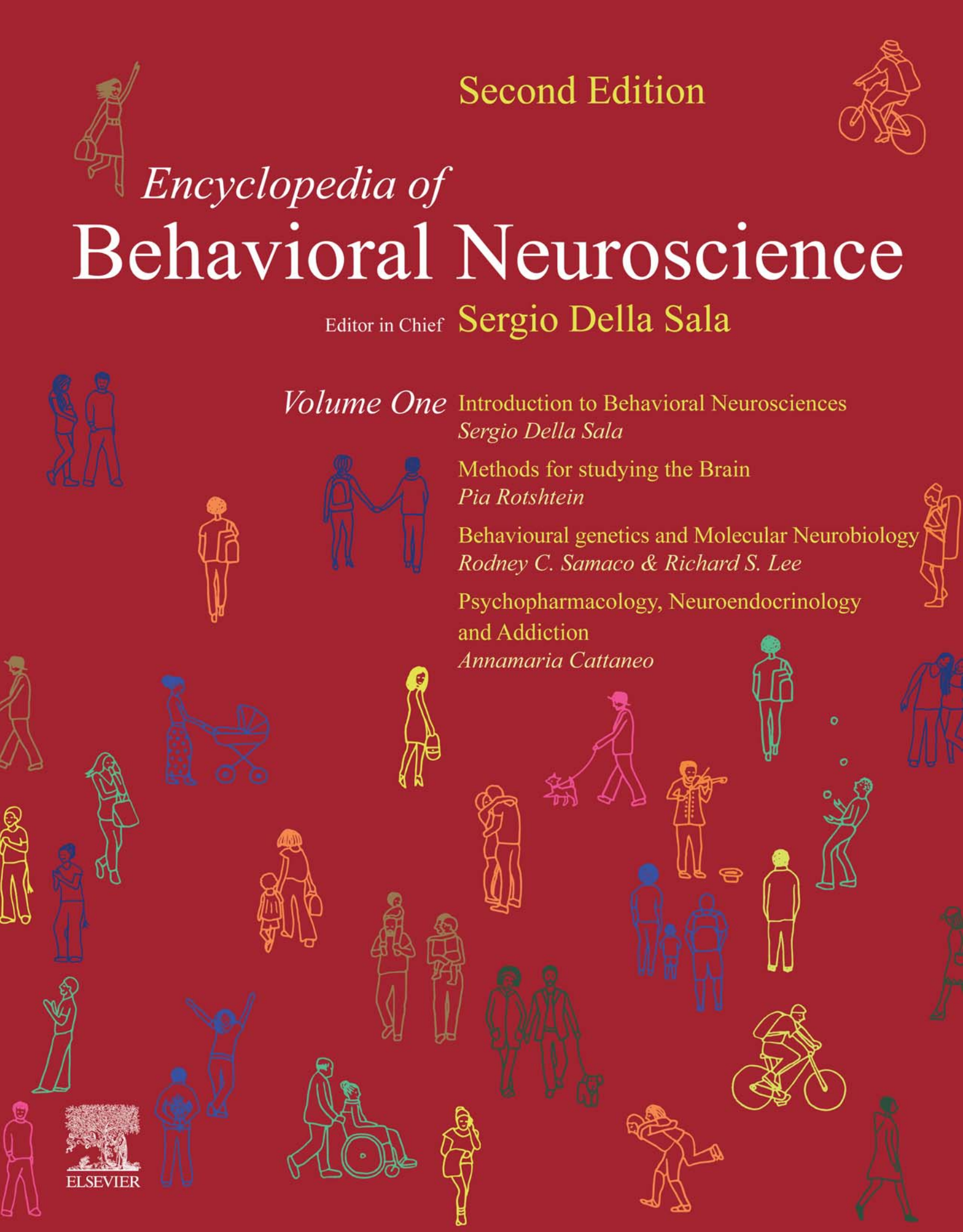
Encyclopedia of Behavioral Neuroscience

Editor in Chief **Sergio Della Sala**

Volume One



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ENCYCLOPEDIA OF BEHAVIOURAL NEUROSCIENCE

SECOND EDITION

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VOLUME 1

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POSTFACE

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Encyclopedias intrigue me. Starting from the term, ἐγκύκλιος παιδεία: enkyklios, meaning "general," and paideia, meaning "education." They are sources aiming to provide a comprehensive background for one or more disciplines. They have a long history, from the *Historia naturalis* of Pliny the Elder to Diderot and d'Alembert's *Encyclopédie*. I grew up consulting the ambitiously named *Enciclopedia Universale*, nicknamed *Le Garzantine*, a winsome diminutive from the name of the Italian publisher (Garzanti) due to their compact format. I loved searching through their pages.

Nowadays general encyclopedias would be implausible. However, there is still room for thematic reference textbooks, like this *Encyclopedia of Behavioral Neuroscience*. Not only do they offer consultation and debating material, but they also provide the opportunity of serendipitous discoveries, which are becoming rare in the existing era of web search. When seeking information from a specific entry, the inquisitive reader may come across other chapters which may grab their attention. These fortuitous encounters may widen our knowledge, increase our understanding, or simply stimulate our curiosity.

To stimulate these coincidental detections the thorough, peer-reviewed entries within the *Encyclopedia of Behavioral Neuroscience* have been ordered by topics, and then alphabetically within them. The ease of consultation provided by alphabetical ordering becomes more useful when items belong to the same topic. Like the virtuous qualities that the perfect lover should possess according to Leonela, the maid character in *Don Quixote: Amiable, Brave, Courteous, Distinguished, Elegant, Fond...*

An encyclopedia is not a book to read from start to end, rather a text to appreciate through navigation, like relishing grapes picked one by one from the bunchstem. Since you have availed yourself of the possibility of skimming through this encyclopedia, online or in its paper version, set back and enjoy the ride.

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History of Behavioral Neurology

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Behavioral Neurology as a Branch of Medicine

Behavioral neurology is primarily concerned with the neurological causes of degraded behavior following disruption of higher brain function. In the early 1970s, it re-emerged as a subspecialty of neurology focused on diagnosing and treating patients with damages, diseases, and disorders of the nervous system and related tissues that alter normal behavior. While some practitioners have studied congenital diseases and geriatric dementias, behavioral neurology came to overlap extensively with the fields of neuropsychiatry and neuropsychology, differing primarily in the degree of medical diagnosis and treatment of patients. The major advances in neuropsychology and neuropsychiatry are thus part of the history of behavioral neurology.

Contemporary behavioral neurology has developed foci in common with the neurosciences, but both have evolved noteworthy differences in remit, scope, and clinical emphasis. As a branch of medicine, the former normally requires expertise in the management of the molecular and neurochemical basis of behavioral disorder, the ability to relate functional and structural conditions to clinical data using imaging techniques and electrophysiological methods, the implementation and interpretation of neuropsychological and neuropsychiatric assessments, and comprehensive clinical diagnosis and therapeutic treatment. By contrast, as a branch of science, the latter has crystalized into an academic discipline concerned with epistemological successes about the neural bases of behavior (basic research) and the use of that knowledge in new technologies and developments (applied research). Medicine is a far older profession than science; by implication, behavioral neurology, as a branch of medicine, is a far older field than neuroscience.

This history of behavioral neurology divides into six eras: ancient, classical, medieval, post-Renaissance, modern, and contemporary. In some cases, the divisions correspond neatly to major intellectual boundaries, such as the division between ancient and classical periods by Galenism and between modern and contemporary periods by Geschwind's (1965) two-part opus. In others, the boundaries are such that no non-arbitrary division can be established.

Ancient

Among the oldest surviving scholarly works in neurosurgery is the so-called 'Edwin Smith Surgical Papyrus' (Breasted, 1930). Now dated to around ^{bce} 1600, the papyrus is an amalgam of 48 case descriptions transcribed from a much older treatise that are sometimes conjectured to derive from the time of Imhotep (floruit ^{bce} ~2645). The first 33 cases describe neck and head injuries; they relate trauma and gross anatomical damage to deficits—including hemiplegia, loss of speech, and seizures—and prescribe various treatments or palliative measures. The papyrus contains a hieretic lexeme for the term *brain*, one of humanity's earliest recorded uses. Similar Babylonean surgical texts offer descriptive taxonomies of symptoms now associated with seizures, headaches, meningitis, narcolepsy, cranial nerve injuries, and sundry other conditions, and associate with them various prognostications ranging from recovery to imminent death (Scurlock & Andersen, 2005). These taxa are invariably bound up with fantastic mythologies; but together with surviving texts from Chaldean, Mycenaean, Chinese, Mayan, etc. civilizations, they show that ancient physicians were familiar with the behavioral consequences of brain damage.

During the archaic period, Magna Graecia was a main locus of innovation. Alcmaeon of Croton (floruit ^{bce} ~490) was an early medical philosopher contemporaneous with the Pythagoreans on the Bruttian peninsula. Although postmortem surgery was rarely performed and culturally proscribed, Alcmaeon excised the eye and possibly the optic nerves (Lloyd, 1975), and arguably was the first to connect perceptual considerations to the construal of the brain as an organ of the sensorium and intellect. From his empirical studies, Alcmaeon inferred that sensory organs are connected to the brain, and the brain to muscles, by channels (*poroi*) and cords (*neura*, *tonoi*), and was an early proponent of the thesis that they transport various 'spirits' (*naturalis*, *zooticon*, and *psychikon*). The pre-

Socratic Miletians—particularly the Anaximenean disciples, such as Diogenes of Apollonia (floruit ^{bce} ~435)—developed this thesis by regimenting descriptions of anterior vascular anatomy, which included considerations of ischemic neuropathy, and postulating the movement of pneuma and its admixture with blood within the brain (hence the etymological connection between the Greek term for air, *αέρας*, and the Latin *arteria*).

The near-eastern Mediterranean from Cos to Alexandria was another major locus of ancient neurological study. Hippocrates (^{bce} 460–375) and the other Asclepiads of Cos and Cnidus summarized then-current medical knowledge into what would become the *Corpus Hippocraticum* (Littré, 1973), a compendium of >60 works by different writers. Hippocrates himself was likely an early advocate of humoralism, which posited four states—sanguine, choleric, phlegmatic, and melancholic—thought to constitute the biophysical basis of personality. Although not gripping, humoralism was importantly false: it anticipated the 19th century concept of homeostasis, and issued naturalistic explanations of psychological temperament by appealing to biological disorders (*dyskrasias*).

Neurology in the ancient period was typically merely responsive: common foci were the treatment of headaches and seizures, combat wounds, and palliative responses to effects of surgical interventions. However, these developments across the Mediterranean basin commenced an important tradition of pre-Hellenistic physical philosophers (*physiologi*) investigating the brain and body, beginning with the dissections by the three directors of the Athenian Lyceum: Aristotle (^{bce} 384–322), Theophrastus (^{bce} 370–287), and Strato of Lampsacus (^{bce} 335–269).

In Alexandria to the south, Herophilus of Chalcedon (^{bce} ~330–260) also performed hundreds of dissections, probably of dubious legality, establishing the distinctions between cerebrum (*enkephalos*) and hindbrain (*parenkephalis*) and between meningeal layers, and leading to intense curiosity about ventricular function. Erasistratus (^{bce} ~304–250), to whom Celsus (^{bce} 26–50 ^{ce}) ascribed human vivisections, further distinguished between neurons and tendons, traced the path of afferent nerves from the hindbrain, and, according to Rufus of Ephesus (~70–150 ^{ce}), hypothesized different functions of sensory and motor nerves (Solmsen, 1961). Erasistratus also anticipated Harvey's discovery of circulation. More notable, though, was his decisive pivot toward empirical methods, which would eventually result in construing the brain as the governing organ (*hêgemonikon*), albeit with pneuma as its central physiological agent.

Classical

Herophilus and Erasistratus were intrepid anatomists, and their replacement of cardiocentrism with encephalocentrism make them the most important figures in ancient neurology. Thereafter, neuroanatomy fell quiescent for three centuries, with empirical discovery ceding to scholarly commentary during the Ptolemaic dynasty.

The transition from the Roman Republic to the Roman Empire, following Octavian's defeat of Marcus Antonius and Cleopatra VII, created the stabilizing conditions under which traditions of anatomical research could eventually be recovered. Marinus of Alexandria (70–120 ^{ce}) helped usher neurology into the classical period (Rocca, 2003). In attempting to relate paralytic symptoms to contralateral damage, Aretaeus of Cappadocia (floruit 140 ^{ce}) noticed the decussation of motor nerves. However, close study of the behavioral effects of neuropathology had to wait upon more systemic empirical explorations.

That jump occurred with Galenus of Pergamon (129–216 ^{ce}), who was by far the most important and influential figure in neurology during the classical period. Like Marinus and his teachers, Galenus performed dissections of cranial nerves, introducing functional distinctions between auditory, facial, oculomotor, optic, trigeminal, and vagus nerves; and he made clinical observations that allowed him to correlate spinal injuries and their behavioral consequences (see **Fig. 1**). Like Hippocrates, he played a scholarly role by synthesizing centuries of scholarship to distinguish between complex structures of the brain from merely spatial parts, including the dura and pia mater, corpus callosum, fornix, and pineal and pituitary glands; but he also broke with some of that

Figure 1 Galenic pig vivisection.

scholarship. He conjectured that the softness of sensory nerves, being more easily alterable, is what provides for the receipt of sensory information, and he localized the sensorium to the cerebrum because of its relative softness, analogously; being harder, Galenus reasoned that the cerebellum is primary in the control of movement. While Galenus's humoralism is notorious, it was his engagement of the pneumatological views of the Athenians and Alexandrians that had lasting influence. Galenus was renown for demonstrations—including competitive 'duels' or 'truth-contests' with other vivisectionists—of his anatomical and physiological knowledge (Gleason, 2009). In one with Martialius (150–190 ce), a cantankerous old-fashioned cardiocentrist, Galenus reportedly ligated an aorta to falsify the thesis that arteries convey pneuma, and then applied pressure to the ventricles ad seriatim to demonstrate stupor, progressive paralysis, and apoplexy.

Ventricular or 'cell' theory at that time postulated three cells, which were thought to allow jointly for the transformation of inhaled air, admixed with cerebral fluids and vital pneuma from the heart, into animal spirit. Each cell served as a register for a different mental function. The anterior-most ventricle received what were thought to be pneumatic presentations of objects from the sensorium, with pneuma being compressed into the middle ventricle to be operated on by reason and imagination, with some of those presentations being deposited as memories into the posterior ventricle. The brain's collapse following cerebrospinal fluid loss from ventricular dissection, as recorded between 169–175 ce in Galenus's *De Anatomicis Administrationibus* (/1956) and *De Usu Partium* (/1968), gives the impression of the kind of 'structural deflating' that would have made pneumatic ventricular theory compelling.

Medieval

The Hellenistic history of behavioral neurology was a quiet subperiod in which the research of Herophilus and Erasistratus happened not to get lost. The classical period ended by repeating that pattern. With the rise of Christendom from Tertullian (155–240 ce) to Constantine (272–337 ce), neurology went dormant; while scholars like Oribasius (325–403 ce) organized medical knowledge into compendia, the hard-won conditions for original discovery slipped away. This was especially so once Athens and Alexandria—despite remaining major loci of medical study—were eclipsed during the transition between the Roman and Byzantine empires.

Pagan commentators passed Galenic views to the Christian clergy via medical scribes, albeit in atmospheres increasingly inhospitable to scientifically-oriented philosophy. Humoralism, for example, was increasingly attacked by theologians like Philostorgias (368–439 ce), as it implied that the ill are beset, not by supernatural malagents (*daimones*), but by unhealthy combinations of natural humors. Unsurprisingly, medieval neurology is frequently disparaged: 'the advances in understanding the brain in medieval Europe are easy to summarize: there were none' (Gross, 1987: 845). However, as Schalick notes, that assessment is too quick: '[medieval neurology] has been described as intellectually stagnant and practically chaotic […] Neither the stagnant nor the chaotic attribute is accurate' (2009: 79). In these circumstances, the passage of Galenic views about ventricular localization persisted, in part because they were underspecified, and thus easily amended and protected from falsification. Posidonius of Byzantium (floruit ~380 ce) and Nemesius of Emesa (floruit ~390 ce), for instance, maintained the commemorative account of the posterior ventricle, but parsed the functions of the middle ventricle—the ratiocinative and the imaginative—into the middle and anterior, respectively. Galenic views were also kept in play by attempted refutations of rival Aristotelian and Neoplatonist views, such as those of John Philoponus (490–570 ce), and by various medical compilers and translators like Sergius of Resh'aina (floruit ~520 ce), Paulus Aegineta (625–690 ce), and Johannitius (809–873 ce).

Neurology was reinvigorated during the Persian Golden Age. Indeed, there are too many figures and developments to recount here. Notable is Rhazes (865–925 ce), who advocated experimental methods and pharmacological treatments, and whose *Kitab-al-Hawi* described various neurological disorders, including hemiplegia, facial palsy, asthenia, and various peripheral nerve injuries. Joveini (floruit ~960 ce) provided detailed clinical descriptions of psychiatric conditions such as mania, dementia, and psychosis, in addition to asthenia, stroke, epilepsy, and tremors. Abulcasis (936–1013 ce) and Haly Abbas (949–982 ce) called forth the Greco-Roman anatomical tradition with their surgical and medical encyclopedias, *Kitab al-Tasrif* and *Kāmil al-Sināa al Tibbiya*, respectively. Alhazen's (965–1040 ce) revolutionary work in optics generated interest in neuroöphthalmology; but it was Avicenna (980–1037 ce) that cast the longest shadow into the Renaissance, renewing interest into ventricular localization of the sensus communis and other 'faculties'.

The advent of the university system, starting with Bologna in 1088, provided an important bridge from the Persian Golden Age and began the institutionalization of European centers of scholasticism. After Frederick II's (1194–1250 ce) decree authorizing one human dissection every five years at the medical school at Salernum, Bologna added a medical school around 1260 and eventually began enforcing the distinction between vocational barber surgeons and university-trained medical faculty. With increased access to cadavers, Bolognese professors such as Guilielmus de Salicetum (1210–1277 ce), who proposed that the involuntary movements originate from the cerebellum, Thaddeus di Alderotto (1223–1303 ce), and Theodoric Borgognoni (1205–1298 ce) began teaching generations of students, including Lanfrancus of Milan (1250–1306 ce) and Mundinus (1270–1326 ce), who would go on to restore the use of anatomical dissection into the late medieval period. In one case, a leathersmith with intact memory was found post-mortem by Borgognoni to have lesions to the fourth ventricle—a cell theoretic anomaly. Lanfrancus innovatively used percussion, string vibration, and other resonance techniques to diagnose skull fractures, and to treat concussions and other traumatic brain injuries. And by 1315, Mundinus was performing university-sanctioned public teaching demonstrations with human cadavers, and composed a dissection manual the following year, *Anathomia Corporis Humani* (1316/1475). Theoretically, many of these

scholars remained committed to the frameworks developed by previous Aristotelian and Galenic commentators; methodologically, however, incremental advancements were made. Antonio Benivieni (1443–1502 ce) and Niccolò Massa (1485–1569 ce) pioneered advances in autopsy, forensic pathology, and neurosurgery. In one notable case, a youth struck with a halberd sustained serious head injuries, which comminuted the skull and penetrated the meninges, rendering him speechless. Massa correctly predicted that bone fragments remained lodged in the brain, and partially reversed the loss of speech by extracting them (Benton & Joynt, 1960).

Renaissance to Enlightenment

Despite the accumulation of countervailing evidence, the ventricular orthodoxy persisted into the mid-16th century. A consequence of these theoretical commitments was the continued fixation on midbrain structures as the 'seats' of reason, imagination, memory, and other mental faculties. To overcome the difficulty in accessing and then learning about those structures, Leonardo da Vinci (1452–1519) used a casting method to create three-dimensional models: he piped hot wax into the third and fourth ventricles and then peeled away the surrounding basal ganglia to reveal their structure (Pevsner, 2019). While the development of this technique returned no theoretical insights into how damages to the ventricles or disorders in pneumatic admixture might alter normal behavior, it amounted to a crude-but-innovative imaging technique. In his *De Naturali Parte Medicinae* and *Medicina*, Fernelius (1497–1558) emphasized the distinction between anatomical structure and physiological function, and brought attention to reflexive behaviors that are not activated by volitional powers of the will. He produced an early description of the spinal canal in *Medicina* to account for a pathway by which ventricular pneuma could be passed down through peripheral nerves into the muscles and sensory organs.

During the Dutch Golden Age, gross anatomy benefited from promotion of the scientific and cultural values of openness and tolerance, which provided for methodological advances in disclosing bodily structure using innovative instrumentation. Equally crucial were the rapid artistic developments in depictive realism. The works of two scholars are notable, here. First are the groundbreaking reports and illustrations of the Flemish anatomist Vesalius (1514–1564). The culmination of his seven-volume *De Humani Corporis Fabrica* (1543), which was the first near-comprehensive attempt to map out various systems of the human body, was a book on the dissection of human nervous systems that repayed close study. Vesalius demonstrated that severance or ligature of nerves disrupts their effect on muscle, and his painstaking work helped set up developments in forensic medicine over the next century (an exemplar of which is Théophile Bonet's (1620–1689) nearly 2000-page compilation, *Sepulchretum sive Anatomica Practica* (1679), which reported on several thousand autopsies performed during the Renaissance). Second is the seminal work of the Dutch physician Pratensis (1486–1558), whose *De Cerebri Morbis* (1549) discussed various cognitive, mnemonic, and psychiatric conditions, as well as tremors, stupor, and other bodily ailments. While sometimes misdescribed as the first textbook focused on neurology or the first compendium of brain disorders (e.g., Pestronk, 1988), Pratensis's research helped regiment the development of neuroanatomy and pathology.

Both scholars initiated a break from the prevailing Galenism. Vesalius's acknowledgment of morphological similarities between the ventricles of non-/human animals led him to question whether they could be the primary loci of mental function, and whether the ventricles serve purposes other than just being mere cavities for admixing different kinds of pneuma (1543: 623). Other anomalies accrued. The Portuguese physician Lusitanus (1511–1568), for instance, described a case of memory loss following trauma to the occipital boneplate, which led to mesencephalic damage but spared the ventricles. In his *Observationes Medicæ de Capite Humano* (1584), Schenckius (1530–1598) collated >500 clinical descriptions of patients with mental and behavioral deficits, including nearly two dozen cases of language disorders. Schenckius also added therapeutic recommendations to his neuropsychological descriptions of speech disruption, and loss of the faculty of reading and writing (*litterarum memoria*) (Luzzatti & Whitaker, 1996), and, in some ways, Schenckius's deviation from the ventricular orthodoxy of the time made him a seminal forerunner to the founding of behavioral neurology.

Nonetheless, historical descriptions of the transition from the medieval era often locate the central pivot with René Descartes's (1596–1650) scholarly output (e.g., Feinberg & Farah, 1997; Koob et al., 2010). Among Descartes's important and lasting contributions is having helped usher in the mechanical philosophy, within which he explored how to account for human behavior in terms of reflex actions by the central nervous system in response to external stimuli. However, these explorations still relied on humoral and pneumatic approaches to Galenic physiology, and so his account of the cerebral seat of sensorimotor coördination fell in line with the conjecture that mechanical repercussions of neuromuscular fluid are transmitted from the sensory organs, and that motor behavior is generally caused by the mechanically gated flow of pneuma from the ventricles, under central mediation by the rational $\psi\upsilon\chi\acute{\eta}$ at the pineal gland.

The upper bound on this mechanical philosophy, for Descartes, was the explanatory problem of treating certain aspects of verbal behavior—especially linguistic productivity and communicative flexibility—in mechanistic fashion:

> [w]e can easily understand a machine's being constituted so that it can utter words, and even emit some responses to action on it of a corporeal kind, which brings about a change in its organs […]. But it never happens that it arranges its speech in various ways, in order to reply appropriately to everything that may be said in its presence, as even the lowest type of man can do. (1637: §5)

Descartes's posthumously published *De Homine* (1662) and *Traité de l'Homme* (1664) did provide a significant framework within which scientists could make progress. But because of this explanatory problem, he simply excepted the rational $\psi\upsilon\chi\acute{\eta}$ from mechanistic psychological explanation (see Garber, 2002; Wright & Bechtel, 2007), which notoriously resulted in a clumsy dualism.

Vivisections by Jan Swammerdam (1637–1680) continued to raise serious doubts about the inheritance of pneumatic ventricular theory. Swammerdam extracted the hearts and brains from an unanaesthetized frogs. Whereas heartless frogs continued to move, brainless frogs did not. Stimulation of laceration-adjacent nerves also caused muscular contraction, demonstrating that movement can occur absent contact between brain and muscle. Swammerdam inferred not only that nervous—not circulatory—tissue is necessary for movement, but that basing behavioral neurology on the transmission of 'animal spirits' (*pneuma psychikon*) is misguided.

In Oxford to the west, Sedleian Professor of Natural Philosophy Thomas Willis (1621–1675) added a morphological critique of Descartes's 'seat of the soul' account. Pace Descartes, non-human animals—as thoughtless brutes without imaginative or inferential capacities—were expected to have a proportionately smaller pineal gland. Willis's anatomical demonstration to the contrary marked a victory of the empirical over the metaphysical. He and his colleagues developed the first neuroanatomical textbook, *Cerebri Anatome*, followed by *De Anima Brutorum*. Willis, who also coined the term *neurology*, directed Richard Lower's dissections, while speculating with Thomas Millington on neuroanatomical structure and function as Christopher Wren illustrated; in addition to refining descriptions of the cortex and nerves, and making new attributions of differing mechanistic functions to the cerebrum and cerebellum, Willis's team demonstrated the value of collaborative effort. Unfortunately, various religious and political reasons motivated Willis, like Descartes, to exclude the $\psi\upsilon\chi\acute{\eta}$ from being construed as a mechanistic explanandum; and Willis's own attempts at cerebral localization were subjected to critique.

In his *Discours*, the undersung neuroanatomist Stenonius (1638–1686) articulated a program for developing neuroanatomical knowledge derived from both scientific principles of verification and falsification and methodological principles of reverse engineering and functional decomposition:

> being a machine, we should not hope to find the brain's artifice by other ways than those one uses to find the artifice of other machines. There is therefore nothing left to do besides what would be done to any other machine, I mean to dismantle piece by piece all its components and consider what they can do separately and together. (1669: 32–33)

Stenonius's methodological principles were employed by Marcello Malpighi (1628–1694), a pioneer of early innovations in microscopy and histology, and Raymond Vieussens (1641–1715), who used histological and other techniques to trace afferent fibrous pathways from the hindbrain, leading to widespread investigations of the corona radiata, centrum semiovale, corpus callosum, and other structures comprising white matter. Others, including the Swiss pathologist Johann Jakob Wepfer (1620–1695), carefully described cases that anticipated localization debates centuries later; for instance, in one postmortem examination of an elderly woman with apoplectic symptoms, Wepfer noted that her sudden loss of speech production, sensation, and motor abilities was likely related to a cavity in left cortex.

The 18th century was a time of marked increases in physiological knowledge, often combined with searching conjecture. Emanuel Swedenborg (1688–1772), following Newton, proposed that nerves operate by vibration, with differences in 'tremulation' and frequency affording gross motor control. Albrecht von Haller (1708–1777) proposed that neurons operate by the near-instantaneous flow of an invisible albuminous 'nervous liquor' or 'nerve juice'—a hypothesis that Samuel Soemmerring (1755–1830) later developed into a transcendental physiology, which was effectively a new twist on an old, ventricular, seat-of-the-soul account (and widely trounced by philosophers like Kant, Lichtenberg, Goethe, and von Humboldt). These hypotheses notwithstanding, Swedenborg distinguished between the role of motor cortex in voluntary movements, associating autonomic or habitual behaviors with subcortical parts. And von Haller helped establish experimental methods in neurophysiology by stimulating nerves of live animals and observing behavioral consequences; he also discovered that density of neuronal innervation is related to sensory capacity and demonstrated that cerebellar damage need not lead to death or respiratory failure.

Another proposal—radical at the time—came in the mid-18th century, when various scientists and other 'natural philosophers', following the advent of Leyden jars for storing charges, suggested that nervous activity may involve electrical conductance. Stephen Hales (1677–1761) is reported to have been among the earliest to reckon 'animal spirits' as spark-like, along with Jean Jallabert (1712–1768), who used electricity's ability to stimulate muscles, and Eusebio Sguario (1717–1764), who presciently advocated using the hypothetical-deductive method to test the hypothesis of neuromuscular electrical conductance.

Modern

Histories of behavioral neurology almost invariably trace the modern period to the lecture tours of Franz Joseph Gall (1758–1828) and his understudy, Johann Gaspar Spurzheim (1776–1832) at the beginning of the 19th century. In part, this is because of the interesting confluence of Gall's radical empiricist philosophy; his physiognomy and radically false phrenology, which were developed in a series of self-promotional roadshow exhibitions; his fierce debates with establishment academics; and his theoretical developments in localization. This 'standard story' omits the many philosophical and scientific influences on Gall. One immediate

predecessor was Johann Gottfried von Herder (1744–1803), whose *Vom Erkennen und Empfinden der Menschlichen Seel* and *Ideen zur Philosophie der Geschichte der Menschheit* attempted to harmonize the competing philosophies of materialistic monism and mind-body dualism. In Herder, Gall found a philosophical framework within which to fathom his experiences as medical student—particularly, during his time at Vienna's Narrenturm, which offered opportunities to relate postmortem dissections with previous clinical observations of psychiatric patients' behaviors. Another predecessor was Johann Mayer (1747–1801), who argued for a program, using forensic autopsies, to predict specific behavioral and cognitive deficits from particular damages. Mayer directly challenged the holism of von Haller, who had lent his name to the thesis that the brain functions as a whole without distinct component operations, and this challenge opened the way for Gall & Spurzheim's localizationism (Finger & Eling, 2019).

Gall ascribed a panoply of >27 different mental faculties and aptitudes, each governed by particular loci in the semi-organized array of the cerebral cortex, and connected to white matter tracts by projection and association fibers. But his serious work attracted scores of critics, and was compromised by the collapse of phrenology. Holists, like Luigi Rolando (1773–1831) and Marie Jean Pierre Flourens (1794–1867), dismissed the search of specific 'seats' for higher-order functions and movements of musculature in the cortex. Rolando demonstrated that galvanic current to the cerebellum induces convulsions, while lesions perturb motor control, and Flourens's ablation and decerebration experiments in 1824 eroded confidence in cerebral localization.

Jean Baptiste Bouillaud (1796–1881) responded by postulating multiple movement centers, including in the cortex, and claimed that the faculty of articulate language had its seat in the brain's anterior lobules. Following Marie François Xavier Bichat's (1777–1802) doctrine of the functional symmetry of paired organs in his *Anatomie Générale Appliquée à la Phsiologie et à la Médecine*, Bouillaud (1825) considered that articulate language is seated in both frontal lobes. He supported this claim by establishing correlations between the presence (or absence) of speech disturbances in patients, as recorded in clinical histories, and the presence (or absence) of anatomical lesions in the anterior parts of the brain, as reported in post-mortem examinations. Bouillaud's 'new organology' remained a marginal initiative for decades, owing to three factors: the general discredit of the old organology of Gall, the lack of a clinical characterization of the 'loss of speech' syndrome, and the fragmentary and disputable character of the collected clinical evidence.

Aphasiology, as a research program, emerged in the French medical scene at the beginning of the 19th century, with the integration of Gall's doctrine of the plurality of cerebral organs and Bouillaud's method of correlating clinical deficits and pathology. In the Parisian Societé d'Anthropologie, a debate emerged over whether brain and skull size positively correlates with intelligence. In April 1861, Ernest Aubertin (1825–1893), who was married to Bouillaud's daughter and worked with him at the Charité, suggested that they ignore such debates and instead return to the localization of neurophysiological function. For Aubertin, anterior lobe development would be a more meaningful correlate of intelligence, residing in the frontal lobes where our higher human functions were seated.

Shortly after Aubertin's presentation, in which he argued in favor of localizing speech functionality to the anterior lobes, Pierre Paul Broca, who was president of the Societé and surgeon of the Bicetre Hospital, found a dying patient named Louis Victor Leborgne, who for 21 years had lost the ability to produce articulated speech. Broca noticed the case's potential as a breakthrough in the cerebral localization of language. Broca (1861a) reported that Leborgne could only pronounce the single syllable *tan* repeated twice at a time. Although the extent of intelligence was undetermined, Leborgne understood almost everything communicated to him, and made accurate numerical responses (by gesturing); the muscles corresponding to phonation and articulation were not paralyzed. Broca named this singular symptomatology 'aphemia': the loss of speech without the paralysis of the organs of articulation and without destruction of the intellect (renamed 'aphasia' by Armand Trousseau in 1864). At the autopsy following Leborgne's death, Broca (1861a) reported that the left frontal lobe was softened extensively, that the convolutions of the orbital region preserved their shape, and there was a large cavity, 'capable of holding a chicken egg', filled with serous fluid, in the middle portion of the frontal lobe. Broca speculated that the original seat of the lesion was the third frontal convolution, such that the faculty of articulated language plausibly resides in that area (see **Fig. 2**). Broca's contribution was immediately well-received, and—although Marc Dax (1770–1837) originally discovered the correlation 25 years prior—Leborgne's case constituted the landmark exemplar of the cortical localization of function. Broca's clinical report was a detailed specification of the speech deficit, and his pathological findings discredited the orbital localization advanced by phrenologists. Finally, his discussion of cerebral convolutions and sulcal anatomy, rooted in Gratiolet's (1854) maps, was new and sophisticated.

In November 1861, Broca presented a second case of Lelong, an 84-year-old man capable of producing only five utterances: *oui*, *non*, *toi* (a mispronunciation of *trois*), *toujours*, and *Lelo* (a mispronunciation of his surname). At autopsy, Broca (1861b) found that Lelong's lesion was at the inferior frontal gyrus, as with Leborgne. In 1863, he presented eight more similar cases of aphasia, in which lesions likewise congregated in the left cerebral hemisphere, which violated the physiological doctrine (advocated by Bichat, Bouillaud, and others) that two organs that are equal and symmetrical have the same attributes. In 1865, Broca withdrew his support for Bouillaud's hypothesis that speech is localized in both 'anterior' lobes, suggesting instead that the center for articulated language was in the third left frontal convolution only (now known as 'Broca's area'). This cerebral dominance was explained, in turn, by the more precocious development of the left hemisphere. In 1906, upon review, Pierre Marie questioned whether the lesions were as precise and localized as Broca had reported, which provoked strong responses from localizationists like Joseph Jules Déjerine (1849–1917) and Christofredo Jakob (1866–1956), a German-Argentinian neuropathologist. Today, we know that the lesions extended cortically and subcortically into medial regions of the brain (Dronkers et al., 2007).

John Hughlings Jackson, considered to be the 'father of English neurology' (Critchley & Critchley, 1998), was another early advocate of the 'clinic-anatomical correlation method'. Jackson confirmed the importance of Broca's area for language production, reporting speech disturbances of 31 patients with left hemisphere damage (1863, 1865). However, he warned that localization

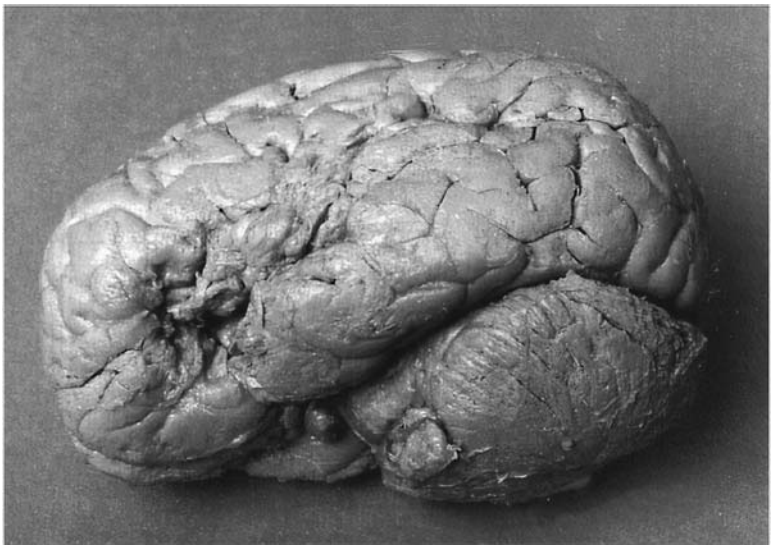

Figure 2 Postmortem photograph of the brain of Leborgne. Excerpted from Dronkers et al.(2007: 1436).

of symptom need not imply localization of function: 'to locate the damage which destroys speech and to locate speech are two different things' (1874: 81). Jackson's main contribution to clinical neurology was his work on epilepsy, which he defined as an 'occasional, sudden, excessive, rapid, and local discharge of gray matter' (1873: 3). He noticed for the first time the predictable temporal sequence of muscle spasms or sensations in unilateral seizures (now known as 'Jacksonian epilepsy'), which indicated that motor areas of the cortex must be organized somatotopically. In 1870, Gustav Fritsch (1838–1927) & Eduard Hitzig (1838–1907) performed stimulation and lesion experiments that demonstrated cortical specialization of motor function in dogs, confirming Jackson's hypothesis.

The impact of Broca's discoveries in the German scientific community was attenuated by the influence of Helmholtz's physiological program, which emphasized the mapping of smaller subcomponent functions onto physiological processes (Roth, 2014). Carl Wernicke's (1848–1904) monograph *Der Aphasische Symptomenkomplex* paved the way for accepting higher function localization in the cortex. By Wernicke's connectionist approach, multiple interconnected cortical regions are necessary for orchestrating higher psychological functions, including language:

> only the most elementary psychic functions can be assigned to defined areas of the cortex […] Everything that goes beyond these simple functions […] is the achievement of the fiber tracts which connect the different regions of the cortex to each other, the so-called association system of Meynert. (1874: 34–35)

The significance of Theodor Meynert's (1833–1892) work is vast. He recognized that the cortex could be subdivided into posterior sensory and anterior motor parts, which are interconnected by projection fibers (connecting cortical to subcortical areas), association fibers (interconnecting cortical regions), and commissural fibers. It was Meynert who first showed that some kind of aphasia (bizarre unintelligible speech patterns with difficulties in language comprehension) could occur following upper left temporal lobe lesions (Geschwind, 1974). From this, Meynert concluded that the temporal lobes contained a 'sound field' that was responsible for speech recognition.

Wernicke considered that his own 1874 monograph followed 'almost automatically' from Meynert's writings and dissections. In its first part, Wernicke introduced a schematic representation of a psychic reflex on the pattern of a reflex arc. In his model, any sensory stimulus *E* leaves a memory image *O* in the sensory part of the brain (i.e., the occipitotemporal lobes). Similarly, bodily movements leave a motor image *F* in the motor (anterior) part of the brain, which can precipitate a movement *B*. The psychic reflex arc is completed by associative fiber tracts connecting sensory (occipital-temporal) and motor (anterior) areas in the brain.

In the monograph's second part, Wernicke introduced his psychic reflex arc schema for language processing, which became the foundation for his concept of the aphasic symptom-complex. In the schema, Wernicke distinguished between motor and sensory component centers and the connections between them. At one side, pure cases of Broca's aphasia, or 'motor aphasia', were considered to be the result of destruction or impairment of motor components for speech, located in the frontal lobes (i.e., in the third left frontal gyrus), precisely where one would expect to find memories for motor images of words. On the other side, a second kind of aphasia, 'sensory aphasia', was produced by the destruction or impairment of the sensory component for speech, located in the left-side of the temporal lobe (so-called 'Wernicke's area'), near the auditory area. The sensory center for speech contained memories for the acoustic image of words. Those patients with pure Wernicke's aphasia showed more fluent speech and larger vocabularies than Broca's patients, but they exhibited difficulties comprehending speech because they could not recognize the acoustic images of

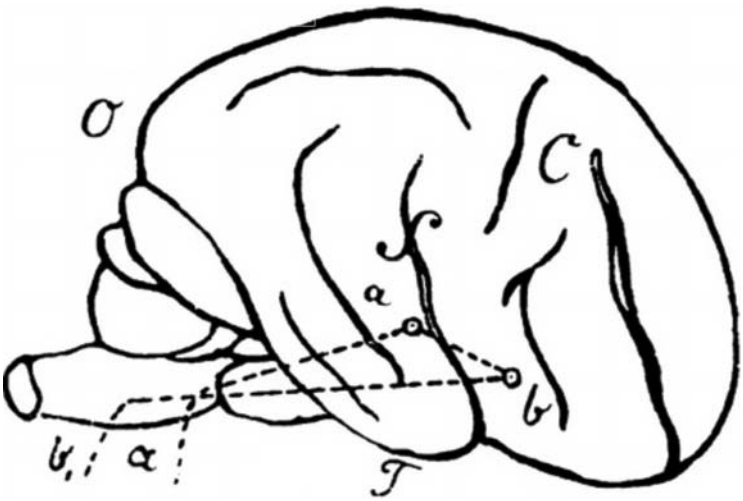

Figure 3 The model from Wernicke (1874: 19).

words. These patients could not monitor their speech output, producing unintelligible or bizarre speech, marked by what Adolf Kussmaul (1822–1902) called 'paraphasic' errors, mispronunciations, word confusions, transpositions, and neologisms. In the third part of his monograph, Wernicke presented several clinical cases of this new kind of aphasic disorder. Wernicke (1874) concluded, '[t]he demonstration of these two types [pure motor aphasia and pure sensory aphasia] must be regarded as conclusive proof of the existence of two anatomically separate language centers'. In his well-known cartoon representation of his model, reproduced in almost every medical textbook, α represents the acoustic nerve that terminates in the temporal sensory language center (a). This center is connected to the frontal motor language center (b), extending to brainstem areas (**Fig. 3**). Given that the model postulated a direct pathway from Wernicke's area to Broca's area, Wernicke predicted the existence of a third type of aphasia, called 'conduction aphasia', in which damage of the system of connecting fibers produced peculiar symptomatology. In patients with conduction aphasia, both speech comprehension and speech production remain intact to some extent. However, damage to the connection between the centers produced failures in repetition, due to the disruption of information transferring from the word listened to the word spoken. The patients exhibited very hesitant spontaneous speech, with abundant paraphasic errors that they consciously try to correct, approaching gradually to their target (i.e., the conduit d'approche phenomenon). Wernicke considered that the relevant connecting fibers were constituted by the arcuate fasciculus around the insula. Current opinion holds that conduction aphasia may not be caused by pure white matter lesions, with the posterior part of the left planum temporale hypothesized to be the critically damaged area in patients with conduction aphasia (Rutten, 2017).

Wernicke's innovative integration of theoretical model-making and the clinico-pathological method has been referred as the 'connectionist' or 'associationist' approach. This approach was developed by Ludwig Lichtheim (1845–1928), Hugo Liepmann (1863–1925), and Heinrich Lissauer, (1861–1891), among others in Germany, and by Déjerine in France. Lichtheim (1885) amended Wernicke's model with a separate center for concept formation. This new component was thought to be a knowledge network of associations that contained the concepts to which words refer (Roth, 2014). This addition enabled him to describe two new types of aphasia: namely, transcortical sensory aphasia, produced by the disrupted connection of Wernicke's area to the concept center, and transcortical motor aphasia, produced by a disconnection of Broca's area and the concept center. Liepmann (1898) provided a connectionist account of deficiencies in the ability to plan and execute complex learned movements (apraxia), in the absence of primary sensory and motor deficits. He distinguished several kinds of apraxia (idio-kinetic, ideational, limb-kinetic), and proposed an anatomical model by which the left hemisphere is dominant for complex movement control and the right hemisphere depends on the left to control actions of the left hand. Lesions in the left parietal lobe would lead to bilateral apraxia, while lesions of the corpus callosum pathway from left to right would result in apraxia of the left hand. Lissauer (1890) provided the first connectionist explanation of a deficit in simple visual recognition of commonplace objects, known as 'visual agnosia'. He distinguished between apperceptive and associative subtypes of agnosia. The first kind would be the effect of lesions primarily located at the visual cortex itself, whereas associative agnosia would be produced by disruptions of transcortical pathways connecting the visual percept with wider associations across various modalities. In later years, Wernicke also speculated about the possibility of a brain region responsible for the encoding of written words (Wickens, 2014). Based on the clinic-pathological method, Déjerine (1891, 1906) proposed the first connectionist explanation of pure alexia, proposing a 'visual verbal' center, a memory of visual images of words, located in the left angular gyrus (See **Fig. 4**).

A negative attitude toward the connectionist approach dominated the beginning of the 20th century. In his 1926 monograph, Henry Head (1861–1940) derisively referred those who endorsed this approach as 'diagram makers' for their tendency to illustrate their models with diagrams of centers in the brain and connections between those centers. The main protagonists of psychoanalysis, anti-mechanism, behaviorism, and Gestalt and experimental psychology adopted more holistic explanations implicating the whole

Figure 4 Joseph Jules Déjerine and his wife Augusta Déjerine-Klumpke.

brain in higher-level complex functions. Theoretical movements notwithstanding, some excellent clinical studies related to localization of function appeared during this period. While seeking new treatments for severe epilepsy, Wilder Penfield (1891–1976) developed a neurosurgical procedure in which he surgically exposed the brain of fully conscious patients (under local anesthesia), stimulated different locations of the cortex with electrodes, and registered the patient's feelings, sensations, movements, and memories, in order to identify the damaged tissue responsible for the seizures (Penfield & Boldrey, 1937). This method allowed him to chart the functional somatotopic organization of the somatosensory and motor cortices, illustrated by the famous sensorimotor homunculi (Penfield & Rasmussen, 1950).

Contemporary

During the first half of the 20th century, neurology and psychiatry developed in isolation, as neurology had abandoned behavior while psychiatry abandoned the brain. The schism between neurology and psychiatry was not there in the late 19th century, however. In fact, the concept of nervous diseases originated in Britain during the 17th and 18th centuries as a reaction against traditional Galenism (López Piñero, 1983). William Cullen (1710–1790) introduced the term *neuroses* as affections of sense and motion without fever or evidence of local disease. The term was applied to disorders now classified as neurologic, such as paralysis, and others considered psychiatric, such as melancholia (Reynolds, 1990). In 1817, James Parkinson published a report of several cases of shaking palsy (*paralysis agitans*), describing the difficulties with walking and posture associated with 'involuntary tremulous motion'. In 1872, George Huntington described a hereditary type of chorea and established the principle of direct inheritability of neurologic disorders (Martin, 2002). In France, Charcot and his disciples made descriptions of multiple sclerosis and other nerve disorders. Throughout the 19th century, the prominent German and Austrian school of neuropsychiatry, headed by Wilhelm Griesinger (1817–1868) in Berlin and Meynert in Vienna, directed the practice of the discipline toward the search for the biological basis of psychiatric diseases. William Gowers' *Manual of Diseases of the Nervous System* (1886) illustrated and classified a variety of nervous diseases discovered by histological methods and clinic-pathological correlations. In the sixth edition of his textbook *Compendium der Psychiatrie* from 1899, Emil Kræpelin (1856–1925) introduced the dichotomy between manic-depressive psychosis and dementia praecox—the latter renamed as 'schizophrenia' by Eugen Bleuler in 1908—and set the foundation of modern systems of psychiatric classification. Kræpelin's student, Alois Alzheimer, reported the case of Auguste D., a 51-year-old woman from Frankfurt who had exhibited progressive memory impairment, disorientation, hallucinations, and psychosocial incompetence in 1906. Histopathologically, the patient was found to have arteriosclerotic changes, senile plaques, and neuro-fibrillary tangles. Kræpelin introduced the eponym *Alzheimer's disease* in 1910. Despite these advancements, the neuropsychiatric program was not immediately successful in establishing correlations between the clinical symptoms of psychiatric diseases and their purported pathological-anatomical markers. This failure partially explains the progressive separation of neurology and psychiatry as autonomous disciplines in the early 20th century; however, the growth of psychoanalysis and psychodynamic psychiatry ultimately forged the divide.

After the Great War, the spotlight of psychiatry shifted to the United States, where the psychoanalytic movement was flourishing. Freudian psychiatrists aimed to redirect the focus of the discipline from psychosis, as manifested within the asylum, to the psychoneuroses, as manifested in everyday life (Freud, 1901/1989). Neuroses were to be explained by subconscious psychological factors, on the conviction that neurotic symptoms were caused by repressed childhood sexual drives, memories, or fantasies that conflicted with psychological or social demands. A psychotherapy was recommended that emphasized dream interpretation, free association, and the elaboration of the analyst-patient relationship itself. At the heights of psychoanalytic dominance, some psychiatrists attempted psychodynamic explanations of psychotic diseases. Frieda Fromm-Reichman (1948) described schizophrenia as a radical form of distrust and resentment, which she attributed to childhood experiences of rejection by 'schizophrenogenic mothers'. Such zany extremes were exceptional, however, since an organic versus functional dichotomy was tacitly endorsed both by neurologists and psychiatrists, implying a division of labor in which neurologists should limit themselves to the search of anatomical causes of neurological alternations, and psychiatrists should focus on the psychodynamic causes of mental disturbances. For many decades, scientific/academic societies, training programs, and authoritative textbooks reinforced this divide (Shorter, 1997).

In the United States, the bridges between neurology and psychiatry began to be reconstructed in the late 1960s, with the reinterpretation of major mental illnesses as biologically-based diseases. Against the idea of schizophrenia as an environmental disease caused by negligent motherhood, Danish studies comparing the prevalence of mental illness in the biological and adoptive families of adopted schizophrenics found a higher prevalence of schizophrenia-related illness among the biological relatives of adopted schizophrenics, but not among their adoptive relatives (Kety et al., 1968). This finding strongly supported a genetic transmission of vulnerability to schizophrenia, and suggested the importance of studying both genetic and environmental influences. Following the emergence of molecular neuroscience, the discovery of new psychopharmaceuticals, and the neuroimaging revolution, conditions like schizophrenia, affective and anxiety-related disorders, autism, and many others came to be recognized as psychiatric disorders with underlying neurological or anatomical abnormalities with biochemical profiles (Post, 2000).

This historical trend toward 'closing the great divide' between neurology and psychiatry (Price et al., 2000) underlies the rapprochement and recent consolidation of these medical fields, which depended not only on the revival of biological approaches to psychiatric disorders but also on the development of behavioral neurology as a medical subspecialization within neurology (Arciniegas et al., 2013). Consensus has it that contemporary behavioral neurology was inaugurated with the publication of Norman Geschwind's (1926–1984) two-part study, 'Disconnexion syndromes in animals and man', which became the manifesto of behavioral neurology. Geschwind expanded upon Wernicke's ideas and synthesized the available clinical evidence to articulate a specifically disconnectionist framework for higher function deficits (see **Fig. 5**).

Geschwind made two new advancements. Firstly, he resurrected a then-forgotten neuroanatomical principle articulated by Paul Flechsig (1847–1929). In his myelogenetic studies of human cortex, Flechsig (1901) inferred an anatomical rule according to which primary sensory areas have no direct neocortical connections between them. There is no long association system directly connecting those early myelinated zones, but all connections between primary sensory areas are indirect; they pass through immediately adjacent parasensory areas, or 'association' areas. Whereas Flechsig intended the rule to apply to sensory cortex only, encompassing motor cortex and connections between the hemispheres, Geschwind generalized it. From his perspective, association cortex is a relay station between primary motor, sensory, and limbic areas. Furthermore, for Geschwind, the evolution of association areas underlay the evolution of higher functions (Catani & ffytche, 2005). In humans, the emergence of a higher-order association area in the inferior parietal lobe (angular and supramarginal gyri) permitted visual, auditory, and somatosensory associations freed from sensory-limbic associations, which may be prerequisite for language.

Secondly, Geschwind (1965) elaborated a broader view of disconnections, in which even pure lesions of an association region could cause a disconnection syndrome. For Wernicke, disconnection syndromes implied a white matter lesion; but for Geschwind,

Figure 5 Norman Geschwind.

large lesions in either association cortex or white matter tracts should be considered 'disconnexion lesions' to the extent that they disconnect primary sensitive or motor areas from other regions of the cortex, whether ipsilateral or contralateral. With this new characterization of disconnection lesions, Geschwind developed a unified connectionist account of an impressive catalog of higher function disorders.

Geschwind distinguished three different types of disconnection syndromes (Catani & ffytche, 2005). Firstly, there are disconnections between sensory areas and the limbic system. Disconnection of somesthetic areas from the limbic system result in pain asymbolia. Disconnection of the primary auditory cortex from the limbic system result in verbal learning impairment. Secondly, there are disconnections between sensory areas and Wernicke's area. Geschwind distinguished between four modality-specific language deficits: (i) tactile aphasia, following disconnections between Wernicke's area and somesthetic areas; (ii) pure word deafness (Liepmann, 1898), following disconnections between Wernicke's region and primary auditory cortex; (iii) pure alexia, which Déjerine described as a disconnection between visual areas and the supramarginal angular gyrus; and (iv) visual agnosia, which Geschwind construed as an indirect disconnection of visual areas from Wernicke's region via the angular gyrus. Thirdly, there are disconnections between sensory areas and motor cortex. As Liepmann (1898) described, disconnections of hand motor cortex from posterior sensory areas result in apraxia; disconnections of Broca's center from Wernicke's center cause conduction aphasia, as envisaged by Wernicke. Concerning interhemispheric disconnections, Geschwind endorsed Déjerine's and Liepmann's accounts of pure alexia and callosal apraxia, respectively.

Geschwind's connectionist framework became paradigmatic. With Harold Goodglass (1920–2002), Edith Kaplan (1924–2009), and others, Geschwind established the Aphasia Research Center at the Boston Veteran Administration Hospital, which became the epicenter of the behavioral neurology revolution in the 1970s. A generation of behavioral neurologists passed through Geschwind's research center, including Frank Benson, Marsel Mesulam, and Antonio Damasio. It is widely acknowledged that 'virtually all behavioral neurologists can trace their intellectual origin directly or indirectly to Geschwind' (Filley, 2016). Geschwind introduced the phrase *behavioral neurology* in 1972 at an American Association of Neurology meeting, and members organized the Behavioral Neurology Society (BNS) a decade later, with several textbooks promptly appearing (Pincus & Tucker, 1974; Mesulam, 1985). Ironically, Geschwind's framework diminished in prominence during 'the decade of the brain' (1990s), as two general considerations obtained scientific acceptance. Firstly, association cortex is now known to be, not a homogenous relay station, but to have specialized functional roles (Zeki et al., 1991). Secondly, the complexity of parallel, feedback, and distributed pathways between, and within, cortical territories became evident (Damasio, 1989; Damasio et al., 2004).

Toward the end of the millennium, new tools and methods swiftly accelerated progress in both cognitive neuroscience and behavioral neurology (Bickle, 2019). Computed tomography (CT) enabled the localization of many aphasia syndromes diagnosed by standardized clinical methods. Positron emission tomography (PET) allowed for identification of different visual pathways in the visual association cortex in humans, improving the explanation of visual agnosia syndromes (Sergent et al., 1992). PET imaging tracers that correlate β-amyloid deposition in the brain have been widely used to develop biomarkers of Alzheimer's disease, years before the onset of clinical symptoms. Magnetic resonance imaging (MRI) and diffusor tensor imaging improved the visualization of white matter tracts, providing for more sophisticated conceptions of white matter dementia (Filley et al., 1988). Despite ongoing controversies, functional MRI (fMRI) has become the essential tool for those interested understanding the functional correlates of behavior and disease.

As a result of these tool developments in imaging, a new framework for behavioral neurology surfaced—large-scale distributed neural networks—which aims for balance between specialization of cortical areas and corticocortical connectivity. This network approach evolved from the convergence of lesion methods and the imaging revolution from the 1980s, which allowed scientists to non-invasively explore patients' damaged brain areas in vivo. Five anatomically individuated large-scale networks became the relevant foci for medical/psychiatric practice: a limbic network for memory, emotion, and motivation; a ventral occipito-temporal network for object recognition; a dorsal parieto-frontal network for spatial orientation; a perisylvian network for language; and a prefontal network for attention, executive function, and comportment (Mesulam, 1999, 2000). Based on neuropathology, neuroimaging, and evidence from transgenic animal models, some researchers have proposed that human neurodegenerative diseases may relate to dysfunction in these large-scale brain networks (Seeley et al., 2009). An early example of this trend has been the discovery of primary progressive aphasia, a syndrome of relatively focal cerebral degeneration with a predilection for the left perisylvian region, without the generalized cognitive and behavioral disturbances of dementia (Mesulam, 1982). The study of frontal lobe function and disease has become another epicenter of research, with raised scientific and social awareness of dementia as a public health issue. Behavioral disorders such as apathy and disinhibition were associated with tissue loss in the ventral portion of the right anterior cingulate cortex and adjacent ventromedial superior frontal gyrus, the right ventromedial prefrontal cortex, the right lateral middle frontal gyrus, the right caudate head, the right orbitofrontal cortex and the right anterior insula (Rosen et al., 2005). These discoveries boosted the study of the context-modulated, complex, integrated large-scale network that underlies social cognition (Kennedy & Adolphs, 2012). More recently, PET and fMRI studies have identified widespread neural networks, defined by functional connectivity, and associated with behavioral functions. The first neural network characterized this way has been the default mode network (DMN) (Raichle et al., 2001). Buckner et al. (2005) demonstrated a remarkable correlation between DMN activity patterns in cortical regions in young adults and the topography of amyloid deposition in elderly AD patients. Network analysis and neuroimaging technologies revolutionized both the theoretical landscape and the clinical practice of behavioral neurologists, opening new avenues for diagnosis and treatment.

Back to the Future

As a branch of medicine that long predates the scientific revolution, behavioral neurology has a rich history. However, it is also enjoying a re-emergence, owing to the renewal of neuropsychiatry and neuropsychology in the second half of the 20th century, new theoretical paradigms, new mathematical and computational tools, and experimental methods. Consequently, behavioral neurology is sometimes ambivalently described as either an old and venerable practice, or else a new discipline undergoing an exciting period of explosive growth (Benson, 1993). This latter description becomes increasingly salient as one refocuses from the medical objectives of diagnosis and treatment to renewed interest in the scientific principles of localization and decomposition and other forms of bottom-up reasoning (Schaffner, 1993). Decomposition and localization are experimental and analytical strategies used in the service of explaining phenomena such as seizures, dyskinesias, disconnection syndromes, and other neurobehavioral conditions, and are two of the cornerstones of what has come to be called 'New Mechanism' in contemporary philosophy of science and medicine (see Bechtel & Richardson, 1993; Thagard, 1998, 2006; see also Glennan & Illari, 2017). The basic idea is for researchers to model the causal relationships leading to a target phenomenon, such that it can be pinned down to a particular system's activities (phenomenal modeling); to take the system apart apart—either actually or analytically—and determine the component parts (structural decomposition) of the system or the component operations (functional decomposition) of its activities; and to assign these parts and operations (localization) while exploring their constitutive organization (systemic analysis). The principles of the New Mechanists are also those used by Aubertin, Wernicke, and Déjerine in the 19th century, and that touch on older philosophical foundations from Gall, Spurheim, and Dax in the 18th century; they are even continuous with the pioneering efforts of early 17th century mechanists and clinicians like Stenonius and Wepfer.

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The History of Human Neuropsychology

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What Is Neuropsychology

A Definition

Neuropsychology as a scientific discipline is a young field, although the earliest attempts to relate mental functions to the brain may be traced back to classical Greece, and Roman Empire (Pagel, 1958; Finger, 1994). Neuropsychology became an independent discipline only in the second half of the 19th century, as an amalgam of several fields: neurology, psychology, neuroanatomy, neurophysiology, neurochemistry, neuropharmacology (Benton, 1988).

The term *neuropsychology* refers broadly to the study of behavior, the mind, and their relationship with the central nervous system, particularly the two cerebral hemispheres and related subcortical structures. *Neuropsychology* was defined as concerning the relationships between "cerebral structures" and "higher mental functions" (Hécaen, 1972), the "neural mechanisms underlying human behavior" (Hécaen and Albert, 1978), "the interrelations of the brain with mentation and behavior" (Benton, 1988), "the relationships between brain, mind, and behavior" (Berlucchi, 2009). Neuropsychology is then placed at the intersection between the neurosciences (neurology, neuroanatomy, neurophysiology, neurochemistry, neuroimaging), and the behavioral sciences (psychology, linguistics), including cognitive and emotional-motivational processes (Hécaen and Albert, 1978).

The Name

The name itself was somewhat new, compared to the early beginning of research that may be qualified as neuropsychological. The North American psychologist Karl Spencer Lashley (Beach, 1961) became research Professor in Neuropsychology. The Canadian psychologist Donald O. Hebb (Brown and Milner, 2003) wrote a book titled *The Organization of Behavior. A Neuropsychological Theory* (Hebb, 1949). The term was also used as the title of a collection of writings, *The neuropsychology of Lashley* (Lashley, 1960). Both Lashley and Hebb were mainly concerned with the neurophysiological basis of learning and memory. Finally, the term "neuropsychology" appears to have been used in 1913 by Sir William Osler in his remarks at the opening of the Phipps Psychiatric Clinic of the Johns Hopkins Hospital (Bruce, 1985; Jeeves, 1987).

The Anatomo-Clinical Correlation Method and Three Basic Assumptions

The main approach of neuropsychology has been one of investigating the neural basis of behavior and of mental processes, making inferences from the abnormal behavior of patients with focal lesions or degenerative disorders to the neural and functional organization of the healthy, undamaged, system. The logic of this approach is well illustrated by a statement of the Italian neuropsychiatrist and physiologist, Leonardo Bianchi, about the functions of the frontal lobes, as inferred by their extirpation in monkeys and dogs (1895, pp. 521–522): "The frontal lobes would thus sum up into series the products of the sensorimotor regions, as well as the emotive states which accompany all the perceptions, the fusion of which constitutes what has been called the *psychical tone* of the individual. Removal of the frontal lobes does not so much interfere with the perceptions taken singly, as it does disaggregate the personality, and incapacitate for serialising and synthesizing groups of representations."

The logic of this *anatomo-clinical correlation* method is based on the following three assumptions (Vallar, 2000):

(i) *Modularity:* the architecture of the human cognitive and emotional-motivational system is modular (Fodor, 1983): "any large computation should be split up into a collection of small, nearly independent, specialised subprocesses" (Marr, 1982).

(ii) *Correspondence:* some relation exists between the functional and the neurological modular organisations. The neural bases of these processes are physically implemented and localized in specific brain regions: cortical areas, white matter fiber tracts and subcortical nuclei, organized in networks (Bullmore and Sporns, 2009) and cell assemblies (Buzsáki, 2010; Harris, 2005; Hebb, 1949), devoted to specific activities.

(iii) *Constancy:* a localized damage to a cortical area or network interferes with the functional activity they support, causing symptoms and signs, that index their dysfunction. Furthermore, after the disruption of the activity of a specific neurofunctional component, the rest of the system operates in a fashion basically similar to the one taking place in pre-morbid conditions, namely: the system, at a functional level, as indexed by the patient's behavior remains *constant*, except for the damaged component(s). This allows meaningful inferences from a pathological behavior to the organization of the healthy, undamaged system.

Neuropsychological Deficits: Dissociations and Associations (the Neuropsychological Syndrome)

Since the inception of neuropsychology, the observations made by investigators of disorders caused by brain damage had the notable feature that deficits were accompanied by aspects of behavior that were unimpaired. This pattern constitutes a *dissociation*, that may be taken as an indication that the function whose impairment causes the deficit is independent from the one supporting the unimpaired behavior. This pattern is outlined in Bianchi's (1895) description of the preserved and impaired performances following bilateral removal of the prefrontal cortex. This type of dissociation, the *single dissociation*, is however compatible with the hypothesis that the function is unitary: the dissociation might be due to the fact that the impaired behavior is more complex, or the task where the patient or the animal fail is more difficult (namely, requires more processing resources), than the behavior or the task where performance is preserved. This problem is solved by the observation of a *double dissociation*, where different patients, or animals (be they groups or single cases), show opposite patterns of impaired and preserved performance. If the neurofunctional systems supporting behavior are similar across individuals, an interpretation in terms of difficulty would be contradictory, since a task, or behavior, should be more difficult for one patient (or group of patients) than for the other. The double dissociation is the most powerful tool to demonstrate the multi-componential architecture of cognition.

Fig. 1 shows an example from a study by Faglioni et al. (1969), contrasting perceptual-discriminative and semantic-associative disorders in the acoustic modality. Right brain-damaged patients had a performance defective in a perceptual task (discrimination of meaningless sounds) but preserved in a semantic-associative task (identification of meaningful sounds). Left brain-damaged patients showed an opposite pattern. This is the *classical form* of *double dissociation*: levels of performance in the tasks unaffected by brain damage are within the normal range; the dissociation is *between* patients (right brain-damaged patients have a better performance level in the semantic task, as compared with left brain-damaged patients; conversely, in the perceptual task left brain-damaged patients score better). Importantly, the performances of left and right brain-damaged patients, taken in isolation, conjure up a single dissociation, with one group of patients being impaired in one out of the two tasks. Were the performances of the brain-damaged patients illustrated in **Fig. 1** overall defective, as compared to those of neurologically unimpaired participants, interpretation would be more complex. Even though the patterns shown in **Fig. 1** were maintained, it would be necessary to hypothesize the effect of an additional, non-specific, general factor, that overall decreased performance level.

Neuropsychological symptoms and signs brought about by brain damage often occur in association, making a *syndrome*. This concept ("a group of symptoms and signs of disordered function, related to one another by some anatomic, physiologic, or biochemical peculiarity", Isselbacher et al., 1994, p. 3) has been widely used in clinical medicine. In neuropsychology, three types of syndromes have been distinguished: (a) *anatomical* (where the association of symptoms and signs is due to the anatomical contiguity of brain regions or neural networks), (b) *functional* (where the association is due to the impairment of a specific mechanism) and (c) *mixed*, sharing features of the anatomical and the functional syndromes (see **Figs. 2–4**).

The anatomical syndrome, given its probabilistic nature and the possibility of being fractionated into a number of subsyndromes or partial syndromes, may be considered *weak* (see a discussion of the classical taxonomy of the aphasias as 'weak' syndromes in Benson, 1979; Poeck, 1983). Furthermore, the anatomical syndrome has no theoretical importance from the point of view of the functional organisation of the cognitive system. A well-known example of association of symptoms produced by

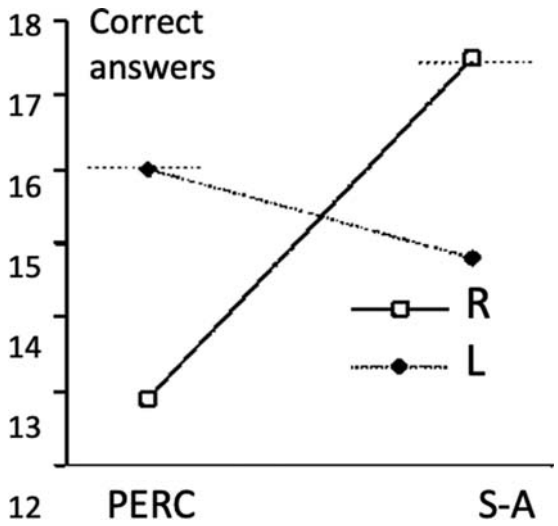

Figure 1 The *classical double dissociation*: an example. PERC.: perceptual task (discrimination of meaningless sounds). S-A: semantic-associative task (identification of meaningful sounds). R and L: right and left brain-damaged patients. Dotted horizontal lines: average performance of control participants. Data from Faglioni, P., Spinnler, H., Vignolo, L.A., 1969. Contrasting behavior of right and left hemisphere-damaged patients on a discriminative and a semantic task of auditory recognition. Cortex 5, 366–389.

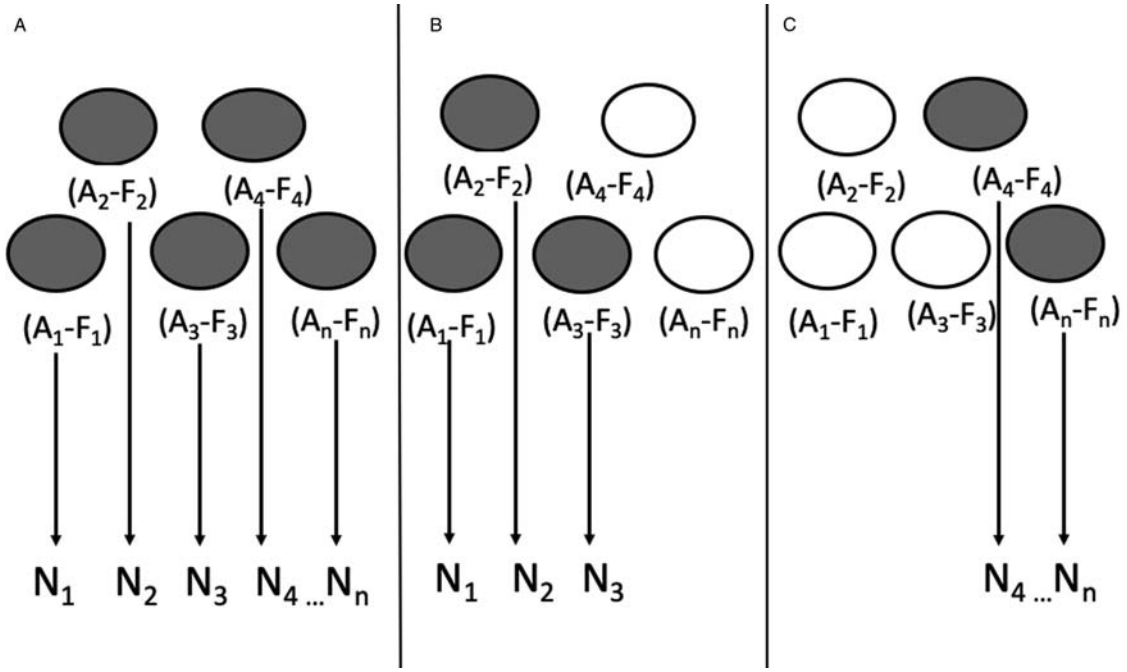

Figure 2 The *anatomical syndrome*. The association of symptoms N_1, N_2, N_3, N_4 … N_n is produced by damage to components F_1, F_2, F_3, F_4 … F_n, localised in brain regions A_1, A_2, A_3, A_4 … A_n. The association occurs because cerebral areas A_1- … A_n) are anatomically contiguous. (A) This syndrome may be observed in a complete form, when all relevant cerebral regions (A_1- … A_n) are damaged. (B) and (C) When the damage involves only some regions (A_1- … A_3, A_4 … A_n) partial forms are observed. Modified from Vallar, G., 2000. The methodological foundations of human neuropsychology: studies in brain-damaged patients, In: Boller, F., Grafman, J., Rizzolatti, G. (Eds.), Handbook of Neuropsychology. Elsevier, Amsterdam, The Netherlands, pp. 305–344.

anatomical contiguity is Gertsmann's syndrome as interpreted by Strub and Geschwind (1983). The co-occurrence of the four symptoms (finger agnosia, left–right disorientation, acalculia, agraphia) is valuable in terms of anatomical localisation, suggesting a left parietal lesion, but cannot be attributed to the derangement of a single functional component (Benton, 1992, 1961). Aphasic disorders, as conceived in the classical anatomo-clinical models, are examples of *strong* anatomo-functional syndromes, with both clinical and theoretical significance (Marshall, 1982): the occurrence of a given association of symptoms reflects the damage of a specific functional component, localised in a brain region.

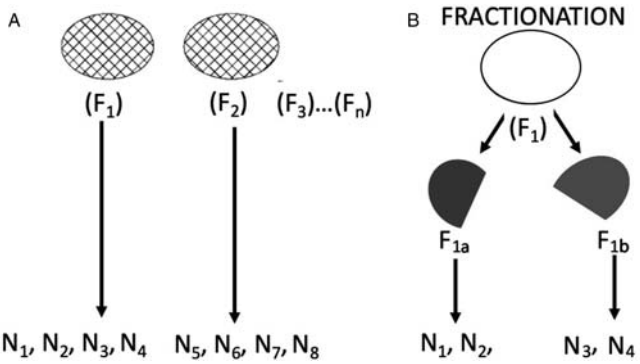

Figure 3 The *functional syndrome*. (A) The associations of symptoms N_1, N_2, N_3, N_4 and N_5, N_6, N_7, N_8 are produced by dysfunctions of components F_1 and F_2, respectively. This association is defined in functional terms, with no reference to the neural components involved. (B) This type of syndrome does not make allowance for partial associations (e.g., N_1, N_2, N_3, but not N_4). Were partial associations observed, this would provide evidence that a component such as F_1 is not unitary, but fractionates instead into more sub-components, such as F_{1a} and F_{1b}, that, when damaged, would be responsible of deficits that may occur independently of one another (N_1 and N_2, N_3 and N_4). The dissociations between deficits of LTM and of STM (Vallar, 1999) and between extra-personal and personal, bodily, spatial neglect (Vallar and Maravita, 2009) provide examples of the fractionation of systems previously regarded as unitary. These systems were subsequently found to have discrete neural correlates. Based on Vallar, G., 2000. The methodological foundations of human neuropsychology: studies in brain-damaged patients, In: Boller, F., Grafman, J., Rizzolatti, G. (Eds.), Handbook of Neuropsychology. Elsevier, Amsterdam, The Netherlands, pp. 305–344.

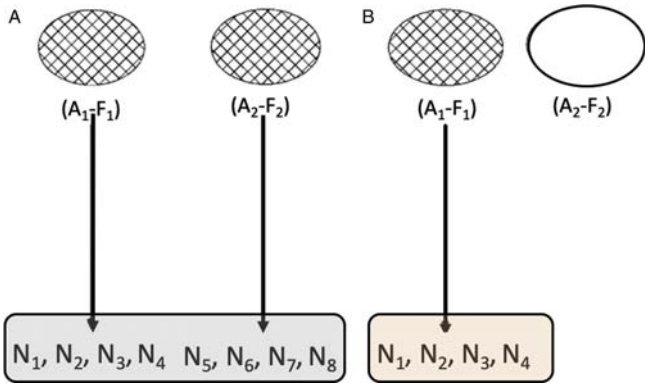

Figure 4 The *anatomo-functional (mixed) syndrome*. This type of association differs from the functional syndrome in that the involved functional components (e.g., F_1 and F_2) have specific cerebral correlates (A_1 and A_2). (A) If the regions A_1 and A_2 are anatomically contiguous a mixed syndrome, comprising the symptoms N_1, $N_2 \cdots N_8$ (gray oval) occurs. (B) A mixed syndrome is, however, bound to fractionate into sub-syndromes (e.g., pink oval: N_1, N_2, N_3, N_4), when the cerebral correlate of a single functional component (A_1–F_1) is selectively damaged. Based on Vallar, G., 2000. The methodological foundations of human neuropsychology: studies in brain-damaged patients, In: Boller, F., Grafman, J., Rizzolatti, G. (Eds.), Handbook of Neuropsychology. Elsevier, Amsterdam, The Netherlands, pp. 305–344.

These assumptions were implicit and not specified in any detail and implication at the beginning of modern neuropsychology, in the mid 1800s. Then, the diagnosis of a defective performance, of an abnormal behavior, was based on the detection of a symptom or sign, evident at clinical observation, and then often conspicuous. The theoretical assumptions of neuropsychology were made explicit and critically discussed only much later (De Renzi, 1967; Shallice, 1988; Teuber, 1955; Vallar, 2000).

Neuropsychological Journals and Books

In 1963, the first scientific journal with a name mentioning the term started to be published: *Neuropsychologia*. "Under the term "neuropsychology", we have in mind a particular area of neurology of common interest to neurologists, psychiatrists, psychologists and neurophysiologists. This interest is focused mainly, though not of course exclusively, on the cerebral cortex. Among topics of particular concern to us are disorders of language, perception and action. Although certain of these disorders can of course be studied only in man, we are none the less convinced that information of great value to human pathology is to be obtained from animal experiment, which may be expected to throw valuable light on the basic mechanisms of cerebral organization". A meeting that took place in Mond See in Austria in 1951 is mentioned: "A small group of European neurologists and psychologists met to discuss disorders of higher mental function associated with injury or disease of the brain". In this, and in successive meetings, the discussion concerned disorders of spatial perception and psychic symptoms associated with lesions of the third ventricle,

disorders of "time sense", of the body scheme, aphasia, alexias, memory disturbances and the Korsakoff syndrome, visual hallucinations and agnosias, constructional apraxia, cerebral dominance, psychological effects of bilateral versus unilateral brain lesions, and perceptual disorders in children with early brain damage. The board of Editors was multidisciplinary and international, including the North American neurologist Derek E. Denny-Brown (Foley, 1982), the French neurologist and psychiatrist Henry Hécaen (Boller, 2006; Hécaen, 1972; Lhermitte et al., 1985; Zangwill, 1984), who was the first editor-in-chief, the North American Karl H. Pribram (Miller et al., 1960; Pribram, 1971) and Hans L. Teuber (1955, 1964; Pribram, 1977; Richards, 1978; Gross, 1994), the Soviet Alexander R. Luria (Cole et al., 2006; Luria, 2012) and the British Oliver L. Zangwill (Stringer, 2017; Weiskrantz, 1988), who may be referred to as cognitive neuroscientists and neuropsychologists.

One year later, *Cortex*, a journal with a very similar scope, was founded by the Italian neurologist Ennio De Renzi (De Renzi, 2006) with the help of Luigi Amedeo Vignolo (Cappa, 2012), both in the Neurological Clinic of the University of Milano, Italy. Also this Board was interdisciplinary and international, including: neurologists, as the British MacDonald Critchley (Joynt, 1998), who had written a monumental monography on the parietal lobe (1953), the French François Lhermitte (1965) and the North American Norman Geschwind, who was revisiting the classical centre-connections models of cognitive functions (1965a, 1965b; Mesulam, 1985a), the neuropsychologists and cognitive neuroscientist George Ettlinger, who was working with adult and children brain-damaged patients and with monkeys (Ettlinger, 1959; Ettlinger et al., 1957), the North American psychologist and neuropsychologist Arthur Benton (1968, 1961), Alexander R. Luria and the child and adolescent psychiatrist Julien de Ajuriaguerra (Garrabé, 2014). After *Neuropsychologia* and *Cortex*, further journals (*Journal of Clinical Neuropsychology*, 1979; *Cognitive Neuropsychology*, 1984; *Aphasiology* and *Neuropsychology*, 1987, and others) started to be, and are currently, published, witnessing the development of neuropsychology.

Beginning from the 1970s, also books on neuropsychology were published. The first was *Introduction à la neuropsychologie* by Henry Hécaen (1972). This book a few years later had an English edition (*Human neuropsychology*), written by Hécaen and the North American neurologist Martin Albert (Hécaen and Albert, 1978). Other books then followed: *Clinical Neuropsychology*, edited by the North American neurologists Heilman and Valenstein (1979), currently in its fifth edition (Heilman and Valenstein, 2011); the *Manuale di Neuropsicologia*, edited by the Italian neurologist Gianfranco Denes and the neuropsychologist Luigi Pizzamiglio (Denes and Pizzamiglio, 1990), translated in English a few years later (1999), and currently in its third edition (Denes et al., 2019); the *Handbook of clinical neuropsychology*, with the British neuropsychologists John C. Marshall and Peter W. Halligan as editors (Gurd et al., 2010; Halligan et al., 2003). The book of the British neuropsychologists Rosaleen A. McCarthy and Elizabeth K. Warrington (McCarthy and Warrington, 1990), *Cognitive neuropsychology. A clinical introduction*, and the one edited by the North American Brenda Rapp (2001), *The handbook of cognitive neuropsychology. What deficits reveal about the human mind*, were more concerned with the functional (cognitive) processing aspects of neuropsychology. Conversely, the book of the North American neurologist M.-Marsel Mesulam (2000a,b), *Principles of behavioral neurology* (1985b), and its second edition, *Principles of behavioral and cognitive neurology* (2000) was more focused on the neurological side of neuropsychological deficits.

Finally, beginning in the late 1980s, and with a second edition in the early 2000s, the neurologist François Boller, with the neuropsychologist Jordan Grafman, edited *The Handbook of Neuropsychology*, a monumental series of volumes, published by Elsevier, that reviews virtually all aspects of neuropsychology. This list of journals, books and handbooks clearly shows that, starting from the 1970s, neuropsychology had become an independent and specific scientific discipline, in the broader fields of neuroscience, cognitive science and psychology.

The development of neuropsychology was accompanied by reflections on its theoretical foundations and methods (Shallice, 1988; see for early contributions Teuber, 1955; De Renzi, 1967; Vallar, 2000, 1999). This may be taken as an indication of the maturity of the discipline.

Early "Neuropsychological" Clinical Observations

The first attempts to relate mental processes to the brain may be traced back to the fifth century B.C. when Hippocrates (460–370 B.C.) located the intellect in the brain and the senses in the heart. Herophilus, later on (c.330 to 260 B.C.), considered the ventricles to be the center of the soul, intelligence and mental functions, whereas Galen of Pergamon (130–200 B.C.) in the second-century B.C. favored the brain substance as the seat of the mind (Pearce, 2019, 2013). Galen described the ventricles in detail as four cavities and their connections, and he thought that those were the sites of storage of *psychic pneuma* (animal spirit); he located the soul and higher cognitive functions in the solid portions of the brain around the ventricles. In Renaissance, Leonardo da Vinci (1452–1519) produced drawings of the skull and the central nervous system based on dissection of the human body (Pevsner, 2002). Andreas Vesalius (1514–64) published in 1543 the *De Humani Corporis Fabrica*, which depicted the brain and other organs in great detail (Vesalius et al., 1973).

Localization of mental functions in the substance of the brain displaced the ventricular localization in the 17th and 18th centuries. In the 17th century, Descartes suggested that the soul resided in the pineal gland. Around 1800 a neuroanatomist from Vienna, Franz Joseph Gall (1757–1828), whose closer co-worker was Johann Gaspar Spurzheim (1776–1832), proposed that the human mind was organized in different innate faculties, which were localized in different organs or centers of the brain, making the cerebral localization of mental functions a central issue in the relationships between brain and mind (Gall and Spurzheim, 1810; Lesky, 1970; Young, 1970). However, Gall also made the questionable claim that measurements of the skull might allow one to deduce the moral and intellectual characteristics of the individual, and other questionable suggestions, as the existence of faculties such as

the "sense of property", the "instinct of providing", "covetousness", "propensity to steal" (VII), along with "memory of things", "memory of facts", but also "sense of things", "educability", "perfectibility" (XI), and "Faculty of spoken language, talent of philology" (XV) (see Finger and Eling, 2019). "Spoken language", or "verbal memory", as originally termed by Gall, was localized anteriorly, in the part of the brain directly behind the eyes, the frontal lobes (Prins and Bastiaanse, 2006). A large-scale clinico-pathological study conducted by Andral (1840) did not support this association. The anatomo-functional correlation approach suggested by Gall is apparent in reports by phrenologists of an association between speech disturbances and anterior cerebral lesions. The localization of language in the frontal lobes, initially suggested by Gall, was supported by the French physician Jean-Baptiste Bouillaud (1825), who based his conclusions on analysing data from two neuropathological casebooks (see Luzzatti and Whitaker, 2001, for discussion and re-analysis of the data). The observations of language disturbances reported before the discovery of Pierre-Paul Broca have been reviewed by Benton (1964), Sondhaus and Finger (1988), Luzzatti and Whitaker (1996), Prins and Bastiaanse (2006).

The "Birth" of Neuropsychology as a Scientific Discipline: Paul Broca 1861

The French surgeon Pierre-Paul Broca (1861a) reported a patient, named *Leborgne*, who suffered from a right-sided motor deficit, and who could articulate only a single syllable, that he typically repeated twice, "tan, tan", to any question was asked to him. For this reason, in the hospital the patient was known by the surname of *Tan*. Comprehension of speech was comparatively preserved ("Tan understood almost everything that was said to him"). Leborgne had lost the faculty of speech over 20 years before Broca examined him, and, a few days after Broca saw the patient, Leborgne died. A *post-mortem* exam revealed a lesion on the surface of the left frontal lobe, involving the region that has become known as Broca's area (and the deficit in language production as Broca's aphasia), which is typically defined in terms of the *pars opercularis* and *pars triangularis* of the inferior frontal gyrus, represented in Brodmann's (1909) cytoarchitectonic map as areas 44 and 45; the lesion extended to the insula, the parietal post-central gyrus, and the first temporal convolution. A few months later, Broca (1861b) reported a second patient, Lelong, with a similar disturbance of speech output and lesion site. The site of the lesions of Broca's patients have been re-assessed by modern neuroimaging methods (Leborgne and Lelong, see Dronkers et al., 2007, showing a medial extension of the lesion, to involve white matter fascicles; Leborgne, see Signoret et al., 1984).

Broca definitely demonstrated, for the first time, a left hemispheric lateralization of language, raising the concept of hemispheric cerebral dominance, but it was not until after World War II that the complementary association between spatial and constructional abilities, in the visual, but also in the haptic and auditory modalities, and the right-hemisphere was definitely shown (De Renzi, 1982).

The "Golden Age": 1861–1914

Following Broca's initial observation, a period of intense activity started, involving clinico-pathological correlations in human patients and animal experiments, the so-called "golden age" (Benton, 1988). The main outcome was the localization of a variety of mental functions: language in the frontal and in the temporal regions, visual and visuo-perceptual capabilities in the occipital lobes (Munk, 1881; Wilbrand, 1887), somatosensory and somato-perceptual capabilities in the parietal lobes (Mayer, 1895; Meyer, 1978), the more complex aspects of behavior, learning and personality in the frontal lobes (Bianchi, 1895, who made ablation experiments in monkeys and dogs). The prevailing view in the second half of the 19th century was localizationist, namely specific brain areas supported specific mental functions. Critics were however advanced. The French physician Marie Jean-Pierre Flourens (1842; see Yildirim and Sarikcioglu, 2007), who made studies ablating anatomically defined brain areas in rabbits and pigeons, and the German physiologist Friedrich Leopold Goltz in the second half of the 19th century (see Goltz, 1960; Tyler and Malessa, 2000) promoted more holistic hypotheses in which brain regions were more or less functionally homogeneous (Benton, 1988).

The Aphasias and Language

After Broca's scientific revolution (Benton, 1988; Kuhn, 1970), a rapid development and increase of knowledge about disorders of language (aphasia) took place. The British neurologist Hughlings-Jackson (1879; see Head, 1915), during a meeting in 1868 in Norwich also attended by Broca (Lorch, 2008) distinguished two broad types of aphasic patients: with paralytic articulation disorders, and with "true" aphasia, with "intellectual" language being more impaired than "emotional" language, in the Jacksonian general theoretical framework of the automatic-voluntary dissociation, with hierarchies of brain function. The French neurologist Baillarger (Alajouanine, 1960) had made a few years earlier (1865) a very similar distinction. In the approaches by Baillarger and Hughlings-Jackson the role of centers (Broca) and of centers and connections (Wernicke) was not crucial, and the anatomical localization of functions was much less definite.

The major advance after Broca's (1861a, 1861b, 1861c) seminal observations was made by the German neurologist and psychiatrist Carl Wernicke, who, on the basis of clinical observations, draw the first centre-connection anatomo-functional model of language (Wernicke, 1874). The model (**Fig. 5**) included three types of aphasia, caused by damage of the left hemisphere. In *sensory* aphasia, a lesion to the first temporal convolution causes a loss of the auditory images of words, with a deficit of auditory

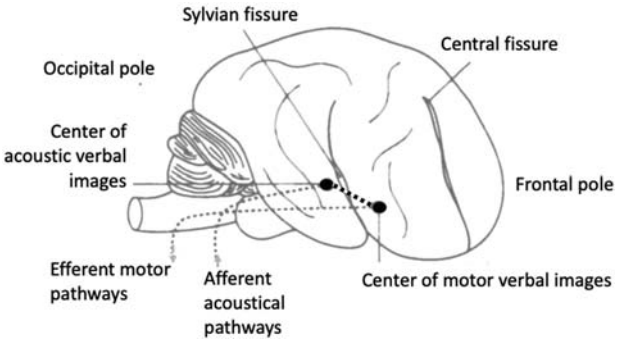

Figure 5 The anatomo-clinical model of language of Carl Wernicke (1874). Damage to the two centers (black circles) of sound and movement verbal images causes *sensory* (Wernicke's) and *motor* (Broca's) aphasia, respectively. Damage to the connection between them (dashed black line) causes *conduction* aphasia. Centers, connections and afferent acoustical and efferent motor pathways (gray dotted lines) are localized in specific regions of the brain. Based on Wernicke, C., 1874. Der aphasische Symptomenkomplex: eine psychologische Studie auf anatomischer Basis. Cohn und Weigart, Breslau.; Modified from Vallar, G., 2019. I fondamenti metodologici della neuropsicologia, in: Denes, G., Pizzamiglio, L., Guariglia, C., Cappa, S.F., Grossi, D., Luzzatti, C. (Eds.), Manuale di Neuropsicologia. Normalità e Patologia dei Processi Cognitivi. Zanichelli, Bologna, pp. 99–154.

comprehension of language, associated with a fluent, but altered, speech. In *motor* aphasia, or Broca's aphasia, a lesion to the third frontal convolution brings about a reduction of speech output, that is nonfluent, while auditory comprehension is comparatively preserved. In *conduction* aphasia, a damage to the white matter connection (the arcuate fascicle) between these temporal and frontal regions produces a disproportionate impairment of repetition, with auditory comprehension being comparatively preserved. The classical models of language and aphasia were completed by the German neurologist Ludwig Lichtheim (1885) who added a "center for concepts", which connected Broca's and Wernicke's areas, and was not localized in a specific cortical region, and other centers involved in reading and writing (**Figs. 6** and **7**). In the models of Wernicke (1874) and Lichtheim (1885) the different linguistic activities resulted from the transformation of representations stored in centers into different types of representation, through connections between centers; these representations were based on specific inputs, and had specific outputs. Accordingly, aphasic deficits resulted from the damage to centers, connections between them or both. For instance, reading aloud involves the pathway "O A M m" (Comston, 2006, see **Fig. 7**).

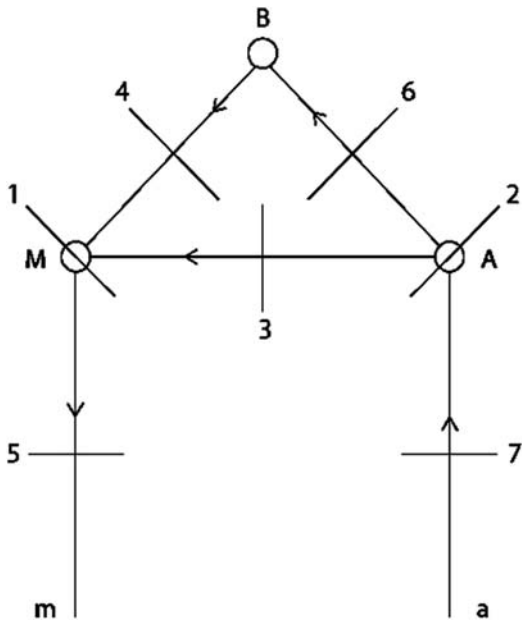

Figure 6 The model of language of Ludwig Lichtheim (1885). A (center of sound verbal images, Wernicke's area), M (center of movement verbal images, Broca's area) and their connection; B (concept center, not localized in any specific cortical region); m (efferent movement) and a (afferent sound) pathways. The model differs from Wernicke's one for the addition of the B center, making a model of language known as the "house" (Eling, 2011; Eling and Whitaker, 2010). The model shows the functional locus of different types of language disorders, resulting from damage to centers (1, 2), connections (3, 4, 6), efferent output articulatory (5) and afferent input acoustic pathways (7). The latter two damages (5 and 7) result in more peripheral disorders, not affecting linguistic centers or connections. Based on Lichtheim, L., 1885. On aphasia. Brain 7, 433–484.

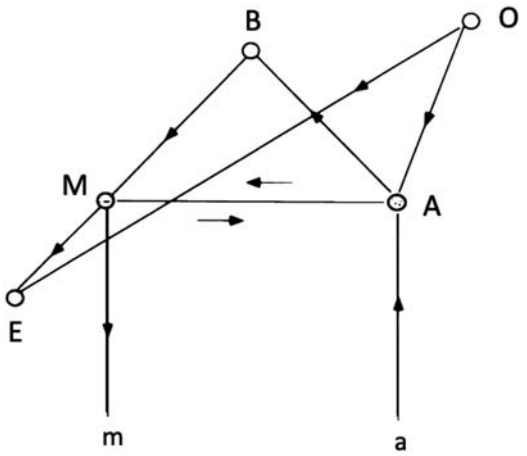

Figure 7 A more complex version of the model of language of Lichtheim (1885). Center O (visual images) sends inputs to A and E (writing center), which receives input also from M. Based on Lichtheim, L., 1885. On aphasia. Brain 7, 433–484.

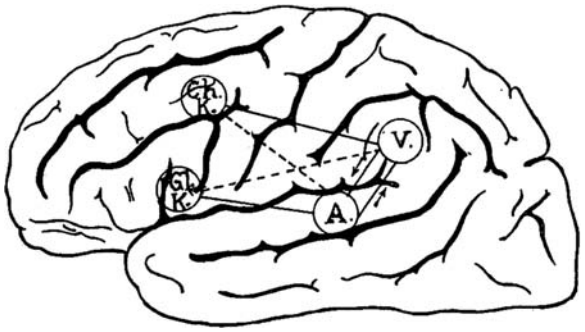

Figure 8 Diagram of Bastian's (1897) approximate sites of four centers and their connections. Dashed lines indicate non-preferential connections. A/V: Auditory/Visual word centers. GKK/CKK: Glosso/Cheiro Kinaesthetic centers. The preferential A-GKK and V-CKK connections denote the relationships between auditory word processing and speaking, on the one hand, and between reading and writing, on the other hand. Reproduced with permission from Jellinek, E.H., 2000. Dr H C Bastian, scientific Jekyll and Hyde. Lancet 356, 2180–2183.

This centre-connection approach was also adopted by the British neurologist Henry Charlton Bastian (1897; see Lorch, 2019; Jellinek, 2004), who, starting from the late 1860s (Bastian, 1869), so before Wernicke (1874), distinguished between visual (parietal) and auditory (temporal) word centers, and glosso- and cheiro-kinaesthetic sensory centers (for tongue and hand movements, for speaking and writing), as shown in **Fig. 8**. Bastian suggested distinctions between discrete disorders in the language system, due to damage to these centers and connections, which could selectively involve reading and writing, auditory speech comprehension and production. At variance from the models of Wernicke (1874) and Lichtheim (1885), Bastian's model included "non-preferred" connections, so that the centers of his model were fully interconnected, resembling, and anticipating, modern neural networks (Poeck, 2001; see also **Fig. 26**). The Wernicke-Lichtheim model was however simpler and closer to the anatomo-clinical observations, and had a much more enduring influence (Lecours et al., 1983).

These models (Bastian, 1869; Wernicke, 1874; Lichtheim, 1885) were based on an "associationist" approach. In addition to primary sensory cortical areas (that receive afferent sensory projections) and primary motor areas (that send efferent projections), there are "associative" areas: they include "primary" (uni-sensory), which store images (or representations) of operations performed in primary sensory areas, and "secondary" (multi-sensory) areas, that store images of objects. Aphasia is brought about by damage to centers, localized in associative areas, white matter connections between them, or both.

A development of the associationist approach was provided by the description by the French neurologist Joseph Jules Déjerine of the mechanisms of "pure alexia", in the framework of the centre-and-connections theoretical approaches of Wernicke (1874) and Lichtheim (1885). Déjerine's (1914; Déjerine, 1892) anatomo-clinical model of language is shown in **Fig. 9**. An example of the associationist approach to neuropsychological deficits is Déjerine's description of the pathological mechanisms bringing about "pure alexia", as shown in **Fig. 10** (see Bub et al., 1993; Henderson, 2009). A similar mechanism had been suggested by Carl Freund (1889), to account for the selective inability to name (not to identify) objects in the visual modality (optische Aphasie, optic aphasia, see De Renzi, 2000; Riddoch, 1999, for reviews). The associationist approach to the component deficits of language is illustrated in **Fig. 11** by the "Bell's" schema of the French neurologist Jean-Martin Charcot (1885; Clarac and Boller, 2009).

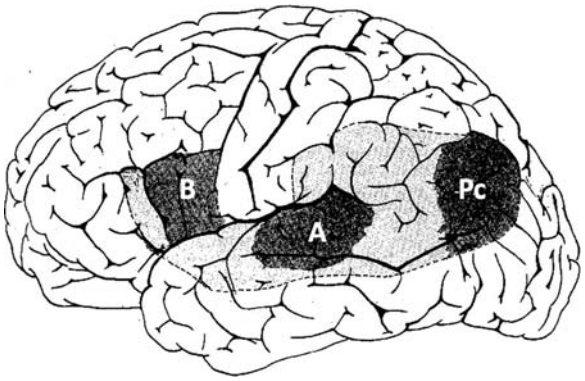

Figure 9 Déjerine's (1914) anatomo-clinical model of language. B: Broca's circonvolution (center of motor images of articulation). A: Wernicke's circonvolution, center of auditory images of words. *Pc*: *Pli courbe* [angular gyrus of the posterior inferior parietal lobule (see Caspers and Zilles, 2018)], center of visual images of words. Based on Déjerine, J., 1914. Sémiologie des affections du système nerveux. Masson, Paris.

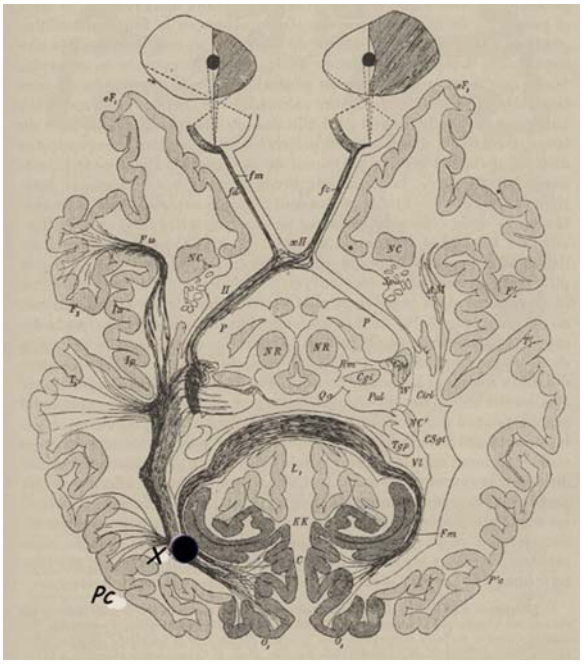

Figure 10 Déjerine's (1914) anatomo-functional interpretation of "pure alexia". Lesion X in the white matter prevents visual input from the right and the left hemisphere to reach area *Pc*. Based on Déjerine, J., 1914. Sémiologie des affections du système nerveux. Masson, Paris.

The associationist approach was prevailing in the second half of the 1800s. A relevant feature was the distinction between language and intellectual abilities, as illustrated by the existence of a concept (Lichtheim, 1885) or ideational (Charcot, 1885) center. Conversely, the French neurologist Pierre Marie (Clarac and Boller, 2009) conceived aphasia as an intellectual, cognitive, disorder, and summarized his view in the equation; "Broca's aphasia = Wernicke's aphasia + anarthria", with the latter being a disorder of speech rather than of language (Lecours et al., 1983).

Other Neuropsychological Disorders Described in the Golden Age

In addition to aphasia, other deficits were observed and reported. Their peculiar feature was that, as aphasic deficits, they were selective, affecting specific aspects of mental activity.

Deficits of Object and Face Recognition: the Agnosias

The German physiologist Hermann Munk (1881), through ablation experiments in the dog, identified the visual center in the occipital lobes, with extensive bilateral lesions making the animal blind, and unilateral damage producing a contralateral hemianopia. Munk also reported that, after limited occipital excisions, dogs were unable to grasp the meaning of many visual stimuli (a whip,

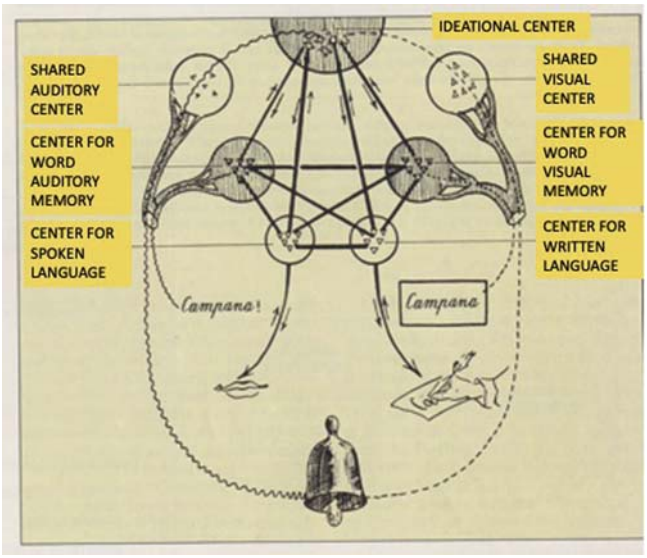

Figure 11 The Bell's (Campana, in Italian) centre-and-connections schema of Charcot (1885). The schema is based on previous work by Wernicke (1874) and Lichtheim (1885). An illustrative example with the centers and connections involved in naming the visually presented bell, repeating its sound, etc., is provided. Modified from Charcot, J.-M., 1885. Lezioni cliniche dell'anno scolastico 1883-84 sulle malattie del sistema nervoso redatte dal dottore Domenico Miliotti. Francesco Vallardi, Milano.

food), that did not evoke the appropriate behavioral response, but nevertheless appeared to be detected, as indexed by the dogs' preserved ability to avoid obstacles. This disorder was termed *Seelenblindheit* (mindblindness). A mind-blind patient, who showed deficits of object and face recognition, and topographical disorientation, was then reported; the lesions involved the occipital lobe bilaterally (Wilbrand, 1892, 1887; see Solms et al., 1996, for review). The term *Agnosia*, coined by Sigmund Freud (1891) gradually displaced *Seelenblindheit*. The German physician Heinrich Lissauer (Lissauer, 1890; see comment in Shallice and Jackson, 1988) a few years later distinguished the stage of conscious awareness of a sensory impression (*apperception*) from the stage of associating other notions with the content of apperception (*association*), that was defective in the studied patient. The lesion of Lissauer's patient, made available by a later *post-mortem* assessment (Hahn, 1895), covered the vascular territory of the left posterior cerebral artery, involving the cuneus, the fusiform and lingual gyri, the splenium of the corpus callosum and deeply the adjacent white matter. The left hemispheric infarction damaged the primary and association visual cortices and interrupted the connections between the occipital cortex in the right hemisphere and the left hemispheric language areas (see Nielsen, 1937). For a long time, however, even the existence of visual agnosia was questioned (Bay, 1953; Bender and Feldman, 1972; Gassel, 1969), but the deficit, in the two stage framework devised by Lissauer (1890) is currently widely accepted by students with a variety of theoretical approaches (Bauer and Demetry, 2003; De Renzi, 1999; Grüsser and Landis, 1991; McCarthy and Warrington, 1990; Mesulam, 2000a,b; Riddoch and Humphreys, 2001). The concept of a distinction between apperceptive *vs.* associative types of agnosia is still influential, being applied to the deficits of face recognition (Prosopoagnosia, Bodamer, 1947; Ellis and Florence, 1990; apperceptive and associative forms of Prosopoagnosia, see De Renzi et al., 1991; De Renzi, 1999), and tactile and color agnosia (see De Renzi, 1999 for review).

Deficits of Movement Planning: the Apraxias

At the end of the 19th century the inability of left-brain-damaged patients to correctly perform purposeful movements, not due to primary motor deficits, as hemiplegia or hemiparesis, had been much less investigated than aphasia, although the term *apraxia* (Steinthal, 1871) had been coined. The disorder had been related to deficits of conceptual thinking (asymbolia, see Finkelnburg, 1870), aphasia and agnosia (see discussion in Canzano et al., 2016; Rothi and Heilman, 1996). The German neurologist and psychiatrist Hugo Liepmann (Goldenberg, 2003; Pearce, 2009) described in the early 1900s apraxic deficits of movement planning, and proposed a centre-connections model of praxis, that localized in the left hemisphere the center for planning movements by limbs of the two sides of the body (see **Figs. 12** and **13**). Liepmann distinguished the mechanisms impaired in apraxia from asymbolic, aphasic and agnosic disorders (Foundas, 2013; Goldenberg, 2009). Liepmann based his conclusions first on the study of a single case, the "imperial counselor", afflicted with syphilis, and admitted to the hospital with a diagnosis of "mixed aphasia and dementia from apoplexy" (Goldenberg, 2003, for discussion; Liepmann, 1905a, 1900). Liepmann made also group ("mass") studies of apraxia, using clear inclusion and exclusion criteria for the 89 patients with unilateral brain lesions, and subjected them to a uniform and theoretically motivated collection of clinical tests (Liepmann, 1908, 1905b).

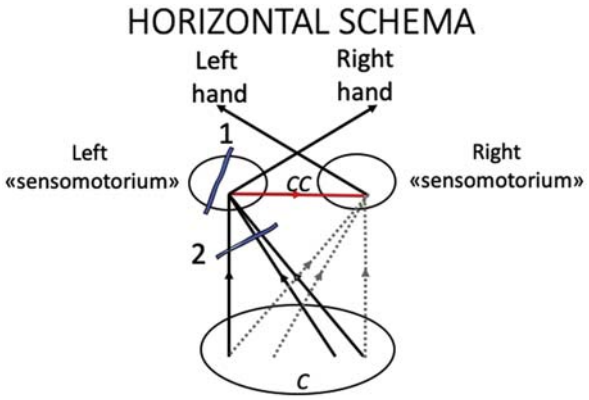

Figure 12 Liepmann's schema for the planning and execution of limb movements (see Goldenberg, 2003) redrawn. The "horizontal schema" (Liepmann, 1908) shows that the "movement formula" arises from connections from the whole cortex (C) to the "sensomotorium" in the left hemisphere, as indexed by black lines. Connections from C to the right hemisphere have only "subordinate significance", as indexed by gray dashed lines. Lesions interrupting these connections (2) or damaging the left "sensomotorium" (1) cause bilateral ideo-kinetic apraxia, masked in the right hand by the primary motor deficit, but apparent in the left hand, that receives the "movement formula" via the corpus callosum (CC, red). Based on Liepmann, H., 1908. Drei Aufsätze aus dem Apraxie-Gebiet. S. Karger, Berlin.

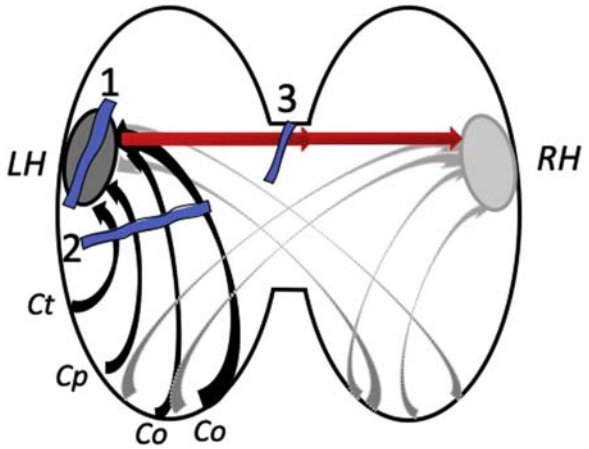

Figure 13 A later version (Liepmann, 1925) indicates that the asymmetry arises early than as suggested in the "horizontal schema", since only connections from the cortex of the left hemisphere (*Ct*, temporal; *Cp*, parietal, *Co*, occipital, black arrows) to the left "sensomotorium" are functionally relevant; connections to and from the right hemisphere are not relevant (gray arrows). A lesion of the anterior two-thirds of the CC (3) causes apraxia of the left limbs. LH/RH: left/right hemisphere. Based on Liepmann, H., 1925. Apraktische störungen, In: Curschmann, H., Kramer, F. (Eds.), Lehrbuch Der Nervenkrankheiten. Springer, Berlin, pp. 408–416.

Spatial Deficits

In the second half of the 1800s, the development of knowledge about disorders of spatial cognition did not result in models as detailed as the Wernicke-Lichtheim box-and-arrows architecture of language processes. Patients showing disorders of topographical memory and orientation were described (Wilbrand, 1887; see Solms et al., 1996). A North American physician, Dunn (1895) reported a patient with a double hemianopia, intact central vision and "loss of the sense of location", with deficits in remembering spatial relationships of familiar streets and rooms of the patient's house, and no other disorders of visual memory, such as face recognition. Dunn (1895) suggested the existence of a "geographic center … on the right side of the brain for the record of the optical images of locality, analogous to the region of Broca for that of speech on the left side in right handed persons". Subsequent observations confirmed the association between left homonymous hemianopia, damage to the right hemisphere and visual disorientation (Lenz, 1905; Peters, 1896). These observations started establishing the view that the right hemisphere had distinctive functional properties with respect to the mediation of behavior, in analogy to the role of the left hemisphere for language (Benton, 1972).

The Frontal Lobe and the Control of Behavior

In the United States, the case of Phineas Gage is an impressive description of the behavioral consequences of damage to the more anterior part of the frontal lobe, the prefrontal cortex, although it should be noted that the adjective "frontal", rather than

"prefrontal" was used at least up to the later 1940, to refer to the site of the lesion, and the resulting disorder ("frontal lobe syndrome", see Benton, 1991). This report by the North American physician John Harlow (1868, 1848; O'Driscoll and Leach, 1998, for review) described a previously healthy 25 year-old railroad foreman, who sustained a penetrating frontal lobe wound. The main sequela of the frontal injury was Gage's striking behavioral change. Before the injury Gage had a balanced mind and was looked upon by those who knew him as a smart businessman, energetic and persistent in executing his plans. After the trauma, Gage was described by Harlow (1868) in this way: "He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible" (Macmillan, 1986, p. 85). In terms of stimulating a surge in the understanding of brain-behaviour relationships, the case of Phineas Gage's turned out to be as relevant as Broca's (1861a) Leborgne case.

This clinical observation found an experimental counterpart in lesion studies in the animal. Early studies suggested involvement of the frontal lobes in complex aspects of behavior. Behavioral abnormalities were described in animals after the extirpation of both the prefrontal lobes, even though vision, hearing, general sensation and gross movement remained preserved (Benton, 1991, for review; Bianchi, 1895; Ferrier, 1886, 1878).

Subsequently, other clinicians reported patients with complex behavioral disturbances, also involving emotional aspects of behavior (Welt, 1888; Jastrowitz, 1888). The terms *moria*, an euphoric excitement, laughter, and silliness without a mood component or appropriate context (Erickson et al., 2016; Jastrowitz, 1888), and *Witzelsucht* (Oppenheim, 1890), a peculiar addiction to trivial joking of a predominantly sarcastic nature (Benton, 1991; Granadillo and Mendez, 2016), were introduced to refer to a specific aspect of these behavioral changes. In a series of 225 patients with gunshot wounds Phelps (1898, cited in Lishman, 1968) reported an association between disturbances of "higher psychic phenomena and psychiatric disturbance" and damage to the frontal lobes.

Awareness of Disease

In the second half of the 19th century a disorder featuring the defective monitoring and awareness of neuropsychological and neurological deficits was observed. The disorders considered in the previous sections involve specific impairments, not the monitoring and awareness of the impairment itself. An early report of unawareness of blindness had been made by Seneca (*Epistulae Morales ad Lucilium, Liber Quintus, Epistula* L), who wrote: "Harpastes, my wife's female clown, has remained, as you know, in my house as an inherited burden.…Now this silly woman suddenly became blind. The story sounds incredible, but I assure you that it is true. She does not know that she is blind. She keeps asking her attendant to change her quarters; she says the house is too dark". This early description of the phenomenon of unawareness of blindness was later mentioned by Michel de Montaigne, in a chapter primarily concerned with malingering (Bisiach and Geminiani, 1991; Critchley, 1953).

The first scientific observation of an association between unawareness of disease and cerebral damage was made much more later by Constantin von Monakow (Professor of Neurology in Zurich, see Wiesendanger, 2006), who (von Monakow, 1885) described a patient with cortical blindness (Papagno and Vallar, 2003): an acquired loss of vision due to bilateral damage to the primary visual occipital cortex, and its connections with peripheral structures, also involving the cuneus, the lobulus lingualis, and temporal areas in the left hemisphere (Leopold, 2012; Melnick et al., 2016), with a preserved pupillary light reflex (Kardon, 1995). The patient did not see obstacles in front of him, was unable to find the food when he had to eat, did not blink when a fist was shown in front of his eyes, and looked as a blind man. The patient did not seem to be aware of his deficit, thinking, as Harpastes, that the environment was dark. The patient showed also word deafness; a deficit in the processing and the identification of the phonemes composing a word, with no major sensory acoustic impairments (Bernal and Ardila, 2016; Poeppel, 2001) and a defective acoustical awareness; notably, his intellectual functions were not disproportionately impaired.

A few years later (Anton, 1893), Gabriel Anton, professor of Neurology at the University of Graz, Austria), reported the case of a man who was not aware of his left-sided paralysis, although being only mildly confused. Non-awareness of hemiparesis (*Nichtbewutsein*) was associated with a temporo-parieto-occipital lesion in the right hemisphere, also involving the white matter and the optic thalamus. A few years later, Anton (1899; David et al., 1993) confirmed von Monakow's observations, reporting a patient with cortical blindness and a *Seelenblindheit* (psychic blindness), featuring an unawareness for the deficit.

Non awareness of left hemiplegia was later reported in a patient with left hemiparesis by Arnold Pick (1898), professor of Psychiatry in Prague. In these patients general mental deterioration was not a main distinctive feature, and was then unlikely to be the main pathological mechanism underlying non-awareness (Anton, 1898; von Monakow, 1885); a somatosensory impairment was not necessarily associated to unawareness of the motor weakness (Pick, 1898), that concerned the left side of the body (Anton, 1893; Pick, 1898).

The existence of a specific deficit of the monitoring of motor function was definitely established by the report of the French neurologist Josef François Babinski (1914), who described two patients with unawareness of left hemiplegia, a deficit that he termed using a neologism, *anosognosia (anosodiaphoria* designated the behavior of patients who, without ignoring the existence of their paralysis, did not appear to attach much importance to it, as if it were a minor disease). Babinski (1923, 1914) noted the lateralization of the deficit to the left limbs, hypothesizing a specific role of damage to the right hemisphere in the pathogenesis of anosognosia (Gainotti, 2019; Papagno and Vallar, 2003).

For aphasia, a suggestion was made by Wernicke (1874) that some aphasic patients may be not aware of their speech output disorder. The defective monitoring of the deficit of speech output has been associated with sensory aphasia (Wernicke's, and

particularly jargonaphasia), but unawareness has been reported in patients with all aphasia types, as classified with reference to all classical aphasic syndromes (Kertesz, 2010; Lebrun, 1987). Patients showing a frontal lobe syndrome are typically unaware of their deficits (Stuss, 1991).

Between World War I and World War II: 1918–45

The period following the end of World War I featured the continuation of single case studies. So, novel patients with anosognosia for left hemiplegia were reported (Barré et al., 1923; Joltrain, 1924). A few years later, a disorder featuring delusional views about parts of the body contralateral to the side of the lesion, such as a variety of feelings of disownership, termed *somatoparaphrenia* (Gerstmann, 1942), was described by the Austrian neurologist Josef Gerstmann, who had moved to the US in the late 1930s (Triarhou, 2008). Gerstmann (1924) also described an association of symptoms and signs (Vallar, 2000, 1999), that became known as the *Gerstmann syndrome* (also *angular gyrus syndrome*), resulting from posterior parietal lesions in the dominant hemisphere, and including finger agnosia, right-left disorientation, agraphia, acalculia, and constructional apraxia (Benke, 2001; see for discussions of this controversial syndrome Benton, 1961; Critchley, 1966). In these years, Kleist (1934) introduced the term *constructional apraxia* to refer to "an impaired bond between visual-spatial functions and the kinaesthetic engrams which are decisive for manual activity", excluding constructive disorders which can be explained in terms of visuo-perceptual impairment or limb apraxia (see, for a discussion of this heterogeneous disorder, Gainotti and Trojano, 2018).

An example of this clinical single case approach is the monograph written by the north American neurologist Nielsen (1946), who presented 240 cases, with about 10% autopsies, and 5% surgical verification. Nielsen localized higher order brain functions by establishing a relationship between the site and extension of cerebral lesions associated with agnosia, apraxia, and aphasia. A similar approach had been used by the Austrian physician Otto Pötzl (1928) in the investigation of disorders of language (Isserlin, 1936), visual perception and spatial orientation (Lange, 1936).

The existence of spatial deficits associated with damage to the posterior regions of the right hemisphere was also established, by reports of individual case studies by the British neurologist Russell Brain (1941), and Andrew Paterson with the psychologist Zangwill (Paterson and Zangwill, 1944) (see Gregory, 2001, for a biography of Zangwill; Mattingley, 1996, for a reappraisal of the study). These disorders include unilateral spatial neglect (Brain, 1941; Paterson and Zangwill, 1944), and topographical disorientation (Paterson and Zangwill, 1945).

After World War II

Memory Disorders: Amnesia and Deficits of Short-Term Memory

In the classical period, and between the two World Wars, neuropsychological disorders of memory had not been investigated in a detail comparable to deficits of language and praxis. Around 1890, a Russian neuropsychiatrist Sergei Korsakoff described a syndrome predominantly characterized by global amnesia, then termed Korsakoff's syndrome (Arts et al., 2017; Talland, 1965; Victor et al., 1971).

It was only in the middle 1950s that human memory, so far envisaged as a basically unitary system (Melton, 1963), started to be conceived as multi-componential, starting from the distinction between short-term and long-term memory (STM, LTM) components, and followed by further fractionations. In these developments, the interaction between studies of human memory in healthy participants and the neuropsychological evidence, that provided a decisive support to the multiple-component view, was very close. The starting point was the report of patient HM, who had a deficit of LTM (*global amnesia*), with no impairment of STM, after bilateral damage to the medial temporal regions, involving the hippocampal cortex (Scoville and Milner, 1957). This study prompted research on the amnesic syndrome, and on the organization of LTM, that proved in turn to include multiple systems: declarative (episodic, and semantic) and procedural memory. These systems, in turn, include multiple components (Eichenbaum and Cohen, 2004; Zola-Morgan and Squire, 1993). A few years later patients with deficits of auditory-verbal STM were described, thus starting the further fractionation of the STM system (Shallice and Vallar, 1990), that were found to include not only verbal, but also spatial and visual STM system (Della Sala and Logie, 2002). **Figs. 14–17** illustrate the increasing complexity and multiplicity of memory systems, both STM and LTM.

Quantitative and Statistically Supported Approaches

A notable feature of the reports mentioned so far is that they were single case, or multiple-single-case, investigations, where patients were studied and reported since the examiners had spotted an apparent, perspicuous and potentially interesting deficit, that they considered worth investigating. This approach also implied that "negative" cases, namely brain-damaged patients with no apparent symptoms and deficits, were not examined. The assessment was "clinical", meaning that testing was not standardized, results were not coded quantitatively, and conclusions were based on the qualitative observation of the patients' behavior. This note is not meant to diminish the relevance of findings in the classical period and up to the end of World War II in the naissance and early development of neuropsychology. These findings, however, were not based on quantitative data, originating from the patients' behavior and responses to standardized and psychometrically controlled tasks. This made replication of results in a successive study

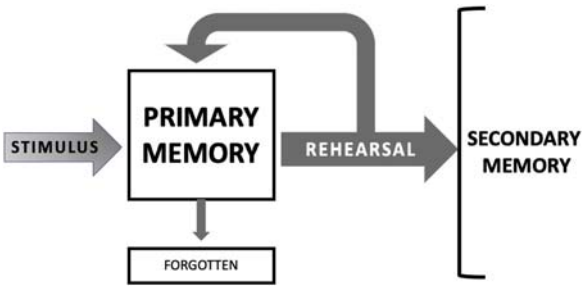

Figure 14 The functional architecture of human memory by Waugh and Norman (1965). Events are stored in a limited capacity temporary Primary Memory. From Primary Memory, events may be forgotten, maintained in Primary Memory through rehearsal, or transferred to Secondary Memory, that is more durable and has larger capacity. Based on Waugh, N., Norman, D.A., 1965. Primary memory. Psychol. Rev. 72, 89–104.

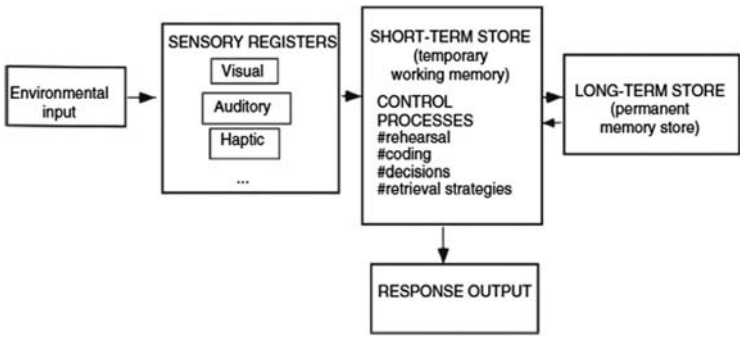

Figure 15 The functional architecture of human memory by Atkinson and Shiffrin (1971), which summarizes the main features of a number of models put forward at that time and then known as the "modal" model (Healy and McNamara, 1996). The model draws a distinction between short- and long-term memory systems (STM/LTM). The two components are organized serially, with temporary storage in STM being a necessary condition for retention in LTM. The short-term store (STS) is a unitary system, not specific for sensory modality, receiving input from different sensory registers, and including a number of control processes, such as rehearsal. The STS plays a central role in cognitive activity, being equated with consciousness. Based on Atkinson, R.C., Shiffrin, R.M., 1971. The control of short-term memory. Sci. Am. 225, 82–90.

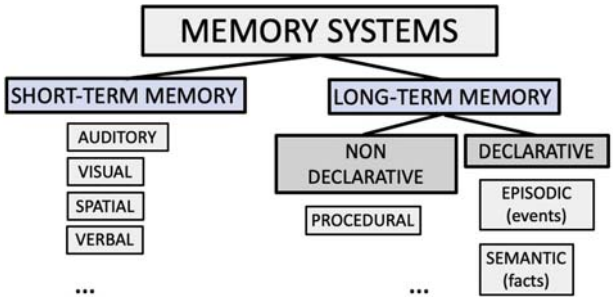

Figure 16 A schematic taxonomy of human memory, where systems are largely organized in parallel, also showing the further fractionation of both STM (Della Sala and Logie, 2002; Vallar and Papagno, 2002) and LTM (Squire, 2004) into multiple components.

difficult, since methodologies and procedures of any study were not specified in any adequate detail. The result was that, since different patients were not assessed in an identical fashion, the comparison of their behavior and performances was not possible. Also, the absence of quantitative data made statistical analyses impossible. In some studies qualitative clinical observations from series of patients were reported, such as the wide array of personality changes in 32 patients undergoing partial resection of the frontal lobes for tumor or abscess (Rylander, 1939).

Group Studies: Quantitative and Statistically Supported Approach

An exception to this state of affairs was the book *Aphasia: A Clinical and Psychological Study"*, written by the Philadelphia neurologist Theodore Weisenberg and the psychologist Katharine McBride, who reported neuropsychological investigations of aphasic patients, recently defined as "a novel work that advanced an essentially equal weighting of standardized psychological testing alongside the clinical neurological examination" (Risser, 2018).

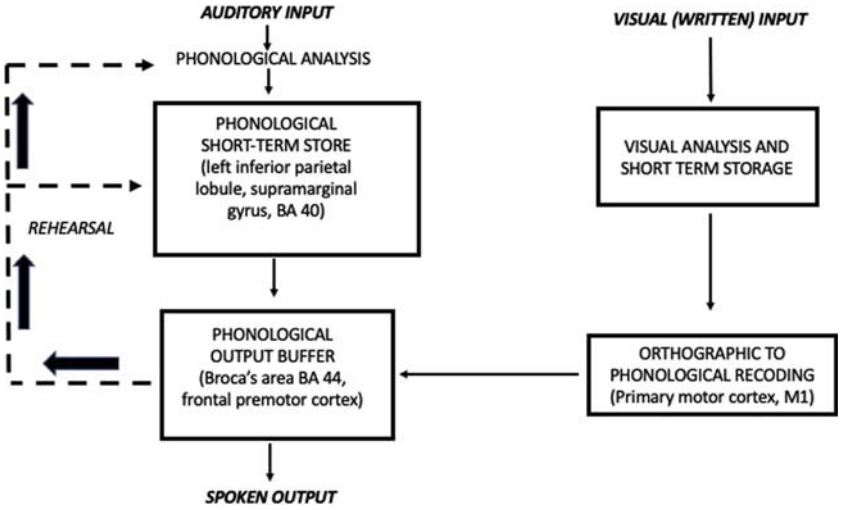

Figure 17 A neurofunctional model of verbal (phonological) STM (Vallar, 2017).

After World War II, the insufficiencies of the qualitative clinical method become increasingly clear, and single case studies started to be described, with areas of impairment and preserved performance being quantified by psychometric tests. The study of the areas of preserved and impaired performance of patient HM, made amnesic by bilateral hippocampal lesions, due to surgery for the relief of uncontrollable epileptic seizures, illustrates this novel approach (Scoville and Milner, 1957).

The single case, or multiple single case, clinical approach was precisely criticized by the Italian neurologist De Renzi (2006) in the late 1960s. In the classical approach very few cases with clinically apparent symptoms are typically examined, using qualitative procedures, not specified in all details and not standardized. Furthermore, "negative" cases, namely patients in whom the function under investigation is putatively damaged, but the symptom of interest is not present, are not considered. The new, modern, neuropsychological method championed by De Renzi (1967) had three main points:

(a) Neuropsychological investigations were to be made in *Groups of Patients* as larger as possible, with lesions (e.g., of the left or of the right hemisphere) putatively able to bring about the deficit of interest. In this way, a sample representative of the general population was available, the impairment was likely to be observed in different degrees of severity, and conclusions from the sample could be extrapolated to the population.
(b) Data from a *Control Group* of healthy participants were to be collected, since their performance could not be errorless, as assumed by the traditional approach, where the single case was investigated, since the symptoms and signs were clinically apparent. Healthy participants had to be as similar as possible to the patients' experimental group for their socio-demographic features (age, sex, level of education).
(c) The *Exam was Standardized*, and its results were expressed quantitatively, numerically, rather than qualitatively. This allowed *statistical analyses*. Parametric analyses, such as the analysis of variance, were preferred, and the data should then have been normally distributed. This allowed to avoid using the less powerful non-parametric analyses. Furthermore, the effects of socio-demographic factors, and of functions that may affect the patients' performance in the task assessing the process of primary interest for the study were controlled by parametric analyses of co-variance. For example the participants' performance in tasks probing a function (intelligence) potentially affecting their performance in the function of interest of the study (memory) was used as a co-variate (De Renzi et al., 1984). Covariance analyses could be also used to partial out the effects of demographic factors, such as education, age and sex of participants on the function of interest (Adams et al., 2008; De Renzi and Faglioni, 1978).

The study of individual patients (single cases) had played however a fundamental role in the birth and early development of scientific neuropsychology. Also for single cases studies, starting from patient HM, standardized procedures for assessment and testing have been developed, as well as specific statistical methods for comparing the patients' performances in different experimental situations, as well as against those of healthy control participants (Crawford and Garthwaite, 2006, 2002; 2002; Crawford and Howell, 1998; Huber et al., 2015).

Positions opposite to that of De Renzi (1967), namely that only the study of individual patients may provide reliable information for the understanding of the functional architecture of the unimpaired system, were put forward in the late 1980s. The main tenet of this view was that group studies are inadequate, since each patient is likely to show a different type of cognitive impairment, due to the complexity of the cognitive system (Caramazza, 1986; Ellis, 1987; Patterson et al., 1985; discussion in Shallice, 2015; Vallar, 2000). An argument of this sort, however, could be applied also to the neurofunctional organization of the cognitive system of healthy participants, that are nevertheless assumed to be homogeneous across individuals. Be as it may, research has been and is continuing to be performed both through single case and group studies.

Images of the Brain and Neuropsychology

The Post-mortem Examination

In the 1800s time period, in man information about the site and the extent of the brain lesion associated with deficits of higher order mental functions, and putatively responsible of them, was available only from a *post-mortem* exam of the patient's brain. There could then be a temporal interval between the clinical observation of symptoms and signs and the neuropathological evidence. The brain of the first patient of Broca (1861a), Leborgne (**Fig. 18**), was examined only many years after the onset of the aphasic deficit. In the second patient (Broca, 1861b), Lelong, the time interval between the onset of the symptoms, the clinical observation and the autopsy was much shorter, about one year (Dronkers et al., 2007). Phineas Gage (Harlow, 1868, 1848) died in 1861, over 10 years after the accident that damaged bilaterally his prefrontal cortex. No autopsy was performed and the probable location of the lesion was determined only more than one century later, based on the examination of the skull (Damasio et al., 1994). The "imperial counselor", whose apraxia was described by Liepmann (1900), died some years later and autopsy was then made (Liepmann, 1905a).

A main problem of this anatomo-clinical correlation was that direct information about the lesion could be gathered even years after clinical observation, when the autopsy could be performed. This implied that the correlation, to be sensible and sound, required that the patient's clinical picture remained unchanged throughout the time of survival after the onset of the deficit, and that the lesion did not change too. Furthermore, the autopsy was unable to detect functional alterations, that could affect the clinical picture, such as von Monakow's (1914) *diaschisis* (Carrera and Tononi, 2014; Feeney and Baron, 1986), featuring a reduction of perfusion and metabolism in remote brain regions, structurally intact, but connected to the damaged area (Finger et al., 2004). Up to the second half of the 1900s, a temporally coincident correlation between the clinical observation of the deficit and the localization of the lesion was possible only for studies in animals, where an experimental lesion was made and its effects were immediately observed (Munk, 1890; Ferrier, 1886; Berlucchi and Vallar, 2018; Berlucchi, 2008; Morabito, 2000; Luciani, 1884; Bianchi, 1895). In humans, the correlation could be done only *post-mortem* by an autopsy. A sensible correlation requires that the neuropsychological deficits remain unchanged from their onset to the patient's death. This is however unlikely. Considering etiologies that bring about a localized lesion, factors that may affect the correlation include: for cerebrovascular lesions, recovery (Murphy and Corbett, 2009), or a successive stroke; for brain tumors, changes in the clinical picture related to their fast or slow growth, with the latter allowing more accommodation by the brain to changes of cerebral blood flow and intracranial pressure, the presence of brain oedema, displacements and herniations; the localized and diffuse effects of craniocerebral trauma. The anatomo-clinical correlation is even more complex for degenerative, inflammatory, infective, related to nutritional deficiency diseases, and for diseases caused by alcohol, drugs, toxins and chemical agents (Ropper et al., 2019). In sum, both behavioral and brain changes may occur during the survival period of the patient, possibly making the correlation less accurate (see de Haan and Karnath, 2018 for a related discussion). In humans, a temporally coincident anatomo-clinical correlation could be obtained only by electrical stimulation of the brain during surgery with the patient awake (Mullan and Penfield, 1959; Penfield and Roberts, 1959). This approach could be used only in patients, who required neurosurgery for a reason such the treatment of post-traumatic epilepsy, as in case example patient C.H. (**Fig. 19**).

In sum, outside the direct evidence from *post-mortem* examination and operative cortical excision and brain stimulation during a brain operation, the imaginary construct, based on clinical neurologic and behavioral findings, about the possible pathology and its localization *in vivo* in the brain was very indirect. It could rely on inferences from images of distribution of crystallized calcium in the head (skull films), of location of cerebrospinal fluid (pneumoencephalogram) and blood (cerebral angiogram) compartments,

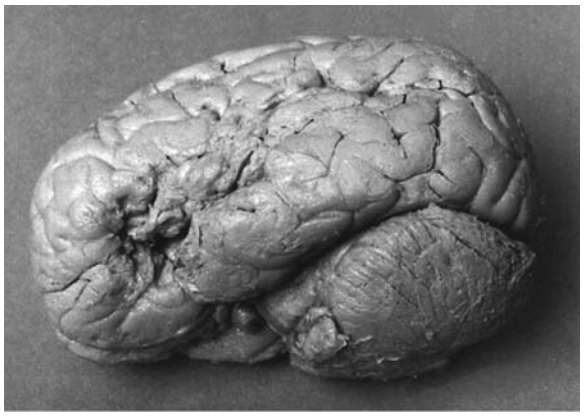

Figure 18 Lateral view of the brain of the first patient, Leborgne, reported by Broca (1861a). Reproduced with permission of Oxford University Press from Dronkers, N.F., Plaisant, O., Iba-Zizen, M.T., Cabanis, E.A., 2007. Paul Broca's historic cases: high resolution MR imaging of the brains of Leborgne and Lelong. Brain 130, 1432–1441. https://doi.org/10.1093/brain/awm042, **Fig. 3**-A).

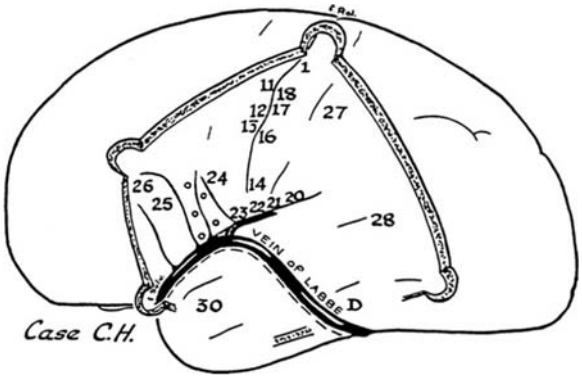

Figure 19 Case C. H. Broken lines indicate the extent of temporal lobe removal. Aphasia (aphasic arrest) was produced by stimulating electrode placed at points 26, 27 and 28, anarthria (motor speech arrest) at points 23 and 24. Reproduced with permission of Penfield, W., Roberts, L., 1959. Speech and Brain Mechanisms. Princeton University Press, Princeton, New Jersey, figure VII-5).

of distribution of blood-brain barrier (isotope scan), of position of third ventricle (ultrasound) and of surface (cortical) electrical activity (electroencephalography) (Oldendorf, 1978).

In vivo Images of the Brain

More direct information came from the advent in the 1970s of Computerized Tomography (CT) Scan, which provides information about the distribution of brain tissue radiodensity. Subsequent developments include the advent of Magnetic Resonance Imaging (MRI), which improved the visualization of both the gray and the white matter of the brain (**Figs. 20–22**). The availability of detailed *in vivo* images of the lesions of patients with neuropsychological deficits allowed more and more detailed analyses of the overlapping of the imaged lesion loci site across patients in group studies, with the aim of identifying the neural correlates of neuropsychological deficits, and, by implication, of the corresponding cognitive functions. **Fig. 23** shows the composite contour maps of the lesions of patients with and without unilateral spatial neglect, in an anatomo-clinical correlation study performed in the 1980s in 110 right-brain-damaged stroke patients (Vallar and Perani, 1986). **Fig. 24** shows the association between disownership for body parts and subcortical damage, in a recent study in 32 right-handed right-brain-damaged stroke patients (Ronchi et al., 2020). **Fig. 25** shows the association of auditory verbal span, a measure of the capacity of phonological

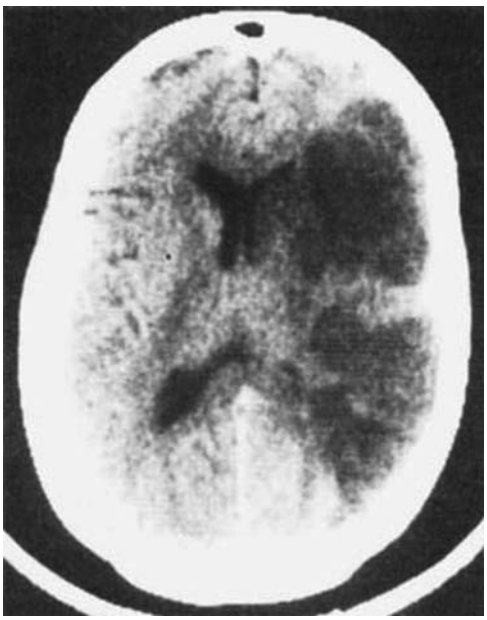

Figure 20 Images of the brain: 1990s. CT Scan image of one patient with left unilateral spatial neglect after right hemispheric damage: hypodense fronto-temporo-parietal area (Vallar et al., 1991, **Fig. 2**).

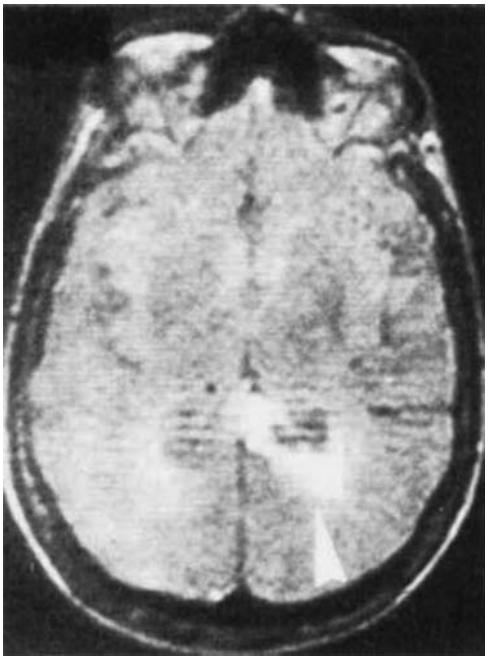

Figure 21 Images of the brain: 1990s. MRI image of one patient with left unilateral spatial neglect after right hemispheric damage: area of abnormally bright signal involving the right occipital paraventricular white matter (white arrowhead) (Vallar et al., 1991, **Fig. 1**).

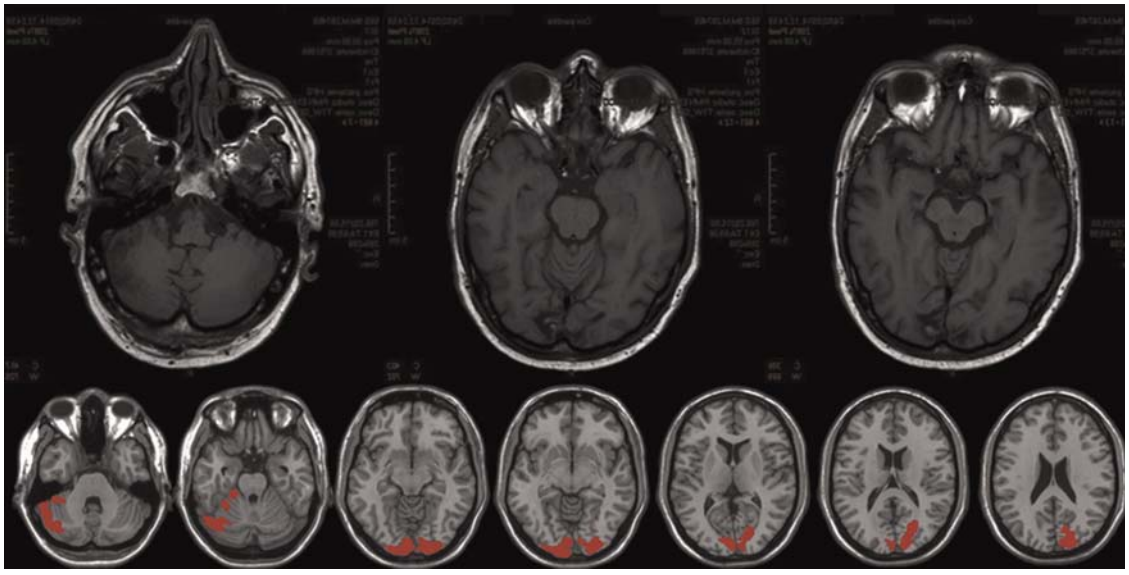

Figure 22 Images of the brain: 2010s. MRI image of a patient with abnormalities of visuo-motor plasticity in adaptation to prisms displacing the visual scene: bilateral occipital and left cerebellar lesions (Calzolari et al., 2015, **Fig. 1**).

STM (Shallice and Vallar, 1990) with damage to the inferior posterior parietal region, at the temporo-parietal junction, in the left hemisphere (Pisoni et al., 2019). The anatomo-clinical correlational evidence may be complemented in two main ways. Firstly, patterns of cerebral activation when patients are involved in specific behavioral tasks, assessing defective and spared functions may be assessed (e.g., Bottini et al., 1995 right-brain-damaged patient R.F., with left, neglect-related, tactile imperception; Paulesu et al., 2017, patient J.B. with defective phonological STM). Secondly, the effects of non-invasive cerebral stimulation of specific cerebral regions in brain-damaged patients, modulating the patients' performance in tasks of interest by electrical or magnetic transcranial stimulation may be studied. This was made for aphasia (Naeser et al., 2010, 2005), spatial neglect (Brighina et al., 2003; Sparing et al., 2009), and ideomotor apraxia (Bolognini et al., 2015). This type of evidence may provide information as for the undamaged regions involved in residual performance, and in recovery. Finally, brain network analysis is likely to be extensively used in the near future (**Fig. 26**).

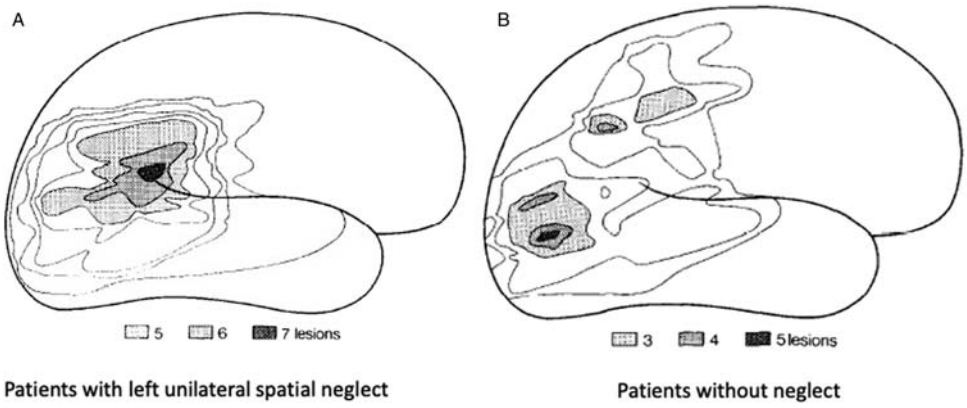

Figure 23 Composite contour maps of the CT-assessed lesions of patients with (A) and without (B) unilateral spatial neglect, examined by a target cancellation task: darker areas indicate regions damaged in more patients, and, by implication, involved in the function of interest. In this study, performed in the 1980s, the region more frequently damaged in right brain-damaged patients with left unilateral spatial neglect was the right supramarginal gyrus, undamaged in patients who did not show the deficit (Vallar and Perani, 1986, **Figs. 5** and **8**).

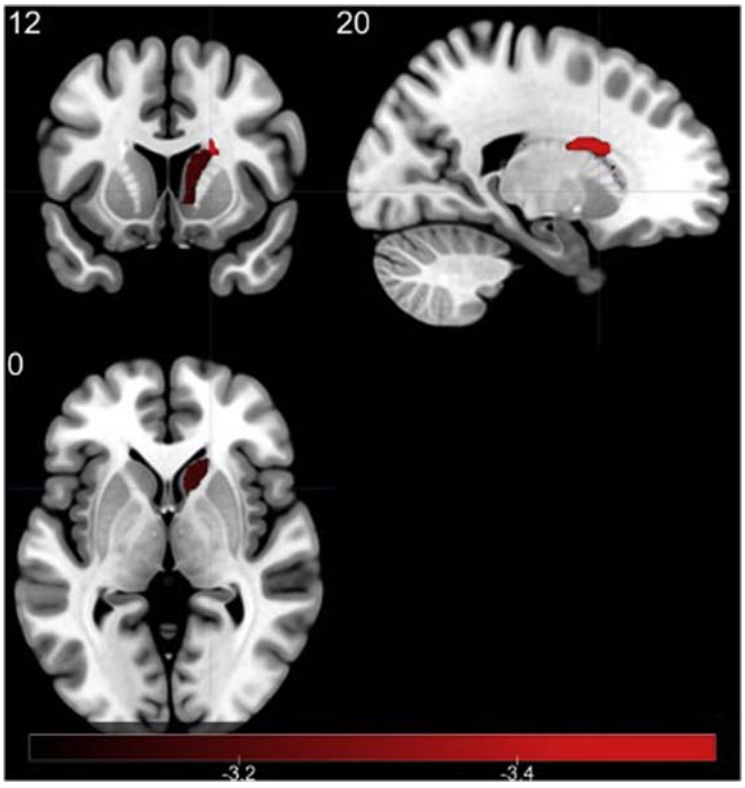

Figure 24 Results of Voxel-based lesion-symptom mapping (VLSM) performed on Voxels-of-Interest (VOIs) of 25 right-brain-damaged stroke patients. Lesion data were compared with ownership scores attributed to the left hand through a visual analogue scale. Reduced feeling of ownership for the left hand was related with damage in the right caudate nucleus and in the anterior part of the internal capsule (Ronchi et al., 2020, **Fig. 2**).

Concluding Remarks. Neuropsychology: Current Status and Future Developments

Since its inception as a scientific discipline in the 19th century, neuropsychology developed from the qualitative clinical observation of individual patients ("single cases" with apparent impairments, the so called "positive cases") to the study of groups of patients, in addition to single cases, collecting, through psychometric tests, quantitative data appropriate for statistical analyses. The investigation of the neural counterpart of the behavioral impairment also evolved from the *post-mortem* autopsy to the more and more detailed *in vivo* visualization of the patients' lesion. Future research is likely to continue to be performed in both single cases and groups, with any etiology of the disease responsible of the patients' cognitive deficit, and to benefit from developments of functional and structural neuroimaging and neurosurgical methods, of procedures of behavioral assessment, such as virtual reality (Negu et al., 2016), and of data analysis.

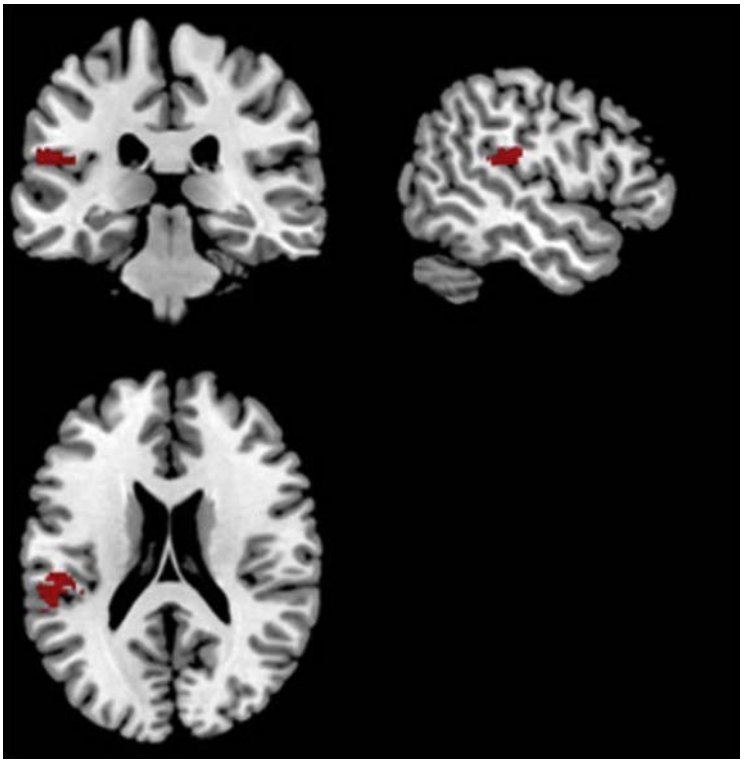

Figure 25 Results of VLSM performed on post-surgery VOIs of 103 patients undergoing awake surgery for glioma resection. Lesion data were compared with behavioral scores on digit span forward (Orsini et al., 1987). Lower digit span scores were related to lesions in the supramarginal gyrus and the superior-posterior temporal areas in the left hemisphere. Courtesy Alberto Pisoni and Costanza Papagno; Modified from Pisoni, A., Mattavelli, G., Casarotti, A., Comi, A., Riva, M., Bello, L., Papagno, C., 2019. The neural correlates of auditory-verbal short-term memory: a voxel-based lesion-symptom mapping study on 103 patients after glioma removal. Brain Struct. Funct. 224, 2199–2211. https://doi.org/10.1007/s00429-019-01902-z).

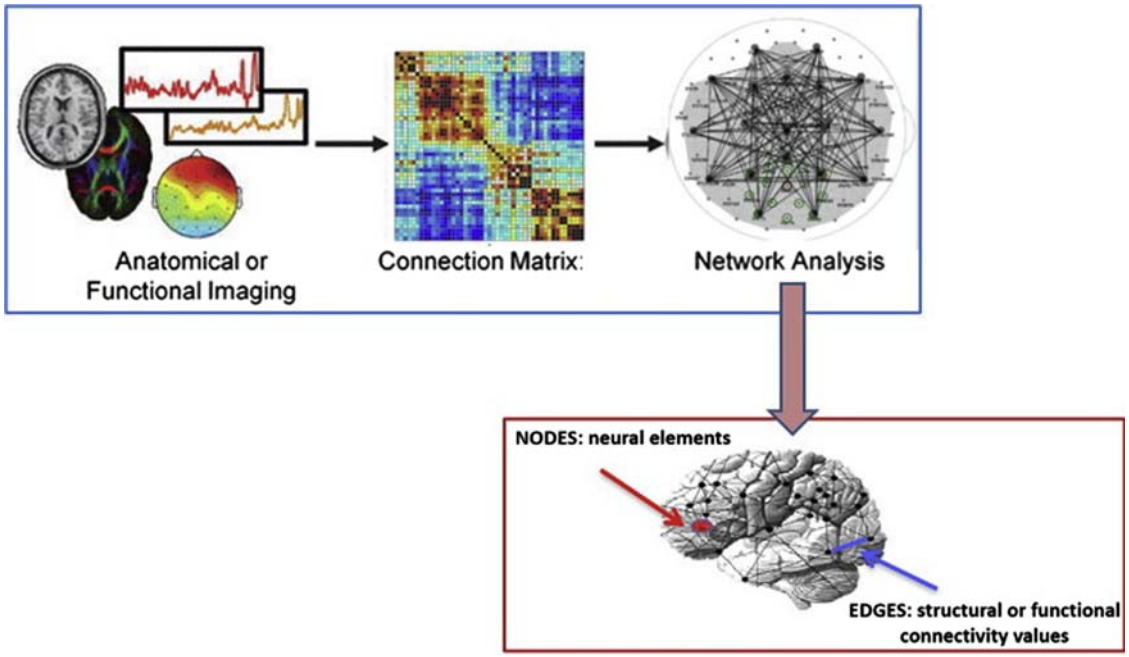

Figure 26 Analysis of brain networks from functional and structural neuroimaging data. **Fig. 1** from Rossini, P.M., Di Iorio, R., Bentivoglio, M., Bertini, G., Ferreri, F., Gerloff, C., Ilmoniemi, R.J., Miraglia, F., Nitsche, M.A., Pestilli, F., Rosanova, M., Shirota, Y., Tesoriero, C., Ugawa, Y., Vecchio, F., Ziemann, U., Hallett, M., 2019. Methods for analysis of brain connectivity: an IFCN-sponsored review. Clin. Neurophysiol. 130, 1833–1858. https://doi.org/10.1016/j.clinph.2019.06.006, with permission of Elsevier.

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Principles of Behavioral and Cognitive Neurology

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Introduction

Behavioral and cognitive neurology are specialties of a particular field which focuses on the clinical aspects of the neural processes associated with mental functioning, including cognitive functions, emotional states, and social behavior. Historically, the main aim of this field has been the phenomenological characterization of intellectual disturbances related to brain dysfunction, which developed thanks to conceptual and technical advances of cognitive neuroscience supported by functional brain imaging, electrophysiological methods, and experimental cognitive neuropsychology. Within this field, the most representative cognitive domains of interest are: episodic, semantic, and procedural memory; sustained, divided and selective attention; executive functions, in terms of problem solving, mental flexibility, and working memory; language, in its production and comprehension subcomponents; ideomotor and ideational praxis; spatial attention and visual processing. On the other hand, the most representative behavioral alterations include: depression as early sign of several neurodegenerative conditions; initiation, executive and emotional apathy; anosognosia, in terms of lack of awareness for cognitive, behavioral or motor disturbances; delusions manifested as persecution, misidentification, and ideas of insertion; visual and auditory hallucinations; disinhibition, in terms of inability to control actions and suppress impulsive behaviors; and, finally, altered eating behavior. The clinical specialty of behavioral and cognitive neurology requires complementary skills to those of general neurology. These represent the principles for this discipline, and can be outlined as follows: the administration and interpretation of mental state examinations through neuropsychological and neuropsychiatric assessments with patients and/or caregivers; the expertise in functional behavioral neuroanatomy, as applied in correlating clinical findings with structural and functional brain markers provided by neuroimaging and electrophysiology; the pharmacological and non-pharmacological treatment of cognitive, emotional, and behavioral disturbances. Thus, core disciplinary areas in behavioral and cognitive neurology require basic knowledge of the neuropsychological, neuroanatomical, neurophysiological, and neurochemical substrates of complex behavior, as well as of the clinical features and pathophysiological correlates of neurocognitive and behavioral syndromes.

The present chapter is focused on reviewing the main cognitive and behavioral functions, and, for each of them, providing neuropsychological and clinical definitions, anatomical correlates and discussing possible associations with specific neurological conditions. Cognitive impairment and behavioral disturbances are indeed commonly related to several neurological and systemic disorders. In fact, these disturbances can be associated with a number of conditions ranging from confusional state (or delirium) to severe dementia in patients affected by neurodegenerative conditions, such as Alzheimer's disease (AD). Neurologists and

neuropsychologists together with primary care physicians play an important role in the detection, assessment, interpretation and treatment of symptoms, disability and needs of patients with cognitive and behavioral alterations.

Cognitive Functions

Memory

> Oliver Sacks: What year is this, Mr. G.?
>
> Mr. G.: Forty-five, man […] We've won the war, FDR's dead, Truman's at the helm. There are great times ahead.
>
> Oliver Sacks: And you, Jimmie, how old would you be?
>
> Mr. G.: Why, I guess I'm nineteen, Doc. I'll be twenty next birthday.
>
> (Looking at the grey-haired man before me, I had an impulse for which I have never forgiven myself—it was, or would have been, the height of cruelty had there been any possibility of Jimmie's remembering it).
>
> Oliver Sacks: Here, look in the mirror and tell me what you see. Is that a nineteen-year-old looking out from the mirror?
>
> (He suddenly turned ashen and gripped the sides of the chair).
>
> Mr. G.: Jesus Christ. Christ, what's going on? What's happened to me? Is this a nightmare? Am I crazy? Is this a joke?
>
> "The lost mariner", from the "The man who mistook his wife for a hat" (Sacks, 1985)

Memory is a collection of mental abilities for storing incoming information, processing the information for consolidation, and making it accessible for retrieval in the short- and long-term (Budson and Price, 2005). Memory disturbances can be caused by lesions in the Papez circuit, the medial temporal lobe, and the prefrontal cortex (Papez, 1995). These regions are crucial for episodic memory, which allows to remember spatial and temporal details of our experience (Budson and Price, 2005). Episodic memory deficits can manifest as anterograde amnesia (inability to form new memories) and retrograde amnesia (loss of previously acquired memories), which may co-occur. Disorders of episodic memory may be transient, like in the cases of concussion, seizures, or transient global amnesia, others can have a variable time course and be reversible, such as those due to medications, hypoglycemia, tumors and Korsakoff's syndrome. A different prognosis is associated with traumatic, hypoxic or ischemic injury, surgical lesions, and viral and limbic encephalitis: they are more severe at onset, then might improve and stabilize. Episodic memory deficits are also present and progressive in neurodegenerative conditions, such as AD (Budson and Price, 2005). In disorders affecting multiple brain regions, such as vascular dementia (VaD) and multiple sclerosis, memory deficits usually progress in a step-wise manner (Budson and Price, 2005).

Patients with AD and other neurodegenerative conditions, such as frontotemporal lobar degeneration (FTLD) and, specifically, the semantic variant of primary progressive aphasia (PPA) (Gorno-Tempini et al., 2011), may experience a gradual loss of semantic memory, which is the knowledge about the world and general information about objects, people, events, and word meaning (Budson and Price, 2005). Patients can be unable to name common objects, animals or known people and/or understand the meaning of common and uncommon words. Semantic memory relies on a distributed network involving inferolateral and anterior temporal lobes. Semantic knowledge may be lost also in conditions such as traumatic brain injury (TBI), stroke, surgical lesions, encephalitis, and tumors (Moscovitch et al., 2006).

Finally, implicit or procedural memory, the ability to learn cognitive and behavioral skills and use them without access to declarative consciousness, is subtended by the basal ganglia, cerebellum and supplementary motor area. Disruption of procedural memory may be caused by tumors, strokes, hemorrhages, and other causes of injury to the aforementioned brain areas. Procedural memory can be also impaired in patients with Parkinson's disease (PD), Huntington's disease and olivopontocerebellar degeneration (Heindel et al., 1989).

Attention

> In the early days I would insist on putting certain items of clothing on back to front or inside out or when filling a cereal bowl with milk, I would continue until it poured over the sides.
>
> From "Living with Brain Injury" (Fairclough, 2002)

Attention can be defined as the preferential allocation of neuronal resources to events that become relevant over a given period of time (Mcdowd, 2007; Mesulam, 2000). Attention can be focused globally or focally, it can be directed externally or internally, and the processing can be parallel or serial (Mesulam, 2010). Different types of attention have been identified: sustained attention, which is the ability to maintain attention over prolonged periods of time; selective attention, the ability to focus on just one source of information among other stimuli; and divided attention, the ability to pay attention to more than one task at the same time.

Neurobiologically, the ability to stay focused and be ready for an expected event (alerting) is subserved by thalamus, frontal and parietal cortices, and is regulated by norepinephrine from the locus coeruleus. The selection of a source of information (orienting) has been linked to the superior parietal lobe, temporal parietal junction, and frontal eye fields, and is modulated mainly by cholinergic inputs from the basal forebrain. The ability to perform two tasks at once or to pay attention to different aspects of a situation before providing an answer, namely the executive control attention, has been associated with the anterior cingulate cortex, lateral prefrontal cortex and the dopaminergic system.

According to Mesulam's attentional matrix (Mesulam, 2000), attentional modulation can be domain-specific (visual neurons mediate domain-specific attentional responses to visual stimuli) or domain-independent. Domain-independent modulations are enabled mainly by the bottom-up influence of the ascending reticular activating system (ARAS) projecting to the thalamus and cortex, and by the top-down influence of the association and limbic cortices (Mesulam, 2010). The ARAS reacts mainly to arousal, while the prefrontal, parietal and limbic regions are more engaged in the modulation of cognitive state, past experience and expectation (Mesulam, 2010).

Attentional disturbances are among the most common and disabling neurological deficits. The most prevalent are: confusional states, whose most common cause is toxic-metabolic encephalopathies; hemispatial neglect, caused by brain lesions throughout the network of cortical and subcortical areas responsible for attention and typically affecting the right hemisphere; and partial attentional syndromes, which manifest as decreased performances in one or more cognitive domains (for instance, changes in visual-based attention can result in reduced detection of stimuli in the environment) (Mcdowd, 2007; Mesulam, 2010). The most noticeable deficits of attention occur with focal lesions due to strokes, with right hemispheric lesions causing more severe attention deficits than those in the left hemisphere (Spaccavento et al., 2019). Furthermore, attention deficits can be observed in many types of neurodegenerative conditions, such as AD, FTLD, and dementia with Lewy bodies (LBD).

Executive Functions

> Some days I felt like I lived with a giant, naughty parrot:
>
> "Oh no! Why did you break Mummy's pot plants?" I would say to him.
>
> "Oh no! … break Mummy's pot plants! Break Mummy's pot plants!" He would reply.
>
> From "Home: New writing" (Conroy, 2017)

Executive functions are defined as high-order cognitive abilities involved in the top-down control of cognition and goal-directed behavior. They include a multitude of processes, such as planning, goal monitoring, problem solving, mental flexibility, working memory, and inhibition of irrelevant stimuli (Smith and Jonides, 1999; Ambrosini et al., 2019; Diamond, 2013). Specifically, working memory is the ability to maintain and manipulate on-line information and is subtended mainly by the prefrontal cortex (Smith and Jonides, 1999, D'esposito et al., 1999), with the ventrolateral part more involved in information online-maintenance and the dorsolateral part in information monitoring and manipulating (Smith and Jonides, 1999). Planning is the ability to identify and organize the steps required to achieve a goal while performing complex tasks. It plays an important role in language, in the organization of words and phrases into sentences, and in the theory of mind for coherently changing one's behavior during social interactions, and it is subtended by the dorsolateral frontal lobe (Shallice and Burgess, 1991). Inhibitory control allows to suppress the processing of motor and/or cognitive information that would interfere with the efficient completion of a goal. It is mediated by the prefrontal cortex together with the parietal lobe and basal ganglia (Dillon and Pizzagalli, 2007). Control behavior, instead, enables to maintain the focus on the information relevant to reach a goal and to shift the attention. It is subtended by the anterior cingulate cortex, anterior insula, and, again, the prefrontal cortex (Dillon and Pizzagalli, 2007).

Executive dysfunction can lead to the inability to concentrate or pay attention, perform complex tasks, solve new problems, organize sentences and phrases in speech, and interact with other persons normally. Furthermore, the failure to inhibit and shift the

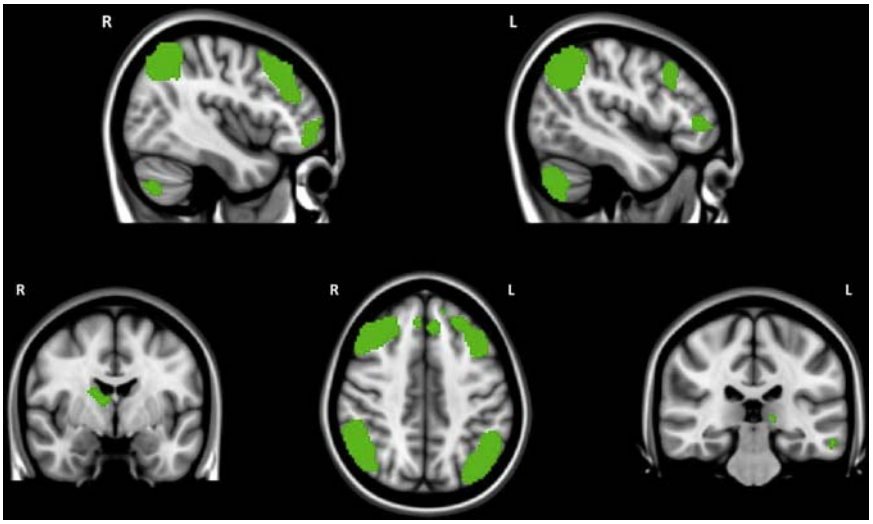

Fig. 1 The executive control network.

focus can lead to perseverative and stimulus-bound behaviors, such as echolalia, echopraxia, and utilization behavior (Shallice and Burgess, 1991). These symptoms highly affect the patient's independence and quality of life (Shallice and Burgess, 1991).

Executive functions are subtended by brain circuits which mainly involve the frontoparietal networks (**Fig. 1**) (Rabinovici et al., 2015). Any disease affecting frontal lobes or their connections with posterior cortical and subcortical regions, such as stroke, tumors, TBI, but also multiple sclerosis, and hydrocephalus, can lead to an impairment of executive functions. Executive functions may also be progressively affected in several neurodegenerative conditions, such as AD, PD, LBD, and FTLD spectrum of disorders, in particular in the behavioral variant of frontotemporal dementia (bvFTD), in progressive supranuclear palsy (PSP), and in almost 50% of patients with amyotrophic lateral sclerosis (ALS) (Rabinovici et al., 2015).

Language

> When I awoke the next morning in the hospital, I was totally (globally) aphasic. I could understand vaguely what others said to me if it was spoken slowly and represented a very concrete form of action.… I had lost completely the ability to talk, to read and to write. I even lost for the first two months the ability to use words internally, that is, in my thinking. […] The part of myself that was missing was (the) intellectual aspect—the sine qua non of my personality—those essential elements most important to being a unique individual.
>
> By Scott Moss in "Injured Brains of Medical Minds: Views from within" (Kapur, 1997)

Language can be defined as a collection of processes that allows humans to communicate using arbitrary symbols. Such processes can be broadly classified in comprehension (i.e., the interpretation of acoustic sounds/written graphemes and complex speech) and oral/written production of single words and sentences. These operations are subserved by several language subsystems (organized in conceptual knowledge, lexical semantics, and syntax) and brain areas (**Fig. 2**) (Friederici, 2011), which can be affected independently by different pathologies causing peculiar patterns of deficits (Damasio and Geschwind, 1984).

For instance, deficits of lexical semantics are caused by damage to the left posterior superior temporal gyrus (Wernicke area) (Hillis, 2010), resulting in a disorder known as Wernicke's aphasia. This condition is characterized by a severe impairment of language comprehension and hyperfluent but nonsensical speech (Damasio and Geschwind, 1984). On the contrary, deficits consisting in halting and effortful speech production define the so-called Broca's aphasia, which is typically associated with lesions of the left inferior frontal gyrus (Broca's area) (Damasio and Geschwind, 1984). In this case, speech is marked by agrammatism and sentences may be produced with the omission of verbs, nouns and function words (Damasio, 1992). Broca's aphasia may also present with a specific impairment of motor planning of speech articulation, known as apraxia of speech, which leads to errors of insertion, deletion, transposition, substitution or distortions of speech sounds (Ogar et al., 2005). In both conditions, patients may present with anomia and be able to retrieve some partial information, such as the first letter or sound, which often activates phonologically similar words, i.e., phonemic paraphasias, or semantically related words, i.e., semantic paraphasias, for output. Other syndromes like transcortical sensory aphasia and transcortical motor aphasia show similar features to the ones present in Wernicke's and Broca's aphasias, respectively. However, differently from them, repetition ability is intact in transcortical aphasias (Damasio and Geschwind, 1984; Damasio, 1992).

Besides the aforementioned ones, other brain regions involved in language processing are the left angular gyrus, the thalamus, and the posterior inferior and middle temporal gyri (Damasio and Geschwind, 1984).

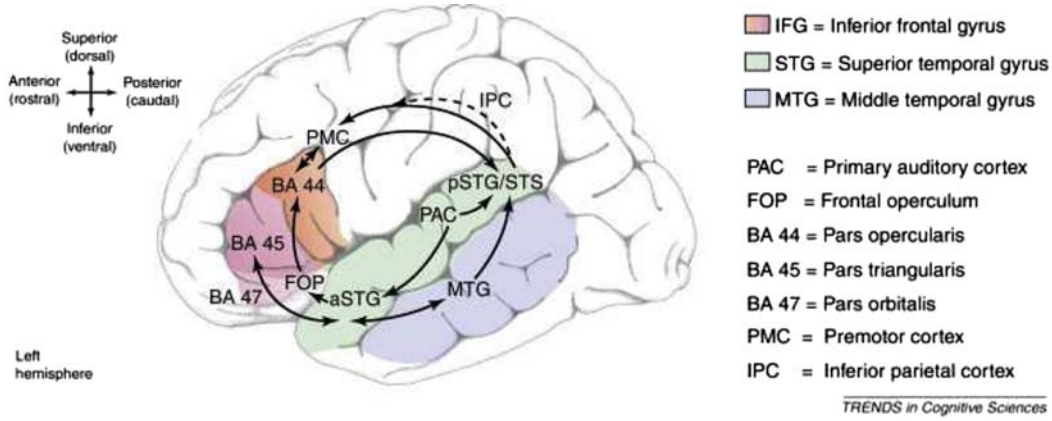

Fig. 2 Language-related regions in the human brain. The cortical language circuit (schematic view of the left hemisphere). The major gyri involved in language processing are color coded. In the frontal cortex, four language-related regions are labeled: three cytoarchitectonically defined Brodmann areas (BA 47, 45, 44), the premotor cortex (PMC) and the ventrally located frontaloperculum (FOP). In the temporal and parietal cortex the following regions are labeled: the primary auditory cortex (PAC), the anterior (a) and posterior (p) portions of the superior temporal gyrus (STG) and sulcus (STS), the middle temporal gyrus (MTG) and the inferior parietal cortex (IPC). The solid black lines schematically indicate the direct pathways between these regions. The broken black line indicates an indirect connection between the pSTG/STS and the PMC mediated by the IPC. The arrows indicate the assumed major direction of the information flow between these regions. Reproduced with permission from Friederici, Angela D. The cortical language circuit: from auditory perception to sentence comprehension. *Trends Cogn. Sci.*, 2012, 16.5: 262–268

Lesions to language processing areas are most commonly caused by strokes, in particular in the territory of the superior or inferior divisions of the middle cerebral artery. However, language dysfunctions may also occur as a consequence of head injury, brain tumors, herpes simplex virus (HSV) encephalitis, and neurodegenerative conditions, such as each of the three different variants of PPA (Damasio, 1992; Gorno-Tempini et al., 2011).

Praxis

> […] Daily life is full of skills required to perform fine and gross motor movements such as cooking, grooming, cleaning and even brushing teeth. Each day feels like a marathon of challenges just to get through what others take for granted. It can be exhausting to live with Dyspraxia but even more exhausting trying to explain it. […]
>
> From a patient's report

Apraxia refers to the inability to perform learned, skilled motor acts, despite preserved motor and sensory systems and coordination (Gross and Grossman, 2008; Heilman and Rothi, 2003; Liepmann, 1920). It concerns the inability in making either meaningful (gesture) or meaningless voluntary movements being not the results of a sensory or a motor deficit.

Apraxia occurs in approximately 1/3 of total cases of left brain damaged patients, such as focal cerebral lesion (e.g., stroke of the left hemisphere). Etiology also comprehends focal neurodegenerative disorders (such as posterior cortical atrophy [PCA]), corticobasal syndrome (CBS), AD, and VaD. However, any other neurologic disorder that hits brain networks responsible for programming forelimb and/or orofacial movements can ideally induce apraxia.

There are two major forms of forelimb apraxia: task-specific and general. Task-specific apraxia is a disturbance limited to one form of activity, e.g., dressing apraxia, constructional apraxia, apraxia of speech, and apraxic agraphia (Heilman and Rothi, 2003). General apraxia, instead, is articulated in: ideomotor, ideational, conceptual, and limb-kinetic apraxia (Heilman and Rothi, 2003).

Ideomotor apraxia is the most common and recognized form of apraxia and can be defined as the inability to perform a gesture when required (by oral command or imitation) (Gross and Grossman, 2008; Heilman and Rothi, 2003; Liepmann, 1920; Leiguarda and Marsden, 2000; Schnider et al., 1997). Performed gestures may appear awkward with incorrect timing, sequencing and spatial position of the limb. The same gestures, however, can be performed normally by patients in their daily life. This phenomenon is called "voluntary-automatic dissociation" (Schnider et al., 1997). Orofacial apraxia can be considered a subtype of ideomotor apraxia and concerns the impairment of skilled movements of mouth, tongue, larynx, and pharynx (Gross and Grossman, 2008). Orofacial and limb apraxia can coexist or be dissociated, suggesting at least partially different neural systems (Ozsancak et al., 2004). While orofacial apraxia is most often associated with lesions in the inferior frontal, deep frontal white matter, insula and basal ganglia, limb ideomotor apraxia is associated with injury to several cortical areas, including the inferior parietal lobe and premotor cortices, but also the anterior corpus callosum, basal ganglia and thalamus.

While patients with ideomotor apraxia have intact motor representations and experience inability on how to execute the action (i.e., a gesture production deficit), ideational apraxia is thought to result from disruption of action representations, responsible for

processing and planning an action (i.e., a gesture representation deficit). Patients with ideational apraxia loose the "concept" of which actions are needed in order to use an object or to correctly sequence a series of acts that lead to a goal (Gross and Grossman, 2008; Heilman and Rothi, 2003; Liepmann, 1920). Lesions that induce such disturbance are located in the left occipito-parietal region (Liepmann, 1920), although damage to the left prefrontal lobe is also associated with sequencing deficits (Heilman and Rothi, 2003).

Conceptual apraxia reflects the loss of mechanical knowledge. Patients with conceptual apraxia may misuse objects (such as a hammer for instance), have difficulty in matching objects and actions, or are unable to judge whether a gesture is well formed (Heilman and Rothi, 2003).

The term limb-kinetic apraxia, finally, refers to a loss of dexterity, including the ability to make precise finger movements (Heilman and Rothi, 2003). Limb-kinetic apraxia tends to be independent of modality (e.g., verbal command *vs.* imitation), with no voluntary-automatic dissociation, and can be difficult to differentiate from limb weakness (Leiguarda and Marsden, 2000).

Spatial Attention and Visuospatial Processing

> Mrs. S […] sometimes complains to the nurses that they have not put dessert or coffee on her tray. When they say, "But, Mrs. S., it is right there, on the left", she seems not to understand what they say, and does not look to the left. If her head is gently turned, so that the dessert comes into sight, in the preserved right half of her visual field, she says, "Oh, there is it—it wasn't there before".

> She has totally lost the idea of "left", with regard to both the world and her own body. Sometimes she complains that her portions are too small, but this is because she only eats from the right half of the plate—it does not occur to her that it has a left half as well. Sometimes, she will put on lipstick, and make up the right half of her face, leaving the left half completely neglected.

> "Eyes right!", from the "The man who mistook his wife for a hat"
>
> (Sacks, 1985)

Spatial attention is the ability to focus on specific stimuli in the external environment; it can be oriented endogenously to stimuli that are relevant for the individual, or exogenously captured by salient stimuli. Spatial attention is implemented in a bilateral fronto-parietal network and disorders of visuospatial processing usually result from damage in these areas induced by focal (mainly vascular) lesions or degenerative conditions (**Fig. 3**) (Bartolomeo et al., 2012). The major disorders of visuospatial processing are the hemineglect syndrome, simultanagnosia, and optic ataxia (Chatterjee and Coslett, 2010).

Hemineglect is a disorder of spatial attention characterized by a domain-specific impairment in distributing attention across the personal and/or extrapersonal space. In neglect, patients preferentially process stimuli in ipsilesional space over those in contralesional space, are inattentive or deny the existence of parts of their own body, or are aware of their contralesional limb but not that it

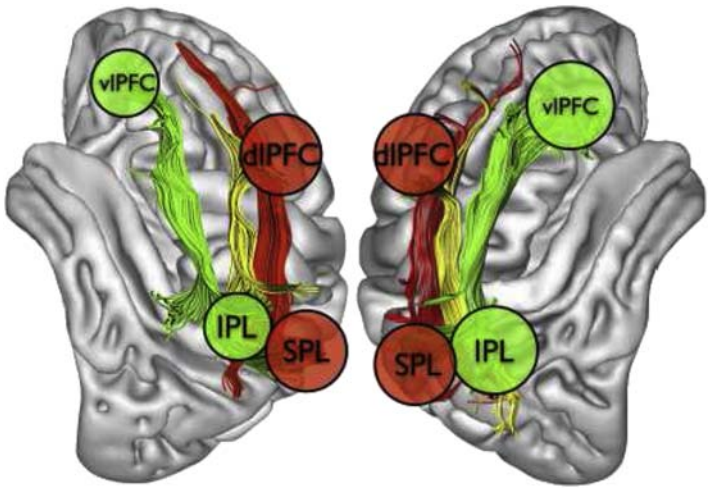

Fig. 3 The attentional networks for visuospatial processing. Schematic depiction of fronto-parietal attentional networks for visuospatial processing in the two hemispheres. Abbreviations. IPL and SPL = inferior and superior parietal lobules; dlPFC and vlPFC = dorsolateral and ventrolateral prefrontal cortex. Reproduced from Bartolomeo P., Thiebaut de Schotten M., and Chica A.B., Brain networks of visuospatial attention and their disruption in visual neglect. *Front. Hum. Neurosci.*, 2012; 6: 110, an open-access article distributed under the terms of the Creative Commons Attribution Non Commercial License.

is paralyzed (anosognosia for hemiplegia). Lesions causing neglect are located throughout the right hemisphere in cortical and subcortical areas responsible for attention, such as the posterior parietal cortex/temporoparietal junction, frontal eye fields, cingulate and supplementary motor cortex, basal ganglia, thalamus, midbrain and superior colliculus (Mesulam, 1981).

Simultanagnosia is the inability to perceive more than one aspect of a visual stimulus at the same time and to integrate visual details into a coherent whole (Coslett and Saffran, 1991). This deficit is associated with bilateral damage to posterior parietal lobes and limited occipital lobe involvement. Simultanagnosia has also been reported in patients with unilateral left occipital lesions, but with less severe disturbance. Lastly, patients with optic ataxia fail to reach accurately for objects, particularly when they are presented in peripheral vision (Jax et al., 2009). Optic ataxia is typically associated with lesions of the posterior parietal lobe. Simultanagnosia, optic ataxia, and oculomotor apraxia (the inability to voluntarily guide eye movements, changing to a new location of visual fixation) are the three classic features of the Bálint syndrome.

Visuospatial deficits are frequently associated with vascular lesions or are present in neurodegenerative conditions affecting posterior brain regions and/or the basal ganglia, such as AD, PCA, PD with cognitive decline, LBD, and CBS.

Social Cognition

> If there is any one secret of success, it lies in the ability to get the other person's point of view and see things from his angle as well as your own.
> Henry Ford, American industrialist

Social cognition is a broad term encompassing a variety of mental processes that enable us to infer other people's intentions, emotions and thoughts, and to use these representations for modulating our behavior accordingly. This ability, which guides our behavior depending on social information, may have made such cognitive processes evolutionarily advantageous and, arguably, may have facilitated the development of civilization (Adolphs, 2009). Social cognition can be divided into several distinct processes, which involve many different brain regions, some of which show overlap between processes (**Fig. 4**) (Green et al., 2015).

The experience to understand other's mental states concerns what is known as theory of mind, namely the ability to deduce other's intentions and beliefs, to take another individual's perspective and build theories about how different people would behave under certain circumstances. The theory of mind is subtended by the medial prefrontal cortex, the temporoparietal junction, and the posterior cingulate cortex (Adolphs, 2009). This function is usually as important as understanding other people's emotions.

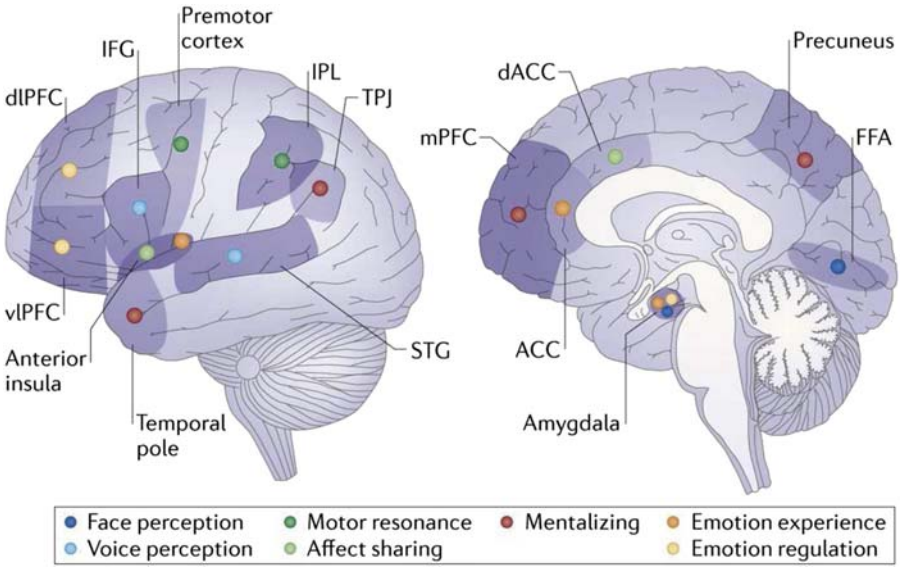

Fig. 4 Brain regions involved in social cognitive processes. Social cognition can be divided into several distinct processes, which involve many different brain regions, some of which show overlap between processes. Perceiving social cues incorporates face perception, which is associated with activation of the amygdala and fusiform face area (FFA), and voice perception, which activates the superior temporal gyrus (STG) and inferior frontal gyrus (IFG). Experience sharing includes the processes of motor resonance, which activates the inferior parietal lobule (IPL) and premotor cortex, and affect sharing, which activates the dorsal anterior cingulate cortex (dACC) and anterior insula. Mentalizing activates various regions, including the temporoparietal junction (TPJ), temporal pole, precuneus and medial prefrontal cortex (mPFC). Emotion experience activates the amygdala, anterior hippocampus (not shown), ACC and anterior insula, and emotion regulation activates brain regions including the dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC) and amygdala. These brain regions and associated social processes are not entirely separate; for example, the anterior insula is involved in both affect sharing and emotion experience, and the amygdala is involved in face perception, emotion experience and emotion regulation. Note that these regions are a representative, but not comprehensive, listing of relevant brain regions for each social cognitive process. With permission from Green M.F., Horan W.P., Lee J., Social cognition in schizophrenia. *Nat. Rev. Neurosci.*, 2015, 16.10: 620–631.

Emotion recognition deficits can follow an impairment of the amygdala, a crucial structure for attributing affective meaning to facial expressions and for regulating social behavior (Adolphs, 2001). An even deeper understanding of other people's feelings that involves a vicarious experience of another person's emotional response is empathy, which seems to be associated with medial prefrontal regions as well as dorsal anterior cingulate cortex and anterior insula (Adolphs, 2009; Lieberman, 2007). Finally, the capacity of instantly recognizing socially relevant stimuli like faces can be considered one of the many expressions of social cognition. Face recognition relies on the activity of highly specialized brain regions, the superior temporal sulcus and the fusiform gyrus (or fusiform face area, FFA), whose lesion causes an extremely disabling condition called prosopagnosia, the inability to recognize familiar faces despite an intact visual system.

Any clinical condition damaging areas involved in social cognitive processes can lead to deficits like poor volitional control of behavior, apathy, lack of guilt and empathy, difficulties at decision making, and in more extreme cases even violent and criminal behavior (Adolphs, 2009). Among the most common neurological causes of social cognition impairment are TBI, epilepsy, brain tumors and neurodegenerative conditions, such as the bvFTD (Cotter et al., 2018).

Mood and Behavior

Depression

> I didn't want to wake up. I was having a much better time asleep. And that's really sad. It was almost like a reverse nightmare, like when you wake up from a nightmare you're so relieved. I woke up into a nightmare.
>
> From "It's Kind of a Funny Story" (Vizzini, 2007)

Depression is a disorder characterized by sadness, mood deflection and diminished interest, which severely limits psychosocial functioning and diminishes quality of life (Malhi and Mann, 2018). Depression can be observed in several neurological disorders, it may precede neurological signs and symptoms, it may be a risk factor in the etiology of some dementias, and it can influence the course of the illness. In neurological conditions it is far more common than commonly believed, and for this reason it is often unrecognized and untreated (Rickards, 2006). Several prefrontal and limbic structures and their interconnected circuits have been implicated in affective regulation. These neuroanatomical areas include the ventromedial, lateral orbital and dorsolateral PFC, anterior cingulate cortex, ventral striatum, amygdala and the hippocampus (Malhi and Mann, 2018).

Elevated rates of depression are observed in people with mild cognitive impairment (MCI), where the presence of depressive symptoms is approximately double than in healthy elderly, and it is elevated in individuals with amnestic more than those with non-amnestic MCI. In MCI, depression usually manifests prior or when the cognitive impairment begins to interfere with the instrumental activities of daily living, and, together with the person's reduced quality of life, the avoidance of coping strategies and the withdrawal from leisure activities, it influences the progression from MCI to dementia. Although depression might be the psychological consequence of the person's perceived cognitive decline, today it is thought as a key part of neurodegeneration. Thus, it could be the result of altered neurotransmitter systems (e.g., the cholinergic) or of a brain vascular dysfunction (Anderson, 2019).

Depression is a key symptom also in PD, mainly as the result of the striatal dopamine depletion (Weintraub et al., 2005). Specifically, the prevalence of a major depressive disorder has been reported in 17% of PD patients, minor depression in the 22%, and dysthymia in the 13%. Depression can present at any time of the disease, it may also precede motor symptoms, being an early prodromal sign of PD (Pfeiffer, 2016). It is also considered a prognostic factor, since patients who develop depression early in the course of the disease have a higher risk of greater motor impairment and disability over time.

Depression is relatively common also in patients hit by strokes and in 14%–42% of patients within the first year after TBI involving the prefrontal grey matter. Also patients with multiple sclerosis and depression present alterations in the prefrontal cortex (PFC), compared to those without depression (Feinstein et al., 2004).

Apathy

> Scientists announced today that they have discovered a cure for apathy. However, they claim no one has shown the slightest interest in it!
>
> George Carlin, American actor, writer, and comedian.

Apathy is a demotivation syndrome, characterised by a reduction in self-initiated, goal-directed activity, which is not due to primary motor or sensory deficits, or other comorbidities such as drug intoxication. Apathy has a triadic structure consisting of initiation, executive, and emotional aspects. Initiation apathy can be defined as the lack of self-generated thoughts or actions, and it leads to difficulties in activating thoughts or in initiating a motor program required to complete an action, and therefore to a reduction of productivity and spontaneity (Levy and Dubois, 2006). Executive apathy is related to a lower interest in being engaged in cognitively challenging efforts and leads to impairment in problem solving, organization, and daily planning. Emotional apathy refers to a flattening of affect, indifference, emotional neutrality, leading to impairment in behavioral and emotional self-regulation (Radakovic and Abrahams, 2018).

Apathy is a common symptom in several neurodegenerative disorders, such as AD, VaD and FTLD, particularly in bvFTD, where the presence of apathy can be used to support diagnosis. Apathy is also the most common behavior change in patients with ALS and it is the most frequently reported neuropsychiatric symptom in patients with PD with cognitive decline. It is progressive in Huntington's disease and it can be observed in multiple sclerosis (Radakovic and Abrahams, 2018). Furthermore, apathy is reported in (other) inflammatory, infectious and traumatic brain pathologies, and it is observed in the 30/40% of patients in the first few months after stroke. Together with inattentiveness, agitation, and poverty of thought, apathy may mimic a depressive state, delaying the precise diagnosis and appropriate treatment (Chong, 2020).

The principal brain regions that subtend apathy are the medial frontal cortex, in particular the anterior cingulate cortex and the orbitofrontal cortex, and subcortical structures including the ventral striatum, medial thalamus and the ventral tegmental area (Le Heron et al., 2019). Specifically, recent studies reported that initiation apathy may be due to lesions to cognitive and limbic territories of basal ganglia and to the medial PFC, including the medial superior frontal gyrus and the dorsal and ventral anterior cingulate cortices; executive apathy can be ascribed to lesions to the dorsolateral PFC and to the cognitive territory of the subcortical structures, mainly the dorsal caudate and the anterior thalamic nuclei; and emotional apathy is more linked to lesions to the orbital-medial PFC and limbic territories of basal ganglia, such as the ventral striatum and ventral pallidum (Levy and Dubois, 2006).

Anosognosia

Neuropsychologist: How are you?

N.S.: I'm fine, really fine.

Neuropsychologist: Why are you in a wheelchair?

N.S.: Perhaps I fell from my bicycle and bruised my leg (touching his right leg).

Neuropsychologist: Which leg did you hurt?

N.S.: (Touching his right leg), this one is fine.

Neuropsychologist: Could you go surfing on the sea should you wish to do so?

N.S.: Why not, if the wind is strong enough.

Case report of a patient (N.S.) with anosognosia for hemiplegia (Cocchini et al., 2002)

Anosognosia can be defined as a frank denial or inability to recognize deficits caused by disease or injury, which creates a significant impediment to optimal medical care and patient recovery. Anosognosia can be divided into three major categories, such as the lack of awareness for motor/sensory, cognitive, and socioemotional functions (Zakrzewski and Rosen, 2014).

A lack of awareness for sensory deficits can be retrieved in Anton's syndrome and hemiplegia. The former is a neurological condition characterized by bilateral lesions of the occipital lobes, where patients are completely blind and yet deny their blindness. The latter is relatively common after acute stroke in the right hemisphere (with parietal lobe and postero/anterior insula involvement), and it manifests as denial of any weakness on the affected side and/or a disturbed sense of ownership of the affected limbs.

Anosognosia for cognitive deficits is usually present in Korsakoff's syndrome and AD. Korsakoff's syndrome is characterized by false belief of having intact memory functioning despite profound impairment in association to the frontal lobe pathology, while AD patients may deny cognitive impairment and believe they function normally and independently, despite receiving assistance with daily activities from caregivers. It is believed that poor memory for recent events is the main reason for anosognosia in AD, and imaging findings link anosognosia to frontal lobe atrophy or metabolic deficits in both AD and Korsakoff's syndrome. The relationship between frontal lobe (particularly the ventromedial frontal cortex, i.e., the subgenual portion of the anterior cingulate gyrus) (Rosen, 2011) and anosognosia is further cemented in bvFTD, where it is a major criterion for diagnostic purposes

(Rascovsky et al., 2011). These patients are often unaware of both their cognitive and socioemotional difficulties. Anosognosia is also retrieved in aphasic disorders due to stroke or neurodegenerative conditions. For instance, patients with semantic variant of PPA complain about their word- knowledge deficits but are unaware of their socioemotional changes, which might be present at the early stages of the disease.

Delusions

Derek Morgan: He said his parents had been replaced.

Emily Prentiss: He just sounds delusional.

Dr. Spencer Reid: You know, he might have Capgras syndrome. It's a delusional disorder in which one believes that their friends and loved ones have been replaced by imposters.

Derek Morgan: Sort of like Invasion of the Body Snatchers.

Dr. Spencer Reid: It typically involves only one sense, such as sight. Basically, the neural connection between the visual cortex and the emotional center of the brain becomes severed, so that looking at a loved one doesn't elicit the same emotional response one would expect.

Aaron Hotchner: So, you think they're impostors.

Dr. Spencer Reid: And the interesting thing is that the auditory connection remains intact, so that if they were to hear a loved one speak and not see them, they'd think that they were real.

From the television series "Criminal Minds" (Season 7, episode 3, "Dorado Falls", 2011).

A delusion is a false belief, based on incorrect inferences about an external reality, which is firmly sustained by the person despite what almost everyone else believes and despite incontrovertible evidence of the contrary. The belief is usually not ordinarily accepted by other members of the person's culture or subculture. Delusions must be differentiated from disorientation, confabulation, overvalued ideas, and misidentification, and they are categorized according to thematic content and the extent to which they become elaborated over time.

Among types of delusions, the most common are the following: paranoid, persecution, grandiose, religious, erotomanic, somatic, thought broadcasting, delusional misidentification, ideas of insertion, ideas of reference, and shared delusions. Delusions arise from altered brain processes, including distorted sensory perception, face or object recognition, reasoning, memory and self-monitoring. They are usually associated with widespread, bilateral disorders such as toxic or nutritional encephalopathy or with lesions of the right cerebral hemisphere. In the elderly, neuroimaging studies suggest a frontotemporal localization of delusions, with right hemispheric lateralization in delusional misidentification and left lateralization in delusions of persecution (Holt and Albert, 2006). In the general population, the critical feature of delusions seems to be a loss of connectivity between frontal regions and more posterior areas mainly of the right hemisphere (involved in the representation of the self). Moreover, the bilateral frontal cortex seems to be involved in delusions of theft and persecutions (Binetti et al., 1995), while content-specific delusions, such as sexual and somatic delusions, result from lesions to the right frontal lobe.

Various diseases present with delusions, for instance Huntington's disease (patients may show paranoia, erotomanic delusions, delusional parasitosis and of bodily decay), Wilson's disease, and acute intermittent porphyria. Other types of conditions characterized by delusions are the Capgras syndrome, which is usually due to right frontoparietal infarcts and brings to the belief that relatives/friends have been replaced by imposters who resemble the originals; the phantom boarder syndrome, resulting from an organic disease (involving parieto-temporal cortices and bilateral orbitofrontal lobes) usually associated with neurodegeneration, which brings to the belief that someone uninvited is residing in the patient's house; and nurturing syndrome, which is a form of pathological bereavement reaction occurring with neurodegenerative conditions, such as advanced AD, due to right frontal alterations. Among neurodegenerative disorders, delusions can be found in AD (especially delusions of theft and suspicion), bvFTD (suspicion), LBD (which can be characterized by Capgras syndrome, phantom boarder syndrome, delusion of theft and persecution, and misidentification of person), and PSP (delusional jealousy) (Butler and Zeman, 2005).

Hallucinations

> A hallucination is a fact, not an error; what is erroneous is a judgment based upon it.
>
> From the book "Logic and Knowledge: Essays 1901–50" (Russel and Marsh, 1988)

Hallucinations can be defined as any perceptual experience that occurs in the absence of external stimuli and is characterized by a compelling sense of reality (Boksa, 2009; Allen et al., 2008).

A clinical syndrome that is known to cause hallucinations in the psychiatric field is schizophrenia. More than 70% of people with schizophrenia experience visual hallucinations, and 60%–90% hear voices. Among neurological disorders, the conditions that are often associated with experiences of hallucinations are: neurodegenerative diseases, such as LBD, where up to half of people affected present with visual hallucinations; brain tumors and epilepsy, which cause different types of hallucinations, including hallucinations of smell and taste, depending on the site of cerebral lesions; migraine and the Charles Bonnet syndrome, where severe sight loss leads to hallucinations.

Neurogenic hallucinations are classically distinguished in irritative and release forms (Cogan, 1973). Irritative forms are known to cause stereotyped and simple forms of hallucinations, such as tinnitus, buzzing, auras and tingling. They have localizing value (i.e., brain lesions cause isolated hallucinations in a single sensory modality), and the patient is not typically aware of the hallucinatory nature of the perceptions (Braun et al., 2003). Release forms, instead, have little or no localizing value and often represent remarkably complex scenes. The patient is typically aware and illusory perceptions often resemble familiar scenes, making the perception more a vivid recollection than an authentic false perception (Braun et al., 2003). Hallucinations may involve any of the senses. However, the most common presentation form in neurological conditions are auditory and visual hallucinations (Boksa, 2009; Allen et al., 2008).

Numerous neuroimaging studies conducted in recent years revealed a distributed network of cortical and subcortical activity associated with hallucinations, including: inferior frontal/insular cortices, anterior cingulum, bilateral temporal and secondary visual cortices, right thalamus and inferior colliculus, left hippocampus and parahippocampal gyri (Allen et al., 2008; Shergill et al., 2004). One of the major concepts on the origin of hallucinations is the idea that hallucinating individuals may misattribute internally generated speech (or sensory stimuli) as coming from an external source. The misattribution of inner speech may be particularly associated with altered engagement of temporal and anterior cingulate cortices, which may erroneously tag internally generated imagery as originating from an external source.

Disinhibition

> The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man.
>
> John Martin Harlow, Phineas Gage's Physician, in "Recovery from the passage of an iron bar through the head"(Harlow, 1993)

Disinhibition can be defined as the inability to control actions and suppress impulsive behaviors in order to adapt them to environmental and social circumstances. It also concerns verbal behaviors, consisting of inappropriate or obscene comments, sexual references, and excessive sharing of personal or intimate details. During conversations, disinhibition can emerge as selfishness and carelessness toward the interlocutor as well as frequent arguing and difficulties getting along with other people (Osborne-Crowley and Mcdonald, 2018).

The case of Phineas Gage, the construction foreman victim of a life-changing accident in 1848, laid the foundation of the modern knowledge about the role of frontal lobes in control of impulses (**Fig. 5**) (Dillon and Pizzagalli, 2007). Before an iron rod was driven through his skull and brain as a result of an explosion, Phineas Gage was described as an intelligent and well-adjusted man. However, despite an apparent full recovery, his friends reported that the responsible and trustworthy man they used to know, had become a disrespectful, impulsive and aggressive new person. Gage was described as irreverent and unstable, and even his language was characterized by obscenities and swear words (Harlow, 1993). This striking change in personality has been studied over the years and has been attributed to the location of Gage's lesion, which presumably involved both anterior orbitofrontal cortices, the left anterior medial frontal cortex and the anterior segment of the right anterior cingulate gyrus (Damasio et al., 1994), all crucial areas for inhibition of inappropriate behaviors. In addition, other areas that are associated with the ability to control actions and suppress impulses are the right inferior frontal cortex and the anterior temporal regions (Knutson et al., 2015).

Besides TBI, any clinical condition affecting these areas may lead to disinhibited behaviors, such as difficulties adhering to social norms, inability to resist temptations and delay gratifications, lack of decorum, hypersexuality and verbal inappropriateness. Among the other most frequent causes of such deficits are strokes and neurodegenerative conditions, like AD in the advanced stages and FTLD, especially the behavioral variant at the early stage of the disease (Rascovsky et al., 2011).

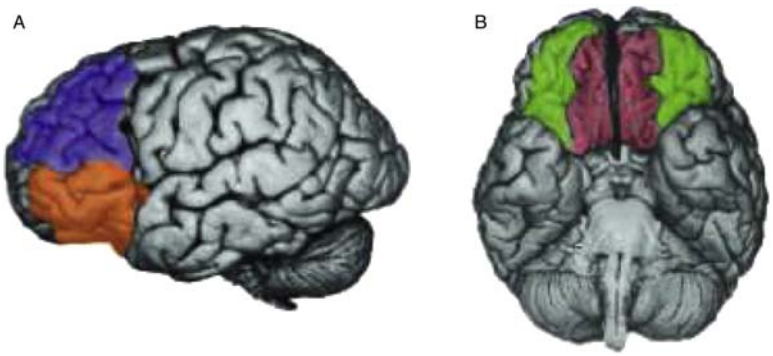

Fig. 5 The brain circuit of inhibition. Regions of prefrontal cortex (PFC) implicated in inhibition. (a) Dorsolateral PFC (blue) and ventrolateral PFC (orange). (b) Ventromedial PFC (red) and orbitofrontal cortex (green). With permission from Dillon D.G., Pizzagalli D.A., Inhibition of Action, Thought, and Emotion: A Selective Neurobiological Review. *Appl. Prev. Psychol.*, 2007; 12:99–114.

Eating Behavior

> (He) eats sugar by the spoonful … (He) eats four desserts after a meal … (She) cooks chicken with mushrooms every day … (She) eats raisins soaked in gin 9 times a day … (He) eats quickly … (She) puts everything in her mouth … (He) eats food from others plates when he is done with his own … (He) shoves food in his mouth.
> Caregivers of frontotemporal dementia patients, adapted from "The Banana Lady and Other Stories of Curious Behavior and Speech" (Kertesz, 2006)

Eating behavior is a complex phenomenon involving physiological, environmental, psychological and emotional components. In fact, food intake is controlled at the physiological level by homeostatic mechanisms aimed at providing a sufficient energy supply to the organism. However, food consumption is also characterized by a strong hedonic connotation associated with the reward system (Benarroch, 2010) and it is modulated by cultural and ethnic factors.

The heterogeneity of these aspects is reflected in the complexity of neural networks and chemical signals implicated in feeding behavior. After passing through the brainstem, peripheral signals carrying information about levels of circulating nutrients and hormones are processed in the hypothalamus. Here, neurons interact with reward circuits, comprising the ventral tegmental area, the nucleus accumbens and the amygdala, which, in turn, modulate the activity of the anterior cingulate cortex, the insula, and the orbitofrontal cortex. These latter areas are crucial for a multisensory integration of food-related signals conveyed by sight, smell, taste and interoceptive information, finally leading to selection and behavioral control of food intake, which is therefore based also on cognitive and emotional components (Benarroch, 2010).

These areas are particularly affected in neurodegenerative conditions, such as FTLD, where alterations of eating behavior might constitute one of the most prominent features (Rascovsky et al., 2011). Patients affected by FTLD, especially the behavioral variant, are known to show altered food preferences that may manifest as extreme selectivity or repetitive, stereotyped choices, as well as obsessions with particular types of food (Rascovsky et al., 2011). Cravings for carbohydrates and sweets are particularly common among these patients (Ahmed et al., 2016), and such food-seeking behaviors may culminate in binge eating episodes and subsequent weight gain. In these patients, the tendency to explore objects orally or even chewing inedible items, a phenomenon called hyperorality, can be also observed.

Other clinical conditions such as brain tumors or TBI may affect feeding-related areas, causing eating abnormalities and dietary changes that may have detrimental effects. One example is hypothalamic obesity, a condition caused by structural damage to the hypothalamus resulting in an impairment of the mechanisms controlling satiety, which subsequently leads to an extreme and pathological weight gain (Benarroch, 2010).

Discussion

The cognitive and behavioral functions that we described in this chapter reflect the amount of complex human high-order abilities, which a person develops during the course of his/her life. Such functions are supported by specific brain circuits that, when affected by a neurological condition, can cause reversible or progressive mental state alterations needing attention and intervention by neurologists specialized in this field. Several clinical conditions that we mentioned in this chapter, such as TBI or neurodegenerative disorders, often affect more than one high-order function leading to a multidomain impairment, which is more disabling for patients, more demanding, in terms of management, for caregivers, and more complex, in terms of intervention planning, for clinicians. One example is provided by TBI, which typically involves the frontal lobe, both in its dorsolateral and ventral components, together with their complex structural and functional connections (e.g., the frontostriatal pathway). This specific anatomical involvement might cause a co-presence of mental slowness, attention deficits, memory impairments, as well as disturbances related

to impulsivity and aggression, with this latter being the major source of distress for both TBI patients and their relatives, even long after the injury (Benedictus et al., 2010). A similar example is provided by AD. AD patients are well known for having learning difficulties and episodic memory disturbances. However, since the earliest phases of the disease, these patients often show temporal and/or spatial disorientation, visuospatial processing alterations, and diminished interests and motivation (apathy). The cluster of all these functions is subtended by interconnected brain regions typically affected by the disease, which include the hippocampus in its entire length, the posterior cingulate in its ventral portion, and inferior parietal lobes (Heindel et al., 1989).

Facing with the complexity of these mental profiles, neurologists cover an important role in the detection, assessment, interpretation and treatment of each of these symptoms. However, due to its complexity, behavioral and cognitive neurology requires abilities that are beyond general neurology, and the expertise of a dedicated clinician must include deep knowledge on the principles of this discipline: awareness of normal functioning of each cognitive and behavioral domain; functional behavioral neuroanatomy; techniques for mental state examination and interpretation; and the neurochemical management of cognitive, emotional, and social disturbances. For this reason, the aim of this chapter was to provide an initial knowledge of the main cognitive and behavioral functions, which is mandatory for any specialist who approaches this field.

Conclusions

In this chapter, we discussed a subfield of neurology, i.e., behavioral and cognitive neurology, which is focused on the phenomenology of mental functioning in relation to brain dysfunction. To this aim, we reviewed the main cognitive and behavioral functions, provided their definitions as well as anatomical correlates, and discussed possible associations with specific neurological conditions that a specialist in this field might be faced with.

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Principles of Neuroanatomy: A Short Introduction

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Brain Components

The human mind is equally the product and pilot of our nervous system's headquarters – our brain, "The most complex piece of matter in the universe" (Bear et al., 2007). Despite centuries of hard work and unquestionable progress, the mysteries of our most cryptic organ remain unsolved.

Our brain is involved in every aspect of our lives. We use it for a wide range of tasks, including, for instance, processing sensations, storing memories, feeling emotions, decision-making, action-planning, etc. All of these intellectual processes are gathered under one broad term: cognition. Although an adult brain only weighs around 1,5 kg – which accounts for 2% of the total body weight – it consumes, on average, 20% of our daily used energy (Raichle and Gusnard, 2002), which can give us an idea of this organ's importance.

The brain is made of nervous tissue (**Fig. 1**), a sophisticated arrangement of neurons, and the cellular units of a nervous system, all surrounded by an army of glial cells – a support team that feeds and protects neurons.

Unlike other animal cells, neurons present with an original geometry: their cellular body, the soma, has two types of prominent extensions or protoplasmic elongations, one axon and several dendrites (Ramón y Cajal, 1894) (**Fig. 1**). This particular form manifests their unique function. A neuron can process information, receiving it through its dendrites then forwarding it via its axon. Because of this original feature, an isolated neuron would be purposeless.

Neurons are team players like any other cell type of our organism. For example, skin cells are like bricks. An isolated brick is not very useful. However, hundreds of them can make a wall, the skin. In other words, numerous cells assemble to build tissue, and as the structural complexity increases, an additional function can emerge. For skin cells, that would be to protect the organism against external aggressions. For neurons, it is even more elaborate as complex communication between neurons comes into place.

Brain Communication

Naturally, as they carry information, neurons are more complex than bricks. Not only do they have to be in numbers, but they also have to be linked to each other to communicate.

The synapse is the point of connection between two neurons: a sophisticated space between the terminations of an axon and a dendrite where information can unidirectionally pass from a first cell to the next one (**Fig. 1**). Connections with peers are essential to a neuron, and if deprived of them, the neuron will degenerate (Bredesen, 1995; Capurso et al., 1997). A single neuron can be connected to up to 10,000 fellow neurons, and we estimate the total number of synapses in our brain to be somewhere between 100 and 1000 trillion (Seung, 2012) for approximately 100 billion neurons (Herculano-Houzel, 2009). This network forms a very dense circuit of interconnected neurons in which information travels step by step, from cell to cell, and can reach even the most distant cells.

Brain Information

The information that flows within the neuronal network is electrochemical (Ramón y Cajal, 1899). Neurons can generate and convey signals: as ions enter or leave a neuron through channels in its membrane, the electrical potential between the interior and the exterior of the cell changes. When this difference reaches a threshold of 15 mV, a succession of electrochemical events take place, and an electrical impulse called action potential is sent along the axon to convey a message.

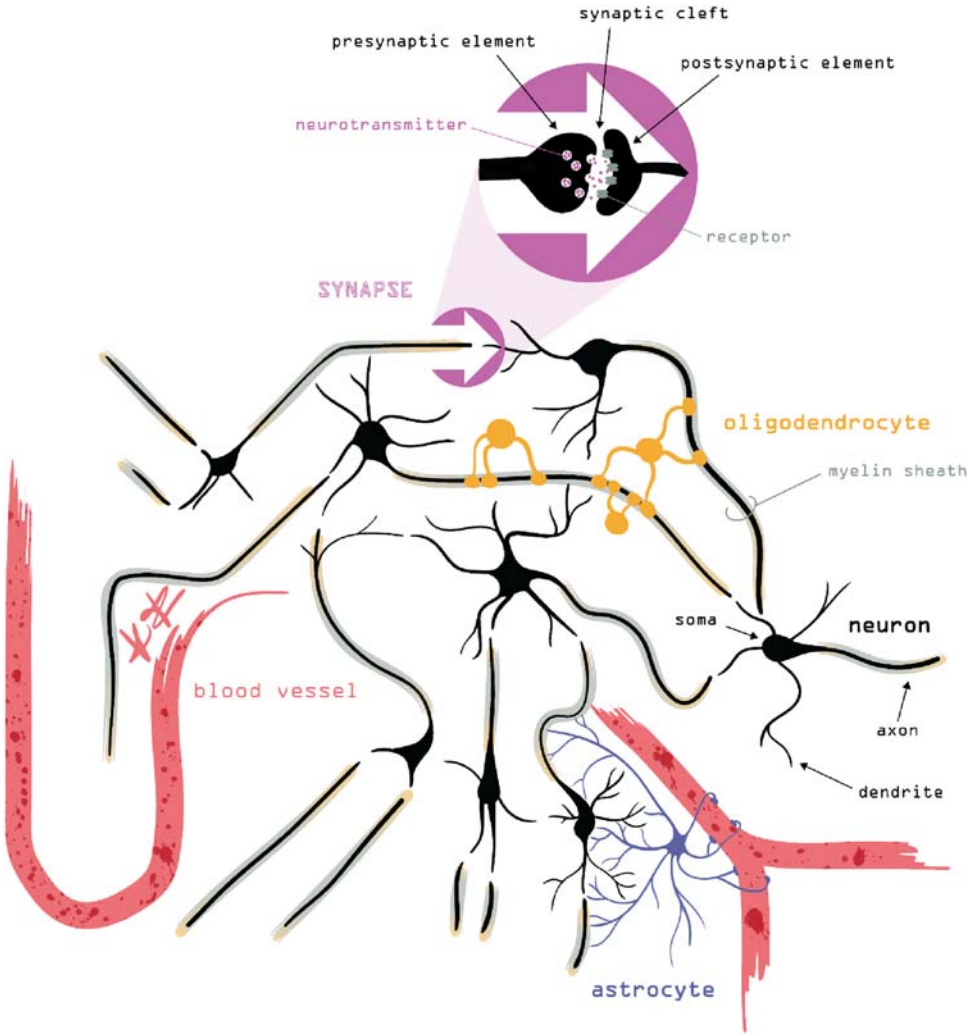

Figure 1 Prototypical representation of the cerebral nervous tissue. This sketch displays the typical interaction between three prominent cerebral nervous tissue cell types: the neurons, the oligodendrocytes and the astrocytes. Note that for clarity purposes, the different elements displayed in this figure are not to scale. A population of neurons conveys and processes electrochemical information inside a neuronal network. To achieve such a task, the geometry of a neuron is very unusual when compared to other animal cells. The neuron's body, the soma, has two types of elongations, one axon and several dendrites that link it to other neurons through equally unusual sophisticated structures called synapses. A close-up view of a synapse can be seen inside a purple circle on the top of the present schema. Electric information diffuses unidirectionally inside the neuronal net. When an electric potential approaches the end of the axon of a neuron, it takes a chemical form to travel the synapse and reach the dendrite of the next neuron. Neurotransmitters contained in vesicles of the presynaptic element are released from the presynaptic element and sent to the synaptic cleft. From there, they can bind with receptors dispatched on the membrane of the postsynaptic element. A second population of cells, the glial cells, including the oligodendrocytes and the astrocytes, supports the neurons in their mission. The oligodendrocytes, with their wrapping processes, cover axons with an insulating myelin sheath that ensures a fast and efficient propagation of electric signals. The remaining space is filled with the most abundant type of glial cells present in the nervous tissue: the astrocytes. For many reasons, they can be considered the caretakers of the cerebral nervous tissue. The most important reason is that astrocytes keep neurons alive by feeding them the nutrients uptaken from capillaries through their vascular end-feet.

The speed of the conduction is not instantaneous; it varies around the range of 300 km/h, subject to the influence of the diameter of the axon (Hursh, 1939) and its myelination (Waxman and Bennett, 1972).

At the axonal termination of a neuron, action potentials are translated into a chemical formula of neurotransmitters – mostly dopamine, acetylcholine, noradrenaline, gamma-aminobutyric acid (GABA), histamine, serotonin and glutamate – that diffuse across the synapse to bind specifically with membrane receptors of the next neuron's dendrite. This transmission is monitored by astrocytes – those glial cells whose function remains arguably the most enigmatic to us. In addition to providing nutrients to neurons and modulating the flow of blood in the nervous tissue, astrocytes can also influence the synaptic exchange by taking up and releasing neurotransmitters (Bear et al., 2007).

As stated before, each neuron has only one axon but many dendrites, meaning that a single neuron can receive several action potentials from various fellow cells. Their most remarkable ability is being able to integrate information – after summing or subtracting the inputs they receive, they purvey the network with an original output that integrates all incoming signals.

This aptitude is at the origin of all cognitive abilities.

This mechanism is similar across all brain neurons. Each neuron can only create one unique type of action potential; thus, the diversity of information does not come from the electrical signal itself but the frequency of its occurrence. As far as we know, neurons cannot produce complex data on their own. Being part of a network, though, they can work together with frequency-coded information. Ultimately, the extreme computational power of the brain arises from the collaborative effort of a tremendous number of single cells.

Brain Organization

Without a crucial extra component, the dense network where information freely travels would end up in a cacophony, which would fail to send information where expected, integrate information when not needed and lead to the opposite of what is required to execute cognitive functions.

A key to managing complex information flow is flawless organization. In an organized neuronal net, the role of each cell is spatially restricted. Thus, every single neuron has a role determined according to its position relative to other neurons in the network.

As expressed by Marcel Mesulam in the foreword he wrote for Schmahmann and Pandya (2006), "Nothing defines the function of a neuron better than its connections," and "the distribution of connections is complex but not chaotic".

Newborns already possess the vast majority of their neurons. As the brain matures and experiences life, the network develops but not randomly. Functionally useful connections will be consolidated: This is called synaptic pruning (Bourgeois et al., 1994; Changeux and Danchin, 1976; Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Rakic, 1986). Such a mechanism will lead to a unique, fine-tuned microscopic connectome in every adult. A connectome is an elaborate arrangement of connections that could be charted as a wiring diagram that is ultimately representative of the individual abilities of each particular brain.

Consequently, if the role of any given neuron within the central nervous system depends on its pattern of connectivity with other neurons, distinctive connectivity patterns can be interpreted as an indication that two different regions serve different functions (Fettes et al., 2017).

Brain Structure

On a cellular scale, the search for specific connectivity signatures to infer any functional role might be tedious, but not impossible; a brain network comprises around 100 billion neurons. Fortunately, at a macroscopic scale, a connectome is also apparent, greatly simplifying the functional interpretation of particular structural arrangements.

The nervous system consists of two subcomponents — the central and the peripheral nervous systems. On the one hand, along with the spinal cord, the brain is part of the central nervous system (CNS) that respectively encloses the spine and the skull. On the other hand, bundles of axons called nerves dispatched all over the body, emerging from or arriving at the spinal cord, form the peripheral nervous system (PNS). Note that the nervous system is hollowed with cavities called ventricles where a liquid, cerebrospinal fluid (CSF), is produced and distributed.

The brain itself is made of three distinct portions: the cerebrum, the largest portion, also called the telencephalon; the cerebellum; and finally the brain stem that connects the ensemble to the spinal cord, thus ensuring continuity between the CNS and the PNS.

Arguably the most sophisticated part of the human nervous system is the cerebrum, a spherical structure formed from two roughly symmetrical halves: the left and right hemispheres, separated by a deep sagittal cleavage, the longitudinal fissure. Both hemispheres present on their surface a landscape of hills and valleys (**Fig. 2**). The bumps and grooves, respectively called gyri and sulci, are quite constant from one individual to another. Therefore, they can serve as landmarks to those who study the brain like standard universal pictograms can help tourists find their way when visiting a new city.

Based on these superficial landmarks, four areas of unequal size conventionally divide each hemisphere: the frontal, the parietal, the occipital and the temporal lobes, named according to the overlying skull bones. Prominent sulci often define lobar boundaries (**Fig. 2**); for example, the lateral sulcus separates the frontal lobe from the temporal lobes, whereas the central sulcus is the demarcation between the frontal and the parietal lobes. Moreover, fifth and sixth lobes are sometimes considered and correspond to the insular lobe, hidden within the depths of the lateral sulcus, and the limbic lobe, which is on the medial side of each hemisphere.

The brain is a stratified construction. Its outer layer, called the cerebral cortex, is made of gray matter, whose gray color reflects the collection of cell bodies gathered in it. This thin folded mantle of gray matter gives the human brain its typical convoluted aspect; the folds materialize on the cerebral surface in the landscape of gyri and sulci. This gray coat is uneven: it is 4–6 mm thick in a vast portion called the neocortex, but it can get down to 2–3 mm in the post-central cortex and areas that form the allocortex (Amunts and Zilles, 2015). Under microscopic inspection, the neocortex is not homogenous; it discloses cytoarchitectural variations. To put this differently, neurons are arranged in various ways in different locations. At least 52 regions with distinctive cytoarchitectures have

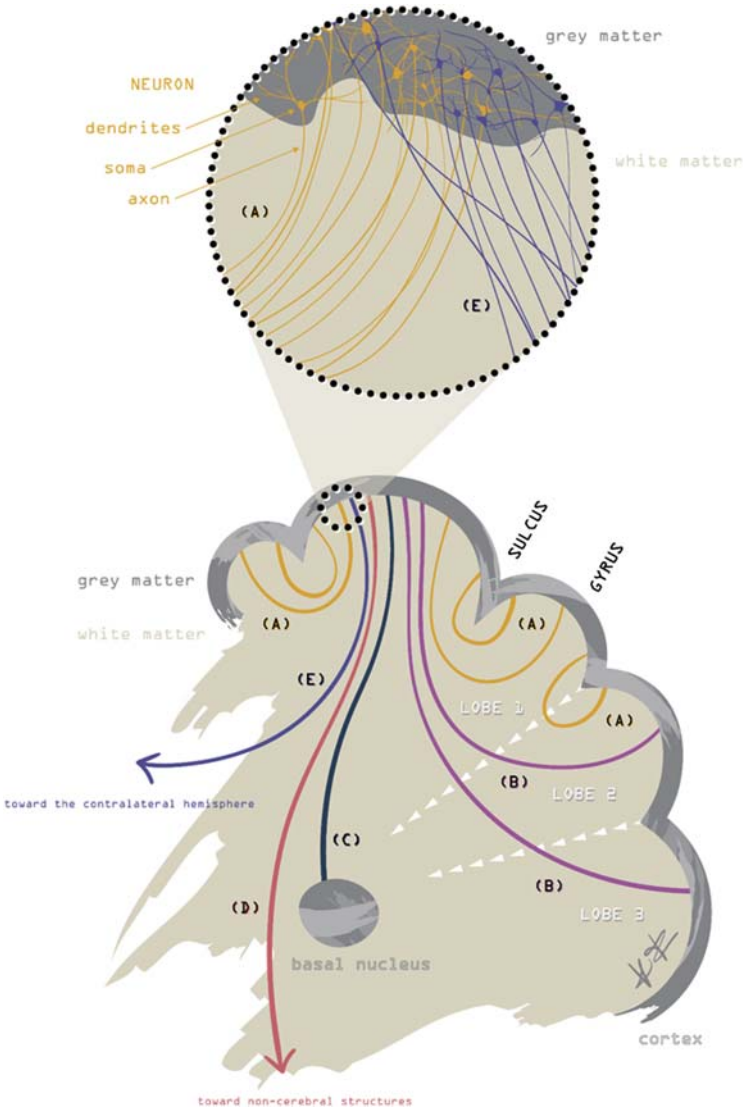

Figure 2 The schematic view of the typical brain white matter layout. The lower part of the figure showcases the typical macroscopic layout of white matter fibres in the human brain. They are presented on a symbolic slice that could be perceived as coronal, sagittal or axial; this is because the typical layout presented in the figure can be found anywhere in the brain independently from any chosen view or orientation. The five most common types of fibres are displayed with at least one termination in the superficial layer of cerebral grey matter (i.e., the cortex) so as to illustrate the basic principles of white matter organisation. White matter connections are layered according to the distance between their termination areas (Forkel et al., 2014). The more superficially a white matter fibre runs, the closer the grey matter areas it connects. The vast majority of white matter fibres in the human brain are superficial and connect adjacent cortical areas in the same hemisphere. These are called short U-shaped fibres (A). Indeed, the most superficial layer of white matter is made of the shortest fibres and has either an intra- or inter-lobar course in a shape similar to the letter "U". Right below, some longer inter-lobar fibres run: the association fibres (B). The most superficial of these fibres connect adjacent lobes of the same hemisphere. The deeper they go, the more distant are the lobes they link, but they are still in the same hemisphere. Deeper than the association fibres run the projection fibres, connecting cortical areas to either basal nuclei (C) or structures outside the cerebrum, for example, the spinal cord (D). The deepest fibres are the commissural ones (E). Unlike the previously described populations of fibres, they link analogous regions of two brain hemispheres. The upper part of the image is an up-close view of the superficial area circled by a dotted line on the slice below. It highlights the fact that macroscopic white matter bundles are made of multiple densely packed axons following a common path. Axonal fibres undergo a fasciculation process during the brain development to form, in an adult brain, the particular layout of white matter bundles presented in this figure. With this close-up view, we highlight in particular how, on a microscopic scale, two populations of axons emerging from the same grey matter area can diverge in two different directions to form two distinct white matter fibres or even tracts ([A] and [E]).

been numbered and mapped on the cortical surface. They are known as Brodmann areas (BA) (Brodmann, 1909), and despite being highly variable across participants (Amunts et al., 1999, 2000), they have proven very helpful in studying brain functions.

Beneath the slender gray-matter mantle, tightly packed axons form a generous inner layer of white matter. The white color occurs due to a distinctive fatty substance, myelin, wrapped around the axons. Myelin acts as an electrical insulator to prevent the loss of

electric charges, similar to a plastic coating on a metallic wire. A very peculiar type of glial cell, known as the oligodendrocyte, produces myelin. With hugging-arm-like elongations, numerous oligodendrocytes encase the entire length of each axon in a myelin sheath (**Fig. 1**). The myelination not only enables the APs to travel long distances with minimal message fading but also fastens their propagation.

The inside of a brain is mostly made of brain nuclei and white matter.

Brain nuclei, excluding the brainstem and the cerebellum, are classically divided into two classes: basal nuclei and the diencephalon. The basal nuclei are further divided into neo-, paleo- and archistriatum. The neostriatum corresponds to the caudate nucleus that, together with the putamen, receives excitatory inputs from the cortex. The paleostriatum includes the whole of the globus pallidus (medial and lateral), and the archistriatum is the amygdala. The diencephalon consists of the system of nuclei that compose the thalamus and the hypothalamus.

On a macroscopic scale, the white matter of an adult human brain is made of an aggregate of fasciculi (an alternative name for white matter bundles) arranged around the ventricles and a system of subcortical nuclei that are gray matter islands in the depths of each hemisphere.

However, it is not a dull white filling nor tangled myelinated fibers (Steno, 1669). During brain development, neurons grow their axons toward more or less distant candidates for synapse creation. On their way, axons with similar trajectories gather up and, when they are many, they form bundles of white matter. Getting closer to their destination, they unbundle, diverge and spread over the targeted territory. This process called fasciculation (Hau, 2015) creates, by grouping parallel axonal fibers, a connectome accessible to naked-eye inspection.

Tracts are divided into three categories: commissural, projection and associative fibers (Meynert, 1885). These three systems can be further divided in fasciculi that baer a name reminiscent of their shape (e.g., arcuate fasciculus), their location and trajectory (e.g., superior longitudinal fasciculus) or their projection (e.g., corticostriatal tract). Note that the short fibers that connect neighboring gyri are sometimes called U-shaped fibers.

Commissural tracts connect both hemispheres. They include the corpus callosum that was the first discovered due to its evident disposition (Vesalius, 1555). The corpus callosum is the most prominent white-matter connection of the brain. It links the two hemispheres and is visible after trepanation when looking between the two hemispheres. The anatomy of its projections is heterogeneous; however, they preferentially link areas that share a symmetrical, functional organization (Karolis et al., 2019). Commissural tracts are essential for integrating the information processed across the two hemispheres. A typical example is the panoramic vision we have that requires the integration of the left and right visual fields.

Projection tracts connect central structures to the surface of the brain. They habitually link the external environment to the brain. For instance, the corticospinal tract mostly links the motor cortex to the spinal cord, ensuring the transmission of motor commands. Other examples of projection tracts typically include, but are not limited to, the thalamocortical connections, the corticostriatal pathway, the fornix and the optic radiations (that are a particular subgroup of the thalamocortical radiations).

Association tracts connect relatively distant areas within the same hemisphere and are evolutionarily expensive, as they can reach lengths of up to 15 cm in the brain. These tracts allow for the fast transmission of information between areas to ensure the hierarchical or integrative processing of information (Pandya and Yeterian, 1991). Typically, the inferior longitudinal fasciculus is composed of long and short fibers (Catani et al., 2003) that ensure the progressive and hierarchical processing of visual information along the ventral visual stream, or the "what" stream (Mishkin et al., 1983). Similarly, the superior longitudinal fasciculus connects the frontal and parietal areas, whose interactions are necessary to produce awareness of the external world (Thiebaut de Schotten et al., 2005, 2011; Bartolomeo, 2007, 2014) and our own bodies (Pacella et al., 2019). Other examples of association tracts include – but are not limited to – the arcuate fasciculus, the uncinate fasciculus and the inferior fronto-occipital tract. Analogous to Brodmann's parcellation of cortical gray matter, mapping the fascicles that form its underlying white matter can prove greatly advantageous to those who study the brain. Indeed, when starting a scientific study on any tangible object of interest, it is best to know its three-dimensional structure beforehand.

Conclusion

In solving our brain's mysteries, "getting to know your way around the brain is like getting to know your way around a city" (Bear et al., 2007). If the microscopic neuronal network resembles a city subway plan with railways, stations and interchanges, at the scale of the entire brain, the macroscopic connectome reminds us more of a world ship map with sea lanes, seaports and transit hubs. Gray matter areas are like continents, and information can navigate through the white matter sea along channels of packed axons. Therefore, we would like to suggest that future investigators avoid exploring the brain without a good map or excellent knowledge of brain anatomy in order not to get lost on the road.

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Neuroanatomical Bases of Human Behavior

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Introduction

Our cognitive functions rely on the fast computational processes occurring at the synaptic level and the efficient propagation of the action potential along neuronal axons. Signal to distant regions is propagated along axons wrapped in a thick coat of insulating myelin that increases both conductivity speed and signal to noise ratio. The fresh cerebral tissue appears cream white or gray in color according to the different distribution of myelin. The *gray matter* of the nervous system lodges neuronal bodies, dendritic arborizations and short axons, all devoid of myelin. The *white matter* conversely contains axons that travel long distance and are therefore highly myelinated. In all parts of the nervous system, regions of gray matter forming nuclei of variable shape and size are embedded in the white matter. In the cerebral hemispheres only, the white matter is surrounded by a strip of gray matter, the cerebral cortex.

This basic anatomical dichotomy of the nervous system has led to assume that cognitive functions are localized in gray matter regions, the role of white matter equated to a passive conducting device. Recent studies show that anatomical changes induced by a motor task occur in both gray and white matter compartments of motor networks. Pharmacological inhibition of molecular signaling that control task-dependant white matter changes causes an impaired ability to learn the task (McKenzie et al., 2014). Hence, both gray and white matter have computational and adaptive properties necessary for a correct processing of the neuronal signal.

Contemporary neuroanatomical models have moved away from a narrow cortical localizationism of cognitive functions and consider information processing within specialized large-scale networks the most valid assumption for understanding the complexity of human cognition and behavior. An advantage of the network approach is the possibility of explaining the observation of similar symptoms in patients with different lesion location (**Fig. 1**).

A network approach to cognitive functions can benefit from anatomical insights derived from classical histological studies and more recent tractography descriptions of connections. Indeed brain networks comprise nodes and hubs in the cortical and subcortical gray matter whose neuronal composition determines a specific pattern of connectivity mediated by short and long white matter tracts..

Gray Matter Anatomy

Neuronal Populations

Three main neuronal populations can be distinguished in the gray matter of the brain (Catani and Zilles, 2020).

Pyramidal cells have the largest diameter and are the most prevalent neuronal type in the cortex. The dimension of their neuronal body is directly related to the diameter and length of their axons. Hence, cortical regions with a high density of the largest pyramidal cells (also called Betz cells) are the primary cortical motor areas that send projections to the distant neurons of the brain stem and spinal cord. Pyramidal cells are excitatory and use glutamate as neurotransmitter.

Spinous stellate cells are the second most numerous neuronal type in the cortex and like the pyramidal cells they use glutamate. They are named spinous for the high density of synaptic spines that cover their radiating dendrites. Their morphology indicates a receptive function. A high density of spinous stellate cells and a wide spreading distribution across the superficial cortical layers is typical of primary auditory, somatosensory and visual cortical areas representing the major target of direct thalamo-cortical inputs. Spinous stellate neurons are small in diameter and therefore when present in a high density they confer a granular aspect to the tissue under the microscope (see granular layers and granular cortex below).

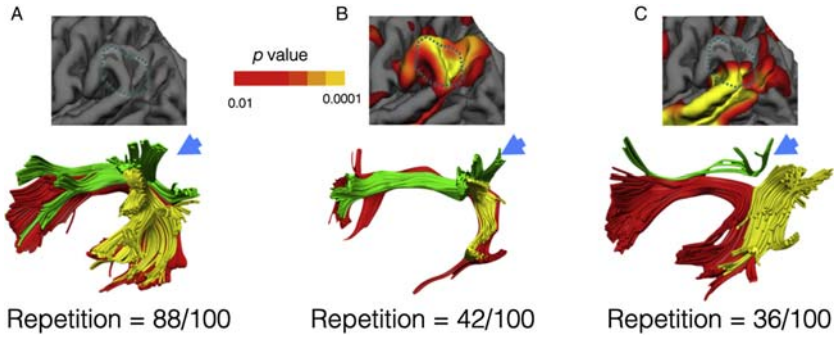

Fig. 1 Lesion mapping and repetition abilities in patients with Primary Progressive Aphasia (PPA). The indirect pathway of the arcuate fasciculus is composed of a posterior (yellow) and an anterior (green) segment connecting perisylvian cortical areas. The long segment (red) connects Broca's and Wernicke's area directly without relay in the Geschwind's area located the inferior parietal lobule (indicated with a blue dashed line). Forkel et al. (2020) have demonstrated that repetition deficits in PPA can be associated with cortical atrophy of the inferior parietal lobule (indicated with a dashed blue line), degeneration of its white matter connections (anterior and posterior segment), or a combination of both gray and white matter lesions. (A) Patient with mild repetition deficit, no inferior parietal cortical atrophy, and mild atrophy of the anterior segment. (B) patient with severe atrophy of the inferior parietal lobule and moderate damage to both indirect segments of the arcuate. (C) Patient with severe repetition deficits, mild atrophy of the inferior parietal cortex and severe damage of the anterior segment.

The third neuronal population, the *aspiny or sparsely spinous stellate cells*, are GABAergic (gamma-aminobutyric acid) inhibitory interneurons. Their axons are confined to gray matter and terminate on pyramidal cells and other interneurons. The morphology of these interneurons is variable and several subtypes have been identified.

Approximately 95% of the cortical neuronal activity is mediated by fast excitatory (glutamate, 80%) and fast inhibitory (GABA, 15%) neurons. The remaining 5% percent is associated with the slow modulatory action of monoaminergic (dopamine, serotonin, noradrenaline) and non-monoaminergic (acethylcholine, endorphins, etc.) neurons located in small subcortical nuclei of the mesencephalon and projecting to the cerebral cortex. This 5% represents the main target of most pharmacological treatments for psychiatric and neurological disorders.

Cortical Layers

The three main populations of neurons show a laminar arrangement in the cortex (**Fig. 2**) (Catani and Zilles, 2020). Six distinct layers are typical of the isocortex, also named neocortex because it developed late during brain evolution. The majority of the isocortex is characterized by well defined six layers (eulaminate) where the four central layers show a distinct alternate distribution of pyramidal and spinous stellate cells, with a high prevalence of stellate cells in layers II (external granular) and IV (internal granular) and high density of pyramidal cells in layer III (external pyramidal layer) and V (internal pyramidal layer). Layer I (plexiform) is scarcely populated by neuronal cells while layer VI is called multiform or polymorphous for the presence of all three types of neurons. The eulaminate isocortex is typical of associative areas while in the heterotypical cortex the pattern of lamination is less uniform and distinction between some of the layers can be blurred.

The granular koniocortex and the agranular/dysgranular cortices represent the opposite extremes of the heterotypical cortex. The granular koniocortex is characterized by the highest density of spinous stellate neurons that invade also layer III and V whose thickness is reduced due to the low number of pyramidal cells. The koniocortex is typical of primary sensory areas.

Conversely the agranular/dysgranular cortex has high density of pyramidal cells that from layers III and V invade layer IV, which is interrupted (dysgranular) or not visible as distinct layer (agranular). The motor and premotor areas of the frontal and the anterior areas of the cingulate gyrus and insula are typically agranular/dysgranular zones.

The remaining of the cortex is termed allocortex which is typically found in the olfactory and limbic regions dedicated to olfactory and gustatory perception, memory, emotion regulation, reward and social behavior. The allocortex is often continuous with other gray matter structures that have developed early during brain evolution and its heterogeneous lamination pattern often includes fewer layers compared to the isocortex, with the exception of the entorhinal cortex that has more than six-layers.

From Cytoarchitectonic to Neuronal Connectivity

The anatomical variability of the isocortex reflects functional differences of individual zones which are strictly linked to their pattern of connectivity (**Fig. 2**). However, while sharp borders between cytoarchitectonic areas have been defined, the passage from one area to another is often gradual and mediated by a transition zone. This is an important observation also for functional considerations. For example, BA3a that lies between the agranular/dysgranular primary motor cortex (BA4) and the koniocortex of the somatosensory BA3b, displays cytoarchitectonic characteristics common to both its neighboring areas, such as low number of spinous stellate neurons and only a fewof the largest pyramidal cells with an incipient layer IV. Even within the areas that are functionally defined as "primary", differences in cytoarchitectonic and connectivity can be quite striking. For example, in area BA3b the layer V is thinner than layer IV whereas the opposite is progressively found in areas BA1

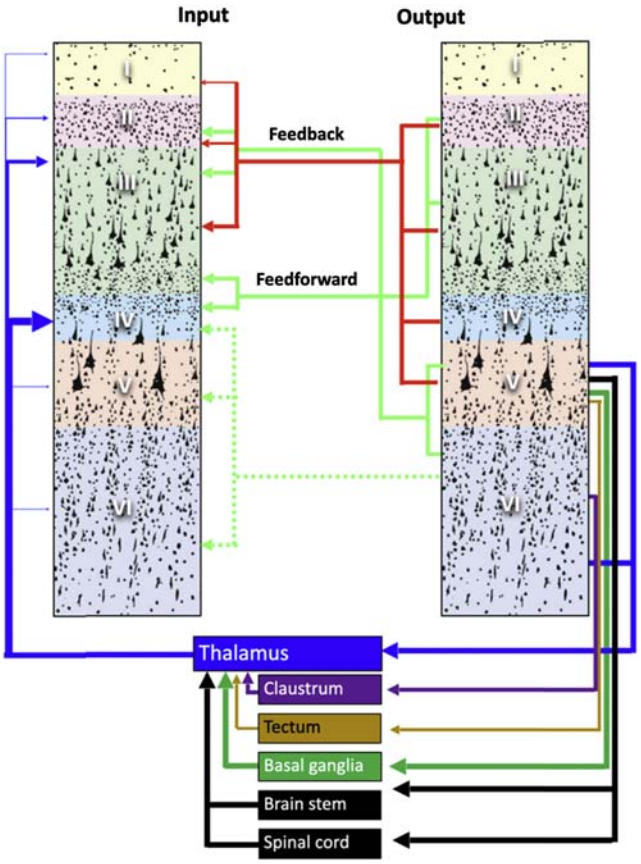

Fig. 2 The pattern of connectivity of a cortical area is defined by the number of pyramidal, spinous, and non-spinous stellate neurons characteristic of each layer. Layer IV has a high density of spinous stellate and low density of pyramidal neurons, which reflects the large number of afferents axons (mainly projection and association fibers) terminating in this layer. In layer V the axons of pyramidal cells contribute to both long distance projection and feedforward association fibers whereas the small number of spinous stellate fibers receive thalamic projections and short association fibers.

and BA2. This indicates a gradual change in the ratio between thalamic afferents (targeting layer IV) and thalamic/associative efferents (originating from layer V) within the primary somatosensory areas.

The axons that leave the cortex and travel within the white matter are grouped together according to common anatomical and functional properties. On average a single oligodendrocyte cell may ensheathe up to 50 axons and by doing so it groups them together into small bundles. Consequently, these bundles travel together in the white matter, project to the same distant target, and carry out a similar function. Myeline ensheathment of axons is a dynamic process directly linked to their functional activity. Cortical neurons engaged in a specific task trigger changes not only in the cortex, through synaptic pruning for example, but they also modify the anatomy of axons. It has demonstrated that high neuronal activity triggers the maturation and migration of oligodendrocyte precursors that leave the cortex and move along the long axons originating from the most active neurons. Increased myelination of these axons guarantees a higher speed of conduction, which is necessary for the efficient control of motor-sensory and cognitive processes.

The function of white matter tracts is not limited to information transmission but also includes aspects that impact on information processing. Collateral axons, for example, branch off the main axon and generally feed back onto their own neuronal bodies or cortical inhibitory neurons. Through these collateral axons, neurons mediate self-modulation of their own firing. Collateral axons and branching are also important to filter, amplify, and distribute signal to multiple cortical and subcortical targets (Waxman, 1972). Hence, in a modern view of white matter networks, axonal fibers constitute not only conducting devices but also nexuses of convergence and divergence, feedback loops, feed-forward connections, and transition points from serial to parallel processing (Catani and Mesulam, 2008).

White Matter Anatomy

Myelinated axonal bundles gather into larger white matter *fasciculi or tracts*. These can be classified into projection, association, and commissural tracts (Fig. 3).

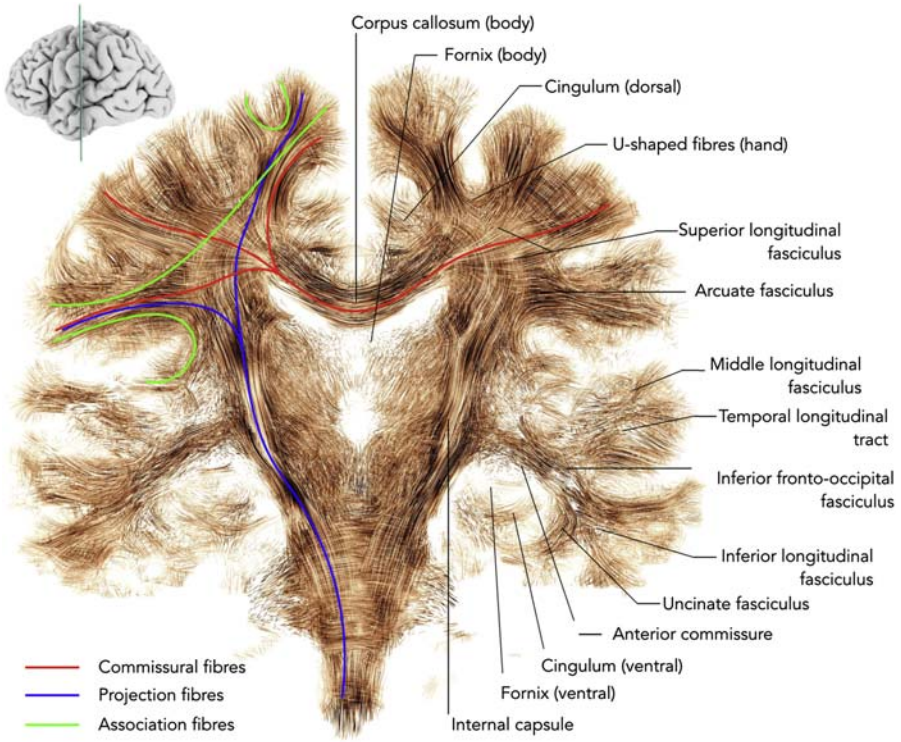

Fig. 3 Classification of white matter tracts and location of the major fasciculi of the cerebral hemispheres passing through a coronal section at the level of the central sulcus. (Image courtesy of Flavio Dell'Acqua published in Catani and Zilles (2020).

Projection Pathways

Projection tracts connect cortical areas to subcortical nuclei and according to their axonal trajectory they can be further subdivided into ascending (from subcortical to cortical) and descending (from cortical to subcortical) projections. The major ascending projection tracts originate from the thalamus and metathalamus (medial and lateral geniculate nuclei) and travel within the internal capsule as *thalamic*, *auditory* and *optic radiations*. The same fasciculi contain a large contingent of descending cortico-thalamic fibers that terminate either in the same thalamic nuclei that send them sensory information (feedback control) or different thalamic nuclei that act as relay stations for cortico-thalamic-cortical loops (feedforward processing). A comparatively smaller but functionally relevant group of ascending fibers, the mesolimbic bundle, originate from the mesencephalic nuclei and projects mainly to the frontal and limbic cortical areas. This extracapsular contingent contributes to the regulation of affect, motivation, and attention.

The majority of non-thalamic descending pathways are axons originating from pyramidal neurons of layer V terminating in the basal ganglia (cortico-striatal), tectum, cranial nerves (cortico-bulbar tract), pontine nuclei, and spinal cord (cortico-spinal system). Finally, the fornix is a descending tract that connects the allocortex of the hippocampal system with the mammillary bodies, hypothalamus, and anterior thalamic nuclei. Projection fibers are relatively well preserved among vertebrates for they adaptive function. They convey and elaborate sensory information for the control of movement and behavior that permits the organism greater chances of survival through modification and exploration of the environment.

Association Pathways

Association tracts are cortico-cortical connections traveling within the same hemisphere. According to their length, association tracts can be separated into short U-shaped fibers connecting adjacent gyri, and intermediate and long association fibers connecting distant gyri. The majority of the U-shaped fibers connect gyri within the same lobe (intralobar) while most of the long association fibers connect gyri from different lobes (interlobar). Association tracts have appearedlate in brain evolution as their development has facilitated the emergence of fine motor skills for tool making, language, flexible cognitive processing, and complex social behavior. The major association tracts of the human brain are the arcuate fasciculus (for language and praxis), the superior longitudinal fasciculus I and II for visuospatial processing motor coordination, the inferior fronto-occipital fasciculus and inferior longitudinal fasciculus for visual processing and the cingulum and uncinate fasciculus for memory, affective regulation and social behavior.

Commissural Pathways

Commissural tracts cross the cerebral midline to connect cortical or subcortical regions of the two hemispheres. Homotopic fibers interconnect corresponding cortical or subcortical regions in the two hemispheres and represent the most prevalent type of commissural connections. Heterotopic commissural fibers connect non-corresponding gray matter regions of the two hemispheres. The largest commissural tracts of the human brain are the corpus callosum and the anterior commissure.

Meynert's Rule and White Matter Concentric Zones

Theodor Meynert was the first to observe a direct relation between the length of the fibers and how deep they travel in the white matter (Meynert, 1885). Among the association fibers, for example, the short U-shaped fibers are always confined in the white matter just beneath the cortex whereas longer association tracts occupy deeper white matter regions. A direct consequence of this is the subdivision of the white matter into concentric zones. This division is particularly evident on coronal images. An internal zone is occupied solely by commissural and projection pathways that form the walls of the lateral ventricles. The external zone contains commissural, projections and association pathways. The concentric zonal distribution of the white matter pathways is the result of serial modifications occurring during brain development. The early period of human brain development (up to 16 weeks) is characterized by the migration of commissural and projection pathways through the core zone, followed by the progressive expansion of the outer zone driven by the exponential growth of association fibers.

Depending on their location, white matter damage can have a significant impact on cognition (Lamar et al., 2008). The use of tractography in individual patients or tractography-derived atlases is improving localization of white matter damage and restoring our confidence in the clinical-anatomical correlation method. Meynert's principle and the concentric zone division has helped to understand that white matter lesions located in the inner core zone, for example, disrupt conduction of the action potential along large commissural and projection pathways and therefore often manifest with extrapyramidal motor deficits, sensory-motor coordination problems and general slowness of cognitive functions (e.g., normotensive hydrocephalus, Binswanger's syndrome, etc.). Conversely, lesions located in the outer zone typically manifest with isolated or combined sensory, pyramidal motor and cognitive deficits attributable to disconnection of specific association or projection pathways.

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Plasticity in the Adult Brain☆

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History of Structural Plasticity in the Adult Mammalian Brain

In the late 19th century, at the dawn of modern neuroscience, researchers began considering the possibility that the adult mammalian brain has the capacity for structural change. Tanzi and Ramon y Cajal speculated that cognitive exertion, or "cerebral gymnastics", could induce change in the dendritic architecture of the adult brain, with Ramon y Cajal writing in 1894 "the cerebral cortex is similar to a garden filled with innumerable trees, the pyramidal cells, which can multiply their branches thanks to intelligent cultivation" (Swanson et al., 2017 p.41). Although originally optimistic, after 30 years of searching for experimental evidence of structural growth, mostly by examining neural tissue after damage, Ramon y Cajal concluded that in the adult brain, "nothing may be regenerated" (Ramon y Cajal and May, 1928, p.750). The concept of plasticity in the adult brain laid dormant for many years, but was re-explored in the 1940s when Hebb proposed experience-dependent mechanisms of adult brain change and Konorski postulated that structural change in relevant neural circuits might underlie learning (Mateos-Aparicio and Rodriguez-Moreno, 2019). It was not until the 1960s that evidence for experience-dependent structural plasticity in the adult brain was obtained by Rosenzweig and colleagues, who showed that rats living in enriched laboratory environments exhibited robust growth in the forebrain, which was accompanied by enhanced learning and memory. These findings, with later contributions from Greenough and colleagues, expanded previously used measures to include the examination of dendrites and synapses, revealing not only that the adult brain can grow by increasing dendritic complexity and connectivity, but that such growth is governed by experience (Leuner and Gould, 2010).

In another set of revolutionary studies on plasticity originating in the 1960s, Altman and colleagues reported evidence of a fundamental form of structural growth in the adult brain, the addition of entirely new neurons to existing circuits in a process known as adult neurogenesis. These studies reported evidence for adult neurogenesis in the hippocampus, as well as other brain regions, in rats, cats and guinea pigs. These findings were repeated and extended in the late 1970s by Kaplan, but not fully accepted by the neuroscience community until the late 1990s, when many research groups demonstrated firm evidence for adult neurogenesis in the brains of rats, mice, monkeys and humans (Gage, 2004). Since that time, debate has raged about where in the brain adult neurogenesis occurs, as well as if it confers meaningful function in humans. Although detractors still exist, the consensus in the field is that adult neurogenesis occurs at a substantial rate in the rodent and human hippocampus. The addition of new neurons to this brain region sets the stage for other forms of structural growth, including the extension of axons, the elaboration of dendrites and the formation of new synapses. Extensive studies carried out in rodents, and a lesser but consistent set of findings in humans, suggest that the process is experience-dependent. Since this area of investigation has provided a rich set of findings about the capacity for structural change in the adult brain, we focus the remainder of this chapter on adult neurogenesis in the hippocampus, with reference to other forms of structural change where relevant.

Adult Neurogenesis: Cell Proliferation, Differentiation and Survival

Adult neurogenesis is a highly regulated process. Progenitor cell proliferation, newborn neuron differentiation and survival act in concert to dynamically influence structural plasticity in the hippocampus (**Fig. 1**). Neural progenitor cells originate in the ventricular zone during embryonic development and travel to the dentate gyrus where they continue to produce adult-born granule cells (abGCs) throughout the lifespan, although proliferation is attenuated in adulthood and with advancing age. The subgranular zone of the dentate gyrus houses two main varieties of neural progenitors. Type 1 progenitors express the markers GFAP, nestin and Sox2.

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This is an update of E.R. Glasper, J.C. Morton, E. Gould, Environmental Influences on Adult Neurogenesis, Editor(s): George F. Koob, Michel Le Moal, Richard F. Thompson, Encyclopedia of Behavioral Neuroscience, Academic Press, 2010, Pages 485-492.

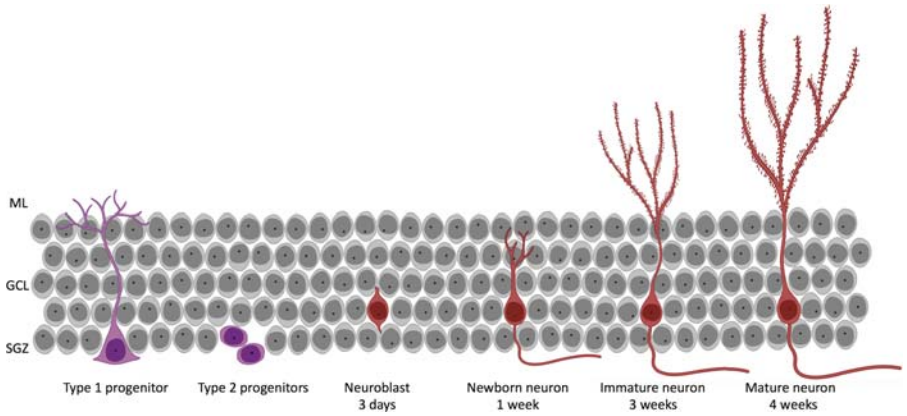

Figure 1 Stages of adult neurogenesis in the hippocampus. Type 1 progenitor cells in the subgranular zone divide and give rise to postmitotic Type 2 progenitor cells. Type 2 progenitor cells migrate a short distance into the granule cell layer as neuroblasts within 3 days. They begin to differentiate into immature neurons and by 1 week extend axons and begin elaborating dendrites. Immature adult-born neurons continue to develop dendrites that span the granule cell layer into the molecular layer and their axons innervate mature neurons in the hilus, CA3 and CA2 by 3 weeks. Immature adult-born neurons continue to mature, with increased dendritic complexity and alterations in neuronal properties as they integrate into hippocampal circuitry. SGZ, subgranular zone; GCL, granule cell layer; ML, molecular layer.

Despite expressing the canonical astrocyte marker GFAP, Type 1 progenitors are morphologically distinct from mature astrocytes in that the former cell type possesses a radial process, which typically spans the length of the granule cell layer. Type 1 progenitors divide at low rates and undergo asymmetric cell division giving rise to Type 2 hippocampal progenitor cells in a process known as cell proliferation. Type 2 hippocampal progenitors exhibit short processes and lack GFAP expression. Type 2 progenitor cells expressing Sox2 are self-renewing, possessing the ability to differentiate into a neuron or an astrocyte. Roughly 90% of Type 2 progenitors develop into immature neurons with the remainder developing into mature astroglia. Once an immature neuron, the cell will express markers including PSA-NCAM, doublecortin and Tuj1 before beginning to integrate into hippocampal circuitry.

Thousands of new neurons are born every day in the dentate gyrus of adult rodents. Numerous factors including hormones, stress, exercise, environmental enrichment and hippocampus-dependent learning influence the proliferation, differentiation and survival of abGCs (Fig. 2). In addition, neurotransmitter modulation has an influence on adult neurogenesis, with a combination of in vivo and in vitro studies revealing, for example, that glutamate release promotes cell proliferation while GABA promotes cell differentiation. In control rodents, nearly half of all abGCs in the dentate gyrus die before successfully integrating into hippocampal circuitry (Fig. 2).

Questions exist regarding whether adult neurogenesis is restricted to the dentate gyrus and subventricular zone, an area lining the anterior wall of the lateral ventricle, which gives rise to new neurons destined for the olfactory bulb. Numerous studies have reported low numbers of immature neurons in a variety of other brain regions, but these findings have often been contradicted by negative reports. One study that extracted neural stem cells from the dentate gyrus, cultured them in a dish and later implanted them in a wide-range of brain regions, found that only when implanted in the dentate gyrus or subventricular zone were these cells

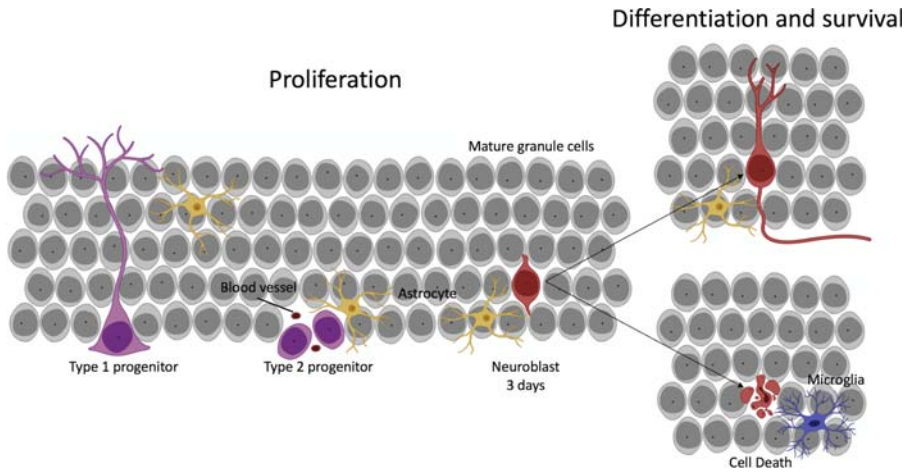

Figure 2 Adult neurogenesis involves proliferation of progenitor cells, as well as differentiation and survival of newborn neurons. Progenitor cell proliferation is promoted by exercise, environmental enrichment, astrocyte signaling, and antidepressant treatment, and is attenuated by aging, stress, and astrocyte signaling. Differentiation is promoted by learning, enrichment, astrocyte signaling and antidepressant treatment. Successful Type 2 progenitors differentiate into neuroblasts, fated to become neurons. Survival of new neurons is promoted by astrocyte signaling, enrichment, learning and antidepressant treatment, and attenuated by aging and stress. Dying adult born granule cells are phagocytosed by microglia. Thousands of new granule cells are created in the dentate gyrus every day, but only a subpopulation survive and functionally integrate into hippocampal circuitry.

able to differentiate into neurons, with stem cells implanted in all other regions dying or differentiating into glia. These findings may suggest that special molecular features of the dentate gyrus and subventricular zone make them conducive to growing new neurons in adulthood, although it is also possible that other brain regions might support adult neurogenesis providing progenitor cells express brain region-specific characteristics. A popular hypothesis proposes that the dentate gyrus and subventricular zone are each examples of a "neurogenic niche", which refers to a region possessing certain molecular characteristics that ultimately enable the proliferation, differentiation and survival of adult-born neurons.

The dentate gyrus is composed of distinct layers, each of which receives inputs from different populations of afferents. The granule cell layer, directly superficial to the subgranular zone, the birthplace of abGCs, receives input from a number of different cell populations, including noradrenergic cells of the locus coeruleus (LC), serotonergic cells of the raphe nucleus, dopaminergic cells from the ventral tegmental area and LC, cholinergic cells of the basal forebrain and GABAergic interneurons from the dentate gyrus. The inner molecular layer, directly superficial to the granule cell layer, receives projections from the lateral septum and supramammillary nucleus as well as from mossy cells located in the hilus. The most superficial regions of the dentate gyrus, known as the middle and outer molecular layers, receive rich inputs from the medial and lateral entorhinal cortices respectively. Projections from the medial and lateral entorhinal cortex provide spatial and nonspatial information, and directly innervate abGCs. Once innervated, abGCs have enhanced capabilities to dynamically influence local circuits in the dentate gyrus via projections to mature granule cells, inhibitory interneurons, hilar mossy cells and pyramidal cells of the CA2 and CA3 regions. The ensemble of afferents to the dentate gyrus promotes adult neurogenesis and has been shown to influence the integration of immature neurons into the hippocampal circuitry.

A combination of in vivo and in vitro studies reveals that astrocytes also play a crucial role in influencing adult neurogenesis and promoting the integration of new neurons into existing hippocampal circuitry. One way in which astrocytes influence adult neurogenesis is through the release of specific molecules. Electron microscopy work reveals that astrocytes make contacts with Type 1 progenitor cell processes located on blood vessels in the molecular layer, enabling astrocyte-progenitor juxtacrine signaling. Astrocytic release of ephrin-B2 activates the EphB4 receptor on progenitor cell contacts, promoting the proliferation and differentiation of abGCs. Astrocyte-derived thrombospondin-1 (TSP1) release also promotes cell proliferation and differentiation, with mouse models deficient in TSP1 demonstrating robust neurogenesis deficits. Astrocytic regulation of adult neurogenesis is bidirectional, with Notch signaling at astrocyte-progenitor contacts attenuating cell proliferation. In addition to forming contacts and influencing type 1 progenitors, astrocytes influence the differentiation and survival of type 2 progenitor cells. Astrocytes alter their processes to envelope the afferent and efferent synapses of abGCs, and can even ensheath the axons of an abGC's potential synaptic partners. The ability to directly influence the dendrites of an abGC, or the axons of potential synaptic partners, enables astrocytes to dynamically modulate the inputs an abGC receives, influencing the development, migration and survival of new neurons. Astrocytes exert additional influence over the dendrites of abGCs, with astrocytic D-serine release controlling the maturation of dendrites, ultimately influencing the integration of abGCs into hippocampal circuitry. It remains unclear whether astrocytes in the dentate gyrus are unique in their ability to influence immature abGCs and contribute to the neurogenic niche. Microglia influence the process of adult neurogenesis by engulfing dying neurons and eliminating their debris.

Intrinsic and Extrinsic Properties of abGCs

Adult neurogenesis presents a major puzzle for researchers. How does a proportionately small population of neurons, less than 0.5% of total dentate gyrus granule neurons, dynamically influence the functions of the hippocampus, including learning, memory, anxiety and stress regulation? The answer to this question likely stems from the unusual characteristics that distinguish abGCs from their mature granule cell neighbors in the dentate gyrus. These unusual characteristics are manifested in both inherent properties, as well as differences in their microcircuitry.

After their production in the dentate gyrus, abGCs exhibit unique electrophysiological properties and dynamic structural plasticity during a discrete time period. These features allow abGCs to functionally integrate into existing hippocampal architecture and induce plasticity in a development-dependent manner unavailable to mature neurons. The survival and integration of abGCs into existing hippocampal circuitry are determined within the first three weeks of development. During the first two weeks of life, abGCs have very low LTP-induction thresholds and exhibit depolarization in response to GABA release, resulting in robust LTP that cannot be inhibited by GABA. At roughly two weeks, abGCs begin to form contacts with mature granule neurons, hilar mossy cells and neurons in CA2 and CA3, influencing these neurons with electrophysiological characteristics not observed in mature neurons. abGCs do not express IEGs in the first three weeks after mitosis despite possessing reduced LTP thresholds and excitatory responses to GABA. From weeks two to four post-mitosis, dendrites emerge and increase in complexity as abGCs begin to display features of mature granule cells. At this time, the neuron's electrophysiological profile transitions to hyperpolarization in response to GABA. At six weeks of age, abGCs begin to exhibit larger LTP amplitudes with increases in mushroom spine density starting around the eight-week time point when the neuron is considered fully mature. Immature abGCs are also highly responsive to experience in that they demonstrate heightened activation in response to hippocampal-dependent spatial learning and preferential reactivation compared to their mature granule neuron counterparts. Heightened activity of immature abGCs with unusual intrinsic characteristics likely enables a wide range of dynamic function across the hippocampus.

Immature abGCs influence the excitability of mature granule neurons (Dieni et al., 2019). Despite the highly excitable nature of immature abGCs, experiments utilizing voltage-sensitive dye reveal that elevated levels of neurogenesis decrease the spread of depolarization in the dentate gyrus. Conversely, complete ablation of adult neurogenesis enhances the spread of depolarization throughout the dentate gyrus. Ablation of abGCs via focal radiation increases susceptibility to seizure after chemoconvulsant

administration and induces in vivo burst activity in mature granule cells. Specific silencing of abGCs younger than seven weeks also enhances the excitability of neighboring mature granule neurons. Recent work reveals that projections from the medial and lateral entorhinal cortex enable abGCs to excite or inhibit mature granule cells via extrasynaptic glutamate release. Stimulation of lateral entorhinal projections induces low levels of glutamate release from abGCs. Low levels of glutamate bind to mGlu-II receptors on neighboring mature granule cells, promoting inhibition. Conversely, stimulating medial entorhinal inputs results in robust glutamate release, overpowering mGlu-II receptors and activating NMDA receptors, exciting nearby mature granule cells (Luna et al., 2019). Taken together with findings suggesting that shortly after their generation, abGCs receive greater input from the lateral entorhinal cortex than from the medial entorhinal cortex, these findings indicate that abGCs also have a transiently unique microcircuitry that likely contributes to their unusual function.

In addition to the unusual intrinsic and extrinsic characteristics abGCs demonstrate at various developmental time points, a single abGC has the potential to contact and influence hundreds of downstream targets. One mature dentate gyrus granule cell innervates roughly twelve CA3 pyramidal neurons. Due to the largely recurrent network of the CA3, a single CA3 neuron then innervates nearly fifty more CA3 neurons. Mature granule neurons additionally send projections to hippocampal CA2, although the average number of neurons innervated via this projection is currently unknown. abGCs also send projections to mature pyramidal neurons in the CA3 and CA2 regions, although the exact number of projections is unclear. Whether via monosynaptic innervation in CA3 and CA2, or disynaptic innervation via projections to neighboring mature granule neurons, a single abGC has the potential to influence a large number of hippocampal neurons, promoting large-scale plasticity throughout the hippocampus. This observation reveals that abGCs are capable of dynamically influencing hippocampal circuitry and function, even when factoring in diminished levels of neurogenesis resulting from aging. In conjunction with the dramatic increase in neuronal innervation, abGCs are far more than just mature granule cells born in adulthood, possessing numerous unusual characteristics that seem to maximize structural plasticity of the adult hippocampus.

Stress Influences Adult Neurogenesis

Stress, experience and environmental enrichment functionally regulate adult structural plasticity in the hippocampus. Stress is perhaps the most comprehensively investigated moderator of adult hippocampal plasticity, as the hippocampus was one of the first brain regions identified as a potential target of stress hormones due to its expression of both mineralocorticoid and glucocorticoid receptors, with mature granule neurons in the dentate gyrus expressing both of these receptors. Mineralocorticoid receptors exhibit a higher affinity for glucocorticoids, making them sensitive to circadian fluctuations in stress hormone. In contrast, glucocorticoid receptors are sensitive to stress-induced increases in glucocorticoid levels, making them sensitive to heightened glucocorticoid release in response to a stressor or exogenous glucocorticoid administration. Immature abGCs lack substantial expression of either receptor until four weeks of age.

It is now clear that exposure to either acute or chronic stressors, both physical and psychological, induce robust morphological changes in mature hippocampal neurons and can attenuate levels of adult neurogenesis at all stages of newborn neuron development (Fuchs and Flugge, 2014). Exposure to stress in adulthood promotes dendritic retraction, reducing dendritic spine density and the number of synapses in the dentate gyrus, CA1 and CA3. Stress-induced atrophy of CA3 apical dendrites is a slow process, requiring three weeks of chronic stress or glucocorticoid administration to confer impairments. Importantly, dendrites often return to their baseline structures within one week after removal of the stressor, indicating that stress-induced alterations of mature hippocampal neurons are a reversible, and potentially adaptive, process (McEwen, 1999).

Glutamate appears to play a role in stress-induced hippocampal plasticity. Stressors are known to increase the release of glutamate in the hippocampus, and attenuating hippocampal glutamate release using the anti-epileptic drug phenytoin, or blocking NMDA receptors, prevents atrophy of CA3 apical dendrites after exposure to stress. Inhibitory signals also play a role in the mediation of harmful stress effects, with benzodiazepine administration providing protection against stress-induced dendritic atrophy via enhanced GABA release. Electron microscopy reveals that stressors promote a reorganization of synaptic vesicles located in granule cell mossy fiber terminals in the CA3 region. After three weeks of restraint stress, rats exhibit densely packed vesicle clusters in the active synaptic zone compared to healthy controls. In addition to altered neurotransmitter vesicles, chronically stressed rats exhibit a greater area of mitochondrial profiles in mossy fiber terminals, suggesting enhanced energy-creating capabilities compared to controls (McEwen, 1999).

Stress-induced hippocampal atrophy may provide adaptive protection against powerful excitatory drive. Atrophy of CA3 apical dendrites attenuates the drive of recurrent CA3 projections, potentially protecting the hippocampus from excessive glutamate release and severe excitotoxic damage. Despite the potential upsides of stress-induced hippocampal structural plasticity, it must be noted that chronic stress has the potential to promote aberrant projections in the dentate gyrus, with one study revealing that high frequency stimulation induced hippocampal epileptic activity in nearly 40% of chronically stressed mice versus 15% of healthy controls.

Across the lifespan, levels of adult neurogenesis in the dentate gyrus have been negatively associated with levels of endogenous glucocorticoids. Levels of adult neurogenesis are highest in youth when baseline glucocorticoid levels are relatively low, and steadily decline with age as glucocorticoid levels increase. Exogenous administration of glucocorticoids attenuates levels of adult neurogenesis via suppression of cell proliferation in the subgranular zone. Administration of glucocorticoid receptor blockers during glucocorticoid administration, as well as during exposure to an acute stressor, buffers the stress-induced attenuation of adult

neurogenesis. Additionally, depleting endogenous glucocorticoid levels via adrenalectomy increases rates of adult neurogenesis, promoting cell proliferation in the subgranular zone. Although the previous findings may present glucocorticoids as a promoter of deleterious hippocampal plasticity, the story is not so simple. Despite inducing a complete loss of endogenous glucocorticoids, adrenalectomy promotes robust death of mature granule cells in the dentate gyrus. Administration of aldosterone, which binds with high affinity to mineralocorticoid receptors present on mature granule neurons, prevents this dramatic cascade of cell death. These findings suggest that mineralocorticoid receptor activation, either through endogenous mineralocorticoids or glucocorticoids, may be crucial for maintaining the survival of mature granule neurons.

Despite the clear link between stress, cell death and loss of morphological complexity in the hippocampus, stress effects should not be viewed as inherently deleterious in nature. Numerous studies illuminate the potential for adaptive stress-induced structural plasticity in the hippocampus. Repeated stressors can perturb hippocampal CA3-dependent learning in a manner that is reversible within hours to weeks after exposure. This phenomenon can be crucial for animals in an environment where immediate survival is more important than exploration of the environment at the time. Additionally, stress-induced reduction of adult neurogenesis and dendritic pruning of the potential targets of mature granule cell targets may protect hippocampal circuits from excitotoxic damage. The unique electrophysiological properties of abGCs enable dynamic function unavailable to mature hippocampal neurons, however it remains possible that this unique plasticity may induce damage if left unregulated.

Stress effects are not confined to the suppression of adult neurogenesis and reduction of neuronal morphological complexity. The emotional valence and perceived controllability of a stressor play a major role in determining the stressor's influence on hippocampal structure, with some stressors causing negative consequences entirely and others promoting positive effects on structural plasticity. Physical activity, such as running, increases endogenous glucocorticoid levels. Despite increased glucocorticoid levels, voluntary running increases rates of adult neurogenesis in the dentate gyrus as well as the total number of dendritic spines.

It is clear that chronic stress plays a significant role in neuropsychiatric illness. Individuals under chronic stress are at higher risk of developing major depressive disorder, anxiety disorders, and posttraumatic stress disorder. The "neurogenic hypothesis of depression" proposes potential interrelationships among stress, adult neurogenesis and mental health (Eisch et al., 2008). This hypothesis posits that the regulation of adult neurogenesis in the hippocampus plays a pivotal role in both the onset and treatment of depression, with hippocampal activity ultimately influencing emotional behavior. One study showed that brain tissue collected from deceased patients with major depressive disorder showed reduced levels of markers of adult neurogenesis in the hippocampus, possibly resulting from heightened endogenous glucocorticoid levels. Antidepressants, anxiolytics, classical and atypical antipsychotics, cannabinoids, deep brain stimulation and even electroconvulsive therapy rapidly confer enhanced levels of adult neurogenesis in experimental animals. After the initiation of antidepressant treatment, improvements in quality of life typically occur within weeks, roughly the same time that the treatment-induced new neurons mature and integrate into hippocampal circuitry (Schoenfeld and Cameron, 2015). Rodents exposed to chronic mild stress exhibit decreased adult neurogenesis, which can be restored by treatment with either the selective serotonin reuptake inhibitor fluoxetine or the tricyclic antidepressant imipramine, but treatment with the former leads to increased susceptibility to subsequent stress, possibly due to the over-proliferation and under-development of abGCs. Blocking the overshoot in adult neurogenesis prevents this negative effect, suggesting that random stimulation of adult neurogenesis may not be appropriate for the restoration of stress-induced effects in all cases (Alves et al., 2017).

The efficacy of short-term ketamine treatment for clinical depression in humans further complicates the claim that adult neurogenesis is a necessary component of the therapeutic efficacy of antidepressants. While the vast majority of treatments for depression take weeks to months to produce improvements in mood, ketamine confers this effect almost immediately and the effects are long-lasting. While the time frame of initial symptom relief is not sufficient for the proliferation and differentiation of abGCs, adult neurogenesis may support the long duration effects of the drug. Along these lines, recent studies have shown that ketamine enhances the production and differentiation of abGCs. It should also be noted that ketamine has been shown to have effects on other forms of structural plasticity, including stimulating the growth of dendritic spines on pyramidal neurons in the prefrontal cortex, which are known to be decreased by chronic stress (Moda-Sava et al., 2019).

Environmental Enrichment and Physical Exercise Influence Adult Neurogenesis

Since the early work of Rosenzweig and colleagues, numerous studies have investigated the influence of enriched environments on structural plasticity. While initial studies focused on plasticity in the neocortex, the hippocampus became an additional focus of these studies, as it showed dramatic structural changes, including increased dendritic spine density, synapse number, rates of gliogenesis and dendritic branching in rodents and monkeys living in enriched environments. Studies also showed dramatic increases in levels of adult neurogenesis in rodents living in enriched environments. Although having access to a running wheel is sufficient to enhance levels of adult neurogenesis, animals exposed to enriched environments devoid of running wheels also undergo similar levels of enhanced neurogenesis, with enrichment conferring major influences on proliferation, differentiation and survival of abGCs. In fact, compared to controls housed in standard laboratory environments, animals housed in enriched environments can exhibit up to a five-fold increase in the number of abGCs. This effect extends into old age, even in rodents previously raised in control environments. Enrichment in old age increases proliferation, differentiation and survival of abGCs after just eight weeks of residence in an enriched environment. Additionally, mice exposed to an enriched environment for only 3 h a week for one and a half years demonstrated heightened levels of neuronal proliferation alongside improved performance on object recognition tasks.

Numerous studies have compared the unique benefits of environmental enrichment and exercise. Physical exercise is known to exert a dominant influence on adult neurogenesis proliferation while enriched environments promote the survival of newborn neurons. Living in an enriched environment with increased physical exertion produces compounding benefits beyond the effects of either experience in isolation. Taken together, the literature on effects of environmental enrichment as well as of physical exercise suggest that the inherent capacity for structural plasticity in the adult hippocampus is great, but under some circumstances, it remains dormant.

Contribution of abGCs to Behavior

Considerable research effort has been made to understand how abGCs influence behavior. Correlational findings in rodents reveal that strain-dependent levels of adult neurogenesis are positively linked with spatial memory performance. Increased rates of adult neurogenesis resulting from exercise or living in an enriched environment also improve performance on tasks of spatial and social memory. Conversely, the natural attenuation of adult neurogenesis observed in aging animals corresponds with impaired spatial memory performance. Additionally, undergoing certain hippocampus-dependent learning paradigms including Morris Water Maze, trace eyeblink conditioning and conditioned food preference increase levels of adult neurogenesis. Rats with higher levels of abGC survival demonstrate better performance on various learning tasks, suggesting that it is the act of learning, and not simply the training, that promotes adult neurogenesis. A large number of studies have investigated the behavioral effects of preventing the formation of abGCs using drugs, focal irradiation or transgenic means. Although some of these studies are contradictory, the majority suggest that reductions in the number of abGCs result in impairments to certain types of hippocampus-dependent learning and memory tasks. Additionally, these studies support a role for abGCs in stress regulation and stress coping in the context of antidepressant treatment. More recent studies have used optogenetics and chemogenetics to inhibit abGC activity without reducing the overall number of abGCs, and have found similar results, including deficits in learning and memory tasks. Related studies have also shown that activation of abGCs is important for the therapeutic efficacy of antidepressants on stress coping and defensive behavior. While the exact role that abGCs play in behaviors related to the hippocampus remains to be determined, an overall picture has emerged supporting the claim that these cells participate in multiple functions of the hippocampus, varying perhaps due to their location along the dorsoventral axis.

Discussion

The adult brain undergoes dynamic structural plasticity in response to numerous factors. Stress, physical exercise, environmental enrichment and learning influence mature hippocampal neuron morphology and the development of abGCs in the hippocampus throughout the lifespan. Stress-induced neuronal alterations are potentially highly adaptive, conferring resistance to potential excitotoxic damage associated with excessive glutamate release by mossy fiber terminals. In addition to inducing reversible structural plasticity in mature neurons, stress can promote beneficial hippocampal function. Enriched environments more generally and physical exercise specifically enhance levels of adult neurogenesis. While numerous factors and experiences alter levels of adult hippocampal neurogenesis, it is important to also consider changes in other forms of structural plasticity that likely work together to allow for flexible behavioral responses that are attuned to the environment.

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Women in Neuroscience: A Short Time Travel

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Glossary

Aphasia Alteration in language production and/or comprehension due to brain injury.

Gender bias Unequal treatment or perceptions of individuals based on their socially constructed gender roles.

Intellectual ability The ability to think or act in a goal-directed way, to create new connections between elements, and to solve problems in new situations.

Nobel Prize Annual international award established by Alfred Nobel and bestowed since 1901 for outstanding achievements in physics, chemistry, physiology or medicine, literature and for work in peace.

Spanish Neurological School The school founded by Santiago Ramón y Cajal in 1902 in Madrid which, also through the numerous prominent disciples, made an extraordinary contribution to understanding the structure of the nervous system.

Introduction

The shaded side of the history of neuroscience shows how women took part to the development of this modern interdisciplinary field from the beginning, despite the plain hurdles in accessing higher education.

Their contribution, acknowledged and sometimes awarded by the scientific community of the time, has been forgotten and in some cases actively removed so as to leave only faint traces in the reference handbooks and academic student textbooks. This scarce presence led to the thesis that women were not inclined to scientific research, and above all they would remain focused on their predisposed role: the care of husband, children, older people. Embarking on a scientific path would have prevented women from stay at home and take care of the family. Furthermore, science required the intellectual abilities of which women were believed to be lacking and it is not necessary to go far back in the years to hear echoes of this belief in university classrooms and lecture halls.

"Women are so grossly under-represented in modern science because, for most of history, they have been treated as intellectual inferiors and deliberately excluded from it" wrote Angela Saini in her book Inferior (Saini, 2017), which encouraged international awareness campaigns on gender discrimination in the scientific world. As for women inferiority, the story begins with Charles Darwin who explained his thesis in the book The Descent of Man and summarized his thought in the correspondence with Caroline Kennard, to whom he wrote in 1881: "I certainly think that women though generally superior to men [in] moral qualities are inferior intellectually, and there seems to me to be a great difficulty from the laws of inheritance, (if I understand these laws rightly) in their becoming the intellectual equals of man" (Saini, 2017). The thesis then found fertile ground in the following decades and became increasingly structured in the academic and general communities. Still today, some maintain that the small proportion of women in major international scientific awards (Nobel Prizes, Fields Medals, etc.) can be explained with the supposed female lower aptitude for abstraction, mathematics, and physics.

Female Nobel laureates are not lacking but they are very few indeed. Between 1901 and 2019, the Nobel Prizes were awarded to 21 women (Marie Curie received it in Physics in 1903 and in Chemistry in 1911) out of 615 scientists. However, cases of women who have been denied the recognition they deserved have emerged in recent years. Lise Meitner, Marguerite Vogt, and more recently Jocelyn Bell Burnell are just a few examples of women who made essential contributions to discoveries that led to Nobel Prizes awarded to their male colleagues.

The impact of removing women from science is still evident today in the small number of celebrations dedicated to the pioneer women of neuroscience, in the limited access to the top positions of departments and laboratories, as well as to the highest academic positions.

Scientific errors, cultural barriers, and gender segregation have led to this removal. Gender bias and discrimination prove to be very effective in leaving women's innovation potential unexpressed through horizontal and vertical segregation (Chiofalo and Metitieri, 2019).

In the next four sections we will illustrate the condition of women in neuroscience through a temporal dimension: recovering the stories of some representative women neuroscientists from the past; referring to the transition from sources sought in the hidden historical archives to the autobiographies accessible online; summarizing the current situation of women in neuroscience; and, finally, tracing the unknowns of the future that with the COVID-19 pandemic are likely to cancel the slightest changes made to diversity in the last few years.

The Past: Five Forgotten Pioneer Women of Neuroscience

Until the early 1900s, it was widely believed that the lower physical strength of women than men implied similar mental weakness and a more delicate nervous system. In the 19th century, different fields in brain research highlighted that sexual differences were reflected in exaggerated gender distinctions: from biology to psychology, to phrenology and evolutionary theory, the scientists claimed that women had fewer intellectual abilities than men (Houghtaling, 2008). Moreover, being at the mercy of their hormones, it was said, women were thought to be emotionally unstable and unable to make decisions. In medicine, this belief justified the idea that women could not reach high standards in their studies and was the excuse with which they were prevented from accessing post-graduate specialization courses and hospital traineeships, which in France remained exclusive to men until 1881 (Digby, 1996). Despite social and cultural barriers, some women managed to enter the academic world, a world for men only, and there to find their place. Among these are five pioneer women of neuroscience born in the late 1800s who produced seminal works in the first half of the last century.

Maria Manasseina and the Foundation of Sleep Science

Maria Mikhailovna Manasseina (1843–1903) was one of the first women to graduate in medicine in Europe (Kovalzon, 2009). She published important contributions to biochemistry, physiology, and sleep deprivation. She discovered that the negative effects of prolonged sleep deprivation originated in the brain and demonstrated that sleep is more important than food for the preservation of life (Bentivoglio and Grassi-Zucconi, 1997). Manasseina published the first comprehensive handbook on sleep in 1889, in Russian. The book was then translated in English (de Manacéïne, 1897) and widely distributed in Europe, becoming the sleep encyclopedia, a reference book in those times. Manasseina stated that sleep represents a definite state of brain activity which is different from the absence of activity, as it was commonly seen at the time: a remarkable intuition, considering that the objective recording of brain electrical activity through the electroencephalogram would have been introduced after more than 20 years. Before studying sleep, Manasseina worked at the Polytechnic University of Vienna, where she had the opportunity to study the alcoholic fermentation process by discovering that it is due to specific components that can be isolated from yeast cells (she called them "unorganized enzymes") rather than the living yeast per se (Lagnado, 1992). The same results were replicated by Eduard Buchner after 25 years and, although he was aware of Manasseina's work, he did not even mention her in his publications. Buchner was awarded the Nobel Prize in Chemistry in 1907 for this discovery and Manasseina's name obliterated.

Laura Forster and Manuela Serra at the Spanish School of Neurohistology

Laura Forster and Manuela Serra were the first two women working at the Spanish Neurological School of Santiago Ramon y Cajal in Madrid (Giné et al., 2019). Although almost all Cajal's collaborators were men, Forster and Serra appeared on the official list of school members drawn up by Cajal in 1922, on the occasion of the Echegaray medal reception by the Royal Spanish National Academy of Physics, Exact and Natural Sciences (Giné et al., 2019).

Laura Elizabeth Forster (1858–1917) was born and initially studied in Australia. She moved to England after the death of her father, and, in 1887, she entered the University of Bern in Switzerland as a medical student and graduated in 1894. She remained working at the Institute of Pathology for the next six years and devoted her research to the study of muscle spindle fibers. Returning to the United Kingdom, she settled in Oxford and attended the Physiological Laboratory under the supervision of Gustav Mann. There, she published a scientific paper on the histology of the lymph nodes of a patient suffering from tuberculosis. To gain more mastery in neurohistological techniques, Forster went to Madrid in 1911, in the Cajal laboratory, where she stayed a few months. Her research focused on the degeneration of nerve fibers after a traumatic lesion of the spinal cord in birds, to compare its effects with what was observed in the previous studies on mammals conducted by Cajal and others. Forster was the first to apply the neurofibrillary techniques to birds and her findings were published in August 1911 in a long scientific paper written in Spanish and elegantly illustrated by six drawings in the style of the Cajal school. Cajal cited Forster's work in his laboratory at least three

times. Laura Forster's scientific career ended in 1912 when at the outbreak of the First Balkan War, she enlisted as a nurse, since women could not serve as doctors on the war front. She also served at the outbreak of the First World War.

Biographical information regarding Manuela Serra is scarce, as reported by Giné et al. (2019). Despite being neither a doctor nor a senior researcher, Manuela Serra conducted her studies on the intracellular fibrils of ependymal cells and astrocytes in the spinal cord of the frog and published a paper in the Cajal laboratory's journal in 1921. In this publication, illustrated by ten drawings, Serra reported for the first time the presence of microglia, which she called "mesoglia", in the white matter.

The women neuroscientists in the Cajal school were admitted as independent researchers or collaborators, a role not as prominent as that of female scientists in other countries, despite their outstanding findings and their relevance for the development of neuroscience.

Augusta Dejerine-Klumpke, an Exceptional Neurologist and Neuroanatomist

Augusta Marie Dejerine-Klumpke (1859–1927) was born in the United States to German parents. She spoke English, German and French, and knowing these languages was a considerable advantage to access scientific literature, since, during the first decades of the 20th century, many scientists still wrote in their native language. Only after the Second World War English became the main language of science. In 1882, following the published work of the German neurologist Wilhelm Heinrich Erb, which described the clinical signs following the injury of the brachial plexus (Bogousslavsky, 2005), Dejerine-Klumpke characterized the paralysis of the lower brachial plexus, that was named after her Klumpke's palsy. During the First World War, together with her daughter Yvonne, she treated soldiers with spinal cord injuries, and founded a professional rehabilitation center near Fontainebleau, thanks to donations from family and friends (Schurch and Dollfus, 1998).

Dejerine-Klumpke contributed significantly, with her husband Jules Dejerine (1849–1917), to the two-volume Anatomie des centres nerveux [Anatomy of the Central Nervous System] (Dejerine, 1895, 1901), one of the most significant works in the field of neurology. In 1908, she took part in the 3-day scientific meeting of the French Society of Neurology in Paris, during which a dispute took place between Jules Dejerine and Pierre Marie, Charcot's most important pupil. The first supported a differential classification of aphasias, while the second claimed the existence of only one type of aphasia (Wernicke's aphasia). For Pierre Marie, Broca's aphasia consisted of adding anarthria to Wernicke's aphasia, and its neuroanatomical basis was to be localized in the "quadrilateral space" which included the basal ganglia and internal capsule. Augusta Dejerine-Klumpke, through neuroanatomical data, proved that Marie's assumptions were incorrect due to the fact that a lesion within the quadrangle is capable of causing aphasia only if it affects the anterior, upper and external parts of the area, thus sectioning the third frontal convolution foot and cap devoted to language skills (Lecours and Caplan, 1984). After Jules Dejerine's death, Pierre Marie took over the chair of clinical neurology and fired Augusta, asking her to free the laboratory from all Dejerines' documents and personal effects. Dejerine-Klumpke, then, together with her daughter, created the "Fondation Dejerine" to collect all their clinical and research works in a museum and a laboratory.

The Foundation collection is currently located in the basement of the Sorbonne University in Paris under the management of the library. In her career, Augusta Dejerine-Klumpke received many prizes and awards: The Anatomy prize for free teaching in 1878–1879, the Godard prize of the Academy of Medicine in 1886, the silver medal from the Faculty of Medicine in Paris, the Lallemand prize of the prestigious Académie des Sciences for her doctoral thesis in 1890, a first Legion of honor for her scientific studies in 1913, and a second in 1921 with the rank of Officer for her strong commitment in the care of wounded soldiers during the First World War. She was the first woman to become president of the French Society of Neurology in 1914 (Berhoune et al., 2014).

Cécile Vogt: Neuroscience to Dismantle Cultural and Political Discrimination

Augustine Marie Cécile Mugnier Vogt (1875–1962) was one of the first women admitted to medical school in Paris. She studied under the neurologist Pierre Marie and his research team at the Bicêtre Hospital and graduated in 1900 with a dissertation in neuroanatomy. In Paris, Cécile met Oskar Vogt (1870–1959), who worked for some time in the laboratory of Augusta and Jules Dejerine at La Salpêtrière Hospital. After getting married, they settled in Germany, Berlin, and at the Neurobiological Laboratory (*Neurobiologische Laboratorium*), the Vogts began a long and productive scientific collaboration that would lead them to landmark discoveries in the field of neuroanatomy and neuropathology. In 1914, Oskar and Cécile Vogt started to work at the new Kaiser Wilhelm Institute for Brain Research (KWI), in Berlin, which later became the Max Planck Institute for Brain Research, as appointed director and head of the anatomy department, respectively.

Cécile Vogt's work on the morphology of the nervous system contributed to a new understanding of the interactions between the different regions of the brain. She conducted systematic clinical-anatomical research and published important studies on the myeloarchitectonic organization of the thalamus, on the pathology of the corpus striatum, and the cytoarchitecture of the cerebral cortex (Klatzo, 2002; Vogt and Vogt, 1919). In her first work on thalamus myeloarchitecture, she identified several thalamic nuclei and their connections. It was a pioneering work for the modern understanding of the thalamus' physiology. Cécile Vogt was among the very few scientists in Europe, together with Sherrington in the United Kingdom, to use cortical electrical stimulation. She countered, also through her research, the pervasive prejudice that women were intellectually inferior to men. In the 1920s, Vogt explicitly stated that her research did not support the hypothesis of a difference between male and female brains (Akkermans, 2018).

Cécile and Oskar Vogt worked also with Korbinian Brodmann, and they were recognized as "key figures in establishing modern brain research" (Klatzo, 2002). In the years following 1933, they became the target of inspections and accusations by the National Socialists and were forced to leave the KWI. From 1937 they moved to Neustadt in the Black Forest and continued to work in their privately funded Institut für Hirnforschung und Allgemeine Biologie (Institute for Brain Research and General Biology). Cécile Vogt had a very productive scientific career for over 60 years, despite the two World Wars and the very tough social and economic situation in Germany. Before they met, Cécile had given birth to a girl, Claire, whom Oskar adopted once married. They had two other daughters: Marthe and Marguerite.

We are in the presence of an entire and unique family of scientists, and remarkable women, since Claire (1838–1978) conducted and published research about pediatric neurology in Paris, and was a pioneer in child neuropsychiatry (Poirier and Poirier, 2020); Marthe (1903–2003) was a leading neurophysiologist and pharmacologist, conducted, in the United Kingdom, pioneering research on neuropharmacology for the treatment of mental illness, and was elected a Fellow of the Royal Society (Wright, 2003); and Marguerite (1913–2007) was an outstanding cancer biologist and virologist, worked at the California Institute of Technology (Caltech), in Pasadena, United States, with Renato Dulbecco, and they were the first researchers to observe that polio virus formed plaques in tissue culture (Rubin, 2017). Vogt and Dulbecco founded the field of molecular virology. Despite her high reputation in the scientific community, Marguerite Vogt never received major awards and honors and was not bothered by the fact that Dulbecco received many awards for their joint work (including the Nobel Prize in 1975) (Wunderlich, 2013). In his Nobel Lecture, Renato Dulbecco acknowledged the assistance of many researchers but forgot the name of Marguerite Vogt, despite the inclusion of five of their joint publications in the reference section.

From Archives to Autobiographies

Many other names can be listed, among those sought in the historical archives or brought to light by historians. The crossed paths between Augusta Dejerine Klumpke and Cécile Vogt were recounted at the 2019 Annual History of Neuroscience meeting in Paris, dedicated for the first time to pioneer women in medicine and neuroscience. That event revealed, among others, the lives and careers of the Italian anatomist Anna Morandi Manzolini (1714–1774); two French neurologists from La Salpetrière, Chiriachitza Athanassio-Benisty (1885–1938) and Gabrielle Lévy (1886–1934); and the Nobel laureate Rita Levi Montalcini (1909–2012). The meeting was also attended by Nicole Le Douarin, pioneer of microbiology, who is also the author of a fascinating chapter in The History of Neuroscience in Autobiography, Volume 7 (Le Douarin, 2012).

Volume 2 of this collection includes the Autobiography of Brenda Milner (Milner, 1998) "the renowned neuroscientist who changed our understanding of brain and behavior" (Watkins and Klein, 2018). Milner was recently celebrated on occasion of her 100th birthday, the July 15, 2018, with a ceremony and a series of conferences at the Montreal Neurological Institute. She continues to conduct research and to support "troops" of scientists from all over the world (Watkins and Klein, 2018). For her discovery of multiple brain systems for memory she was awarded the Kavli prize in 2014 with John O'Keefe and Marcus Raichle. The awards ceremony was captured in a very representative image in which Brenda Milner was the only woman to stand out with her blue dress among many white men in black (**Fig. 1**): the non-diversity in science at its peak. Although unintentionally, Brenda Milner continues to be a role model for several generations of women neuroscientists as well as for young students who want to pursue a scientific career. Her work has also become popular through a comic book and the children's book Good Night Stories for Rebel Girls 2 (Watkins and Klein, 2018).

The place reserved for women in neuroscience is well illustrated in the indices of the ten volumes of the above-mentioned collection The History of Neuroscience in Autobiography, published by the Society for Neuroscience (SfN) from 1996 to 2018: 17.5 out of 143 essays are authored by distinguished women neuroscientists, corresponding to about 12% of all chapters by seniors, singles or couples.

The Present: From Admitting the Gender Gap to Initiatives to Reduce It

In recent years many initiatives have been launched to move toward gender diversity in the field of neuroscience.

Society for Neuroscience provides opportunities to empower women scientists and increase awareness for gender bias, through the Women in Neuroscience initiative (WIN), created in 1980. WIN is an international organization that aims at promoting professional advancement and facilitating communication between women working in neuroscience (Haak, 2002).

Women neuroscientists are still underrepresented in books, conferences, and various aspects of academic life. Data from the Women in Neuroscience Repository (WiNRepo) show that women: author significantly fewer papers as first or last contributor than men; - are awarded significantly fewer prizes; - and appear significantly less as speakers in departmental seminar series and conferences (Schrouff et al., 2019). WiNRepo is an initiative aimed at increasing the visibility of women in neuroscience, addressing gender bias through proposed solutions at different levels of intervention, and taking responsibility for promoting equal opportunities to new generations of neuroscientists.

Conscious and unconscious gender bias, combined with widespread sexual harassment in both academia and laboratories, can raise barriers that drive young women away from academic careers (National Academy of Science, 2018). Awareness of any gender biases can be increased by getting data periodically. This is the aim of Bias Watch Neuro, an initiative carried out through a Website

Figure 1 KAVLI prize laureates 2014. Courtesy of the Norwegian Academy of Science and Letters http://english.dnva.no/c42030/index.html.

that tracks the gender ratio among speakers in conferences and authors of papers published in key journals, to raise awareness among the organizers and the neuroscientific community.

Under-represention of women in neuroscience also has implications for the general population, biasing the studies in the medical field, where: women's health is understudied, women are less represented in clinical trials, and many neuroimaging studies come from groups of highly educated white subjects. Female invisibility begins in animal studies on brain disorders, which are more likely to be conducted on male animals (Criado Perez, 2019), and comes to the diagnosis of head injury whose outcomes in women are historically attributed to chronic emotional disorders and, therefore, less investigated with neuroradiological tests, compared to men (Casper and O'Donnell, 2020).

Adequate representation of women in neuroscience can improve by acting on institutional, organizational, cultural, and historical levels.

The achievement of women awaits to be recognized and celebrated to strengthen the tradition of women who pursue research or academic paths and offer new generations equal opportunities in the field of neuroscience.

The Future: Women in Neuroscience After the COVID-19 Pandemic

The scenario that will follow the health emergency of the SARS-CoV-2 pandemic could neutralize the small progress made in recent years to promote a greater presence of women and in general a greater diversity in opportunities to study STEM (Science, Technology, Engineering, and Mathematics) disciplines, to devote to scientific research, to pursue an academic career, to take part in conference panels, and to be awarded international prizes.

The closure of schools and universities to control COVID-19 transmission in 188 countries could have a differential impact on high education and job opportunities of women, who provide the majority of informal care at home (Wenham et al., 2020).

The response policies and practices to the indirect impact of outbreaks such as COVID-19 must, therefore, be effective to not perpetuate or exacerbate gender, cultural and socio-economic inequalities in education and professional career.

Although the World Health Organization (WHO) Executive Board recognized the need to include women in the decision-making process for planning outbreak responses (WHO, 2005), there is currently inadequate representation of women on scientific committees and task forces for COVID-19 appointed by national governments.

This makes it uncertain whether long-term investments are made to foster diversity. However, without any targeted intervention, data on publication records, allocated funds, and career advancements over the next two years will show that women in academia who are also engaged in informal home care were disadvantaged in 2020 (Minello, 2020; Viglione, 2020).

Conclusion

Despite visible and invisible social and cultural barriers, women have reached pioneering milestones in neuroscience since the dawn of this modern discipline. The women neuroscientists who conducted their outstanding research in the early 1900s have been

almost completely forgotten and, with rare exceptions, there is no trace of their work in science handbooks or university textbooks. Few women neuroscientists have been awarded major international awards, just as the percentage of women in the historical collections of eminent senior neuroscientists that extends to the present day is small. Some initiatives have been undertaken to address gender bias, discrimination, harassment, lack of support for work-life balance, and to increase diversity and equal opportunities in accessing scientific research and academic career advancements.

A cultural change, institutional actions, and the promotion of historical projects are among the needed solutions to increase awareness of bias and barriers, and to continue building a safer, diverse, collaborative, and innovative environment for the whole neuroscientific community.

Building a more inclusive environment is not an enterprise that can be left to individuals, it must be planned through a competent, integrated and widespread decision-making process (Chiofalo and Metitieri, 2019), that is even more important to address in light of the new challenges posed by the COVID-19 pandemic.

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Brain Imaging☆

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Introduction

Brain imaging refers to techniques that employ an interaction between brain tissue and various forms of energy (eg, electromagnetic or particle radiation), rather than physical incision, to capture positional data about the structure and function of the brain. Such data are used to create corresponding brain maps. Structural images delineate brain tissues such as white vs. grey matter, vasculature, and bone, based on their physical properties (tissue density or nuclear resonance characteristics). Functional images capture physiological activities in the brain (metabolism, blood flow, chemical composition, absorption) typically coupled to neuronal firing. Functional imaging has two possible aims. In clinical applications the goal is typically to differentiate normal physiological activities in a healthy brain from those in perturbed states (eg, stroke, Alzheimer's disease). In cognitive neuroscience the goal is to understand how brain function mediates human cognition and behavior (eg, memory, language, vision). Attaining these goals depends on the nature of the measured signal, spatial and temporal resolution, and practical constraints such as invasiveness and cost of each technique.

Brain Imaging Techniques

Brain Structure

Magnetic Resonance Imaging (MRI)

The most powerful method of structural imaging today, largely succeeding X-ray dependent computed tomography (CT) in non-clinical settings, is magnetic resonance imaging (MRI). Magnetic resonance imaging is based on nuclear magnetic resonance (NMR), the tendency of certain nuclei to resonate when placed in a magnetic field, independently discovered by Felix Bloch and Edward Purcell in 1940s. In MRI a strong electromagnet, typically 1.5–4.0 Tesla (T) for human imaging, is first used to produce net nuclear magnetization in hydrogen atoms in the body. Radiofrequency pulses are then applied at the resonant frequency of the hydrogen atoms, which displaces them into a higher-energy state (ie, out of alignment with the net magnetization). As the protons then return to their original state they release energy, creating an oscillating magnetic field that can be picked up (via electromagnetic induction) by a conductive coil placed perpendicular to the field. This signal is localized spatially by using a combination of magnetic field gradients in different planes to produce unique spin properties across the brain that can be used to reconstruct the spatial location of the signal source. The contrast in MR images is obtained by modifying the timing of both radiofrequency pulses and signal acquisition to take advantage of natural differences in physical properties of the different tissues, such as the time needed for the tissue to

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return to the net magnetic field after excitation. Typical MR images capture detailed 3D structure of the brain distinguishing between tissues such as grey and white matter, cerebrospinal fluid, bone, fat and air, as well as being able to detect the presence of abnormal tissues such as tumors or cysts.

An advantage of MRI is its extreme flexibility in the types of signals that it can measure (**Fig. 1**). *Diffusion* MRI includes a family of imaging sequences optimized to detect movement of water molecules over time. The measurement of directional diffusion signals facilitates characterization of white matter structure in the brain. White matter comprises axonal projections of neurons, the fiber tracts that connect different brain regions. Diffusion MRI is therefore the basis of MRI-based tractography methods for imaging structural connectivity of the brain. When used to measure overall diffusion this family of techniques is very sensitive to changes that occur early in stroke and other neurological disorders. In complement, *perfusion* MRI encompasses imaging methods that monitor the passage of a contrast agent through selected brain tissue, to derive kinetic parameters such as cerebral blood flow and volume, and mean transit time. Changes in these parameters can be used to detect abnormal tissue, such as tumors, which are associated with greater vasculature, and blood volume, than gray matter. Arterial spin labeling (ASL) is an example of perfusion MRI that is particularly advantageous because the contrast agent is created by magnetically tagging arterial blood water prior to imaging it within the tissue of interest. In comparison to an image of the same tissue without a magnetic tag, ASL allows for derivation of blood flow parameters without a need for an externally administered contrast agent (eg, gadolinium, also see **PET, SPECT** below). The combination of diffusion and perfusion MRI can be used to detect stroke and other cerebrovascular disorders. MRI spectroscopy techniques measure yet another family of signals based on the attachment of hydrogen protons to other molecules that reveal regional concentration of specific metabolites (eg, choline, creatine, glutamate, glucose). Concentration differences can be used to assess neural cell integrity and energy metabolism. Finally, one of the most powerful applications of MRI is to measure brain function (see **fMRI** below) by measuring changes in oxygenation of hemoglobin in the blood.

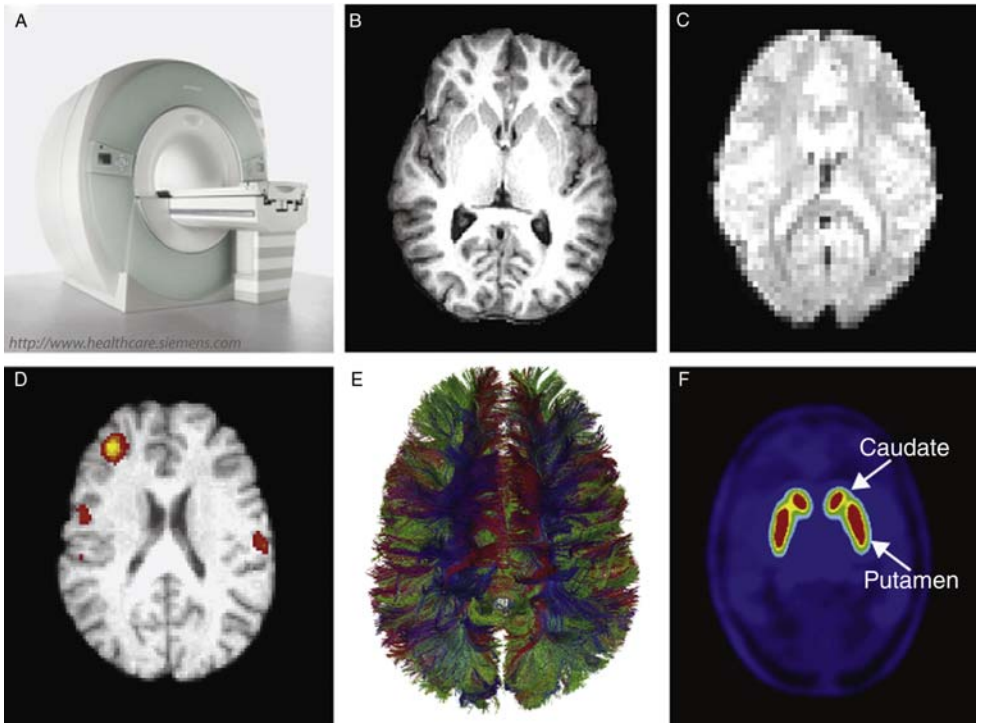

Figure 1 Maps of the brain vary with the type of signal detected. In (A) magnetic resonance imaging (MRI), the signal typically arises from variation in magnetic properties of hydrogen atoms across different brain tissues, producing (B) high-resolution (~1 mm) structural images that delineate structures such as *white* vs. *grey* matter, deep nuclei, bone and ventricles. MRI can also be used to detect brain function by measuring the oxygenation level of blood hemoglobin. The resulting images (C) are of lower resolution (~3 mm) at the gain of higher temporal resolution. Comparisons of the resulting images across tasks or states reveal (D) the locations of task-specific changes in brain metabolism. Localization of these changes is improved by overlaying the activation maps onto a structural image. (E) Diffusion MRI is sensitive to hydrogen movement within *white* matter, which can be used to map fiber tracts that connect *grey* matter in the cortex. An alternate measure of brain function is shown in (F). Here the binding potential of D2-like dopamine receptors for the radioactive tracer [^{18}F] fallypride is revealed using positron emission tomography (PET). The density of the receptors increases (hot colors like *red* and *yellow*) in caudate and putamen structures of the basal ganglia compared to other parts of the brain (*blue*). Figure (D) has been provided courtesy of E. London, UCLA. Figure (E) has been provided courtesy of J. Brown, UCSF.

Brain Function

Electro- and Magnetoencephalography (EEG, MEG)

Electroencephalography (Fig. 2), first described by Hans Berger in 1924, and more recent MEG, first introduced by David Cohen in 1968, measure electrical signals resulting directly from post-synaptic potentials in the apical dendrites of Pyramidal neurons of the cortex. Such potentials produce currents running along the length of the neuron that summate across neuronal assemblies due to the parallel configuration of such neurons (ie, creating electrical dipoles). This summation produces a measurable voltage (V) potential at the scalp surface, measured by EEG. Perpendicular to these currents arises a magnetic field that also summates across neurons and is measured by MEG. In EEG changes in scalp voltage potential are measured by electrodes placed on the scalp, in a montage of between 32 and 256 equidistant electrodes. Changes in voltage (approximate range of 10–100 μV) can then be recorded across time at each of the electrodes. In MEG magnetic fields at the scalp are measured using a superconducting quantum interference device (SQUID) containing highly sensitive detectors, mounted within a helmet that surrounds the scalp surface, that translate the magnetic field back into current values. SQUIDS are necessary because the summed magnetic fields produced by pyramidal neurons are small, about 10 fT (femtoTesla), while noise in daily urban environments (ie, cars, power lines) averages between 10^6–10^9 fT.

In both modalities the resulting signals can be used to monitor brain activity across time. In the continuous signal, changes in frequency composition of the signal are associated with transitions between stages of sleep, alertness and awareness during anesthesia. In both EEG and MEG, these signals can also be assessed during a time window associated with a cognitive event of interest to reveal the timing of processes associated with that event (ie, event-related potentials, ERPs). For instance, a visual flash produces changes in the potential within 100–150 ms that correspond to early sensory processes that precede identification of type of flash or response generation. These cognitive indicators, ERPs, can be used to establish *when* along the processing pathways errors occur if an individual fails to correctly process the visual flash. In complement, this event-related analysis can be performed in the spectral domain to identify changes in power across frequencies following the event (ie, event-related spectral perturbations, ERSPs). Visual processing of a stimulus such as a visual flash will, for instance, reduce the power in 8–12Hz oscillations in the M/EEG signals. Because oscillations in M/EEG signals are though to be directly related to the synchronization of firing within neuronal populations in cortex, and because such synchronization arises through unique interactions of inhibitory and excitatory neurons, changes in spectral power captured by M/EEG have the potential to describe and quantify neural population dynamics—an active domain of neuroimaging research.

Positron Emission and Single Photon Emission Computed Tomography (PET, SPECT)

The advent of nuclear medicine in the 1940s and 1950s and subsequent developments in production of radioactive isotopes and gamma ray detectors have contributed to emission computed tomography modes of brain imaging. These methods include PET and

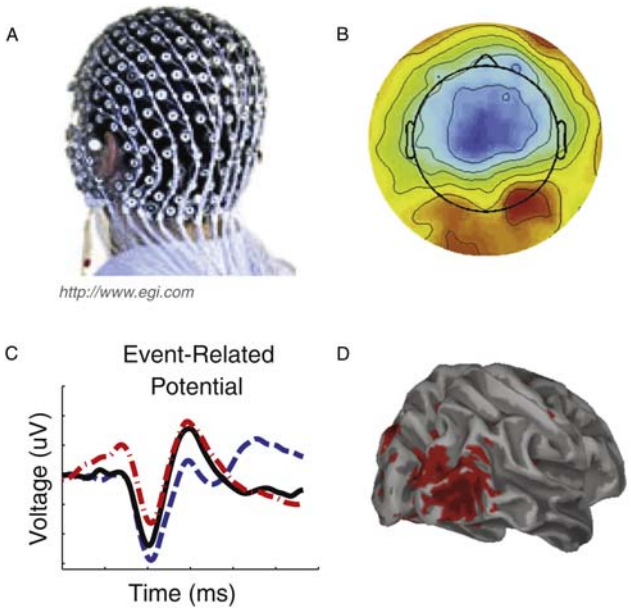

Figure 2 High temporal resolution of brain activity is provided by (A) electroencephalography (EEG), as well magnetoencephalography (MEG, not shown) both of which measure electrical activity produced in the cortex. In EEG the data are sampled using electrodes that rest on the scalp (A), typically embedded in a cap. The signals at each electrode can be used to provide topographic maps of the potential distribution on the scalp (B), which evolve and change with sub-second resolution. The evolution of electrical potential with respect to an event, referred to as event-related potential (ERP), at a single electrode across three conditions is shown in figure (C). The spatial resolution of EEG is limited to the scalp and locations of the neural activity in the cortex can only be obtained through analytical modeling. These so-called "source models" provide estimates of the signal source locations (D). However these models are inferior in accuracy to the high spatial resolution offered by MRI techniques (**Fig. 1**).

SPECT. They are used to measure either blood flow and/or metabolic processes in the brain by measuring radiation energy emitted from radioactive isotopes that are intravenously injected, and subsequently distributed by the circulatory system of the brain. In PET, isotopes can be created to measure blood flow (eg, ^{15}O), blood volume (eg, ^{11}CO) or metabolic operations such as glucose metabolism or dopamine synthesis (eg, ^{18}F). As these isotopes are circulated in the brain they release positrons that collide with an electron, annihilate and release two gamma rays traveling in opposite directions. Coincidence detectors determine the source of the collision and the number of collisions occurring, providing information about location and concentration of that compound in the brain. From this information, a three dimensional image of the metabolic effects on the radioactive isotope in the brain can be reconstructed. For instance, glucose labeled with ^{18}F has been effectively used to measure increased glucose metabolism in visual and auditory sensory cortices in response to visual vs. auditory stimuli respectively, and in motor cortex during finger tapping movements. Changes in metabolism across various areas of the cortex can also be tracked, for instance as a function of metabolic maturation during development or with the progression of disease. A similar process applies to SPECT, however single photon emission isotopes (eg, ^{123}I, ^{111}In) are used instead of positron-emitting isotopes and the detectors are gamma cameras designed to measure single photon emission rather than coincidences. Unlike PET, SPECT isotopes have been developed primarily for measurement of cerebral blood flow changes, not metabolic processes. Thus while this technique can detect the effects of a stroke on blood flow patterns, it cannot detect functional changes in which blood flow is less affected than metabolism, such as altered synthesis of the neurotransmitter Dopamine in Parkinson's disease.

Functional Magnetic Resonance Imaging (fMRI)

Although MRI has been in use since the 1970s and has many applications in structural imaging, its application to measuring brain *function* (rather than structure) was not possible until 1990 when Seiji Ogawa and colleagues demonstrated that the oxygenation state of blood hemoglobin modulates MRI signal around large veins. This finding resulted in development of MRI sequences sensitive to changes in blood flow in the brain, without the need for any exogenous contrast agent to be injected. In functional MRI, the contrast arises from the effects of deoxygenated hemoglobin on the magnetic field. As demonstrated by Ogawa, when blood hemoglobin lacks oxygen it has magnetic properties that disturb the effects of magnetization in its vicinity and thus lowers the measured signal. In contrast, when hemoglobin is oxygenated it has less effect on neighboring molecules and thus produces a net larger signal during an MRI scan. The utility of this finding to measuring brain function is that both blood flow and local hemoglobin oxygenation increase in response to neuronal activity, thus increasing the local MRI signal. This is referred to as the blood-oxygen-level-dependent (BOLD) signal. While there are other ways to measure functional activity with fMRI, BOLD-fMRI is by far the most popular method. The BOLD response provides a robust but indirect measure of brain activity and, like PET, can detect active regions during perceptual and cognitive tasks in both healthy and diseased brains.

Functional Near-Infrared Spectroscopy (fNIRS)

The blood oxygenation response that accompanies brain activity can also be quantified using near infrared light. In the infrared range of the light spectrum, skull tissue is transparent, whereas oxygenated hemoglobin and deoxygenated hemoglobin absorb some of the light, but to a different extent. Emergent light can thus be used to monitor the relative levels of oxygenated and deoxygenated hemoglobin. The fNIRS technique exploits this phenomenon, using an arrangement of optodes placed on the skull, similar to EEG, to direct near infrared light through the skull and brain tissue. The light is emitted with either light emitting or laser diodes, and detected emerging from nearby skull and tissue by using a photodiode or photomultiplier tube. The emitter–detector pairs cover the surface of the skull to produce a tomographic image of oxygenated, deoxygenated and total hemoglobin in the blood. This signal reflects the metabolic response of the cortex and can be interpreted in the same way as BOLD-fMRI signals.

Applications

While the nature of the signal characterizes broadly the utility of neuroimaging techniques, their dominant applications are ultimately constrained by spatial and temporal resolution as well as practical constraints, such as invasiveness or cost, of each technique.

Spatiotemporal Resolution

Imaging techniques vary in both spatial and temporal resolution, which constrains the types of questions that they can answer within their imaging domain. For structural imaging, high spatial resolution is the primary objective (since structures are relative immutable over time, with change over the course of months to years), whereas functional imaging requires high spatial and temporal resolution (since neuronal function occurs over milliseconds at a spatial scale of microns). Functional imaging modalities fall into two categories: those that directly reflect neuronal activity (EEG/MEG) and those that measure metabolic processes associated with neuronal activity (fMRI/fNIRS/PET). These categories are also defined by trade-offs between spatial and temporal resolution. The former (EEG/MEG, c.f., **Fig. 2**) provide excellent temporal resolution (<0.04 s) but low spatial resolution ($\sim$10 mm), whereas the latter provide better spatial resolution (fMRI: 1–5 mm, PET: 4–8 mm) at the cost of temporal resolution (fMRI: $<$1–6 s, PET: 60–1000 s). An exception is fNIRS, a metabolic technique, which offers better temporal resolution than its competitors (0.1–0.5 s), with some loss to spatial resolution (5–10 mm).

The differences in spatiotemporal resolution determine how the two categories of methods are applied. EEG and MEG are well suited to examine the dynamics of brain function because they provide continuous and temporally precise measures of neuronal activity. One application of such data is for monitoring of brain states. For instance, the EEG signal is useful in diagnosing the quality and type of sleep that an individual engages in during the course of a night, or in monitoring the alertness of an individual in an anaesthetized state. Both EEG and MEG can also be used to analyze the dynamics of brain function. For instance, the processing sequence of an audiovisual stimulus can be obtained by comparing the timing of signal over visual vs. auditory cortices following stimulus onset. The questions that EEG and MEG can answer are thus tied to the idea of *when* processes happen and only coarsely related to where they happen.

In contrast, PET and fMRI can answer the question of *where* better than the question of *when* neuronal activity occurs. Both techniques provide spatial resolution under 10 mm, with fMRI potentially providing resolution down to 1–2 mm. This implies that these techniques are more accurate in localizing where within the visual and/or auditory cortex the audiovisual stimulus is processed. If the visual stimulus involves motion, for instance, it will produce the strongest activity in region V5/MT of the visual cortex relative to other visual processing regions such as V1 or V4. Unlike EEG or MEG, these techniques do not dissociate which perceptual modality was processed first, visual or auditory, because such processing occurs at the time scale of milliseconds, well below that of either PET or fMRI. Finally, fNIRS offers considerably poorer resolution than fMRI or PET, with its view limited to superficial structures of the brain (ie, within 10 mm of the surface of the brain). While its temporal resolution appears to be better than either fMRI or PET, it remains poorer than EEG or MEG and, combined with the loss in spatial resolution, render this imaging modality inferior in most circumstances. Its applications are thus largely determined by yet another factor, practical considerations.

Practical Considerations

The utility of imaging methods, particularly in the functional imaging domain, is also influenced by two practical considerations: invasiveness and cost. The invasiveness of a technique has the effect of distinguishing between clinical and cognitive neuroscience applications. This is apparent in the comparison of PET and SPECT with EEG, MEG, fMRI and fNIRS. The former rely on radioactive isotopes that must be injected into the bloodstream, and thus are invasive techniques. The latter use intrinsic signals to quantify function. Reliance on radioactive isotopes has two effects, both of which make PET and SPECT unsuitable for most cognitive neuroscience applications. First it increases health risk, which is less easily justifiable by the benefits of basic research relative to clinical applications. Second, invasiveness has the effect of constraining the amount of data that can be acquired. This is undesirable because the neural signals related to cognitive processes are often relatively small, and many repeated observations are required to maximize the power and interpretability of the experimental results. However sampling is restricted in both PET and SPECT because safety concerns about side-effects of radiation limit the number of times that an individual can be tested, and because the number of scans obtained within a session is constrained by the distribution time and half-life of the isotope. For instance, for ^{15}O with half-live of 2.03 min, approximately 60 s are required for the isotope to circulate throughout the brain and 10 min are required between dosage injections (ie, 5 half-lives) for most of the isotope to be eliminated from the body between scans. In a 60 min session no more than six scans can be administered with 60 s temporal resolution. EEG, MEG, fMRI, and fNIRS are not limited in the amount of data that can be collected on an individual, and thus are more suitable to cognitive neuroscience applications.

Cost also has a role in the utility of imaging methods. For instance, whereas PET is considerably more accurate than SPECT, the latter is cheaper and uses more easily accessible isotopes. Its availability makes it a more common tool in clinical settings. EEG and MEG are less disparate in quality, but the necessity for SQUIDs as detectors in MEG make it much more costly than EEG. Consequently EEG is more prevalent than MEG in both clinical and research settings. MRI, in contrast, is relatively common in both clinical and research settings making it both a popular and accessible tool. Its higher spatial and temporal resolutions make it a more powerful imaging modality than fNIRS, even though the two measure the same type of signals. However, a new set of practical considerations is emerging that may increase the utility of fNIRS relative to fMRI. Unlike fMRI, fNIRS is relatively robust to head motion. This property becomes very important in studies of individuals who are unable to remain still for the duration of an fMRI scanning session. This may include infants and children, and special populations such as children and teens with attention deficit hyperactivity disorder or motor tic disorder, which are characterized by movement. Functional NIRS as an imaging modality thus has a presence in studies of brain development in infants and young children.

An emergent constraint on the applications of brain imaging modalities has surfaced with an increasing presence of neural imaging in the popular domain, including an increase in personal medicine tools, so-called brain training programs and a growing interest in neurofeedback. The desire to bring neuroimaging technology into an office, school or home setting has defined *portability* as an important distinguishing factor between the imaging modalities. Modalities like PET, SPECT, fMRI and MEG are not portable and are unlikely to become available to the average consumer. In contrast, EEG and also fNIRS are relatively cheap to manufacture, are small and can be adapted to record robust signals in most recording environments, making them excellent choices for real-life applications.

Challenges and Future Directions

Current spatial and temporal resolution of neuroimaging methods defines bounds on the information available about brain structure and function. In MR imaging of brain structure the limitations are dictated primarily by technology. For instance, magnet

strength and sequence design determine the signal to noise ratio (SNR) and availability of tissue contrast, and these dictate ability to resolve grey versus white matter, white matter fiber tracts in DTI or types of metabolites visible in MRS. It is standard for MR hardware to operate at 3 T magnetic strength, but extensive testing has been performed at 7 T. At this higher-strength magnetic field, spatial resolution can increase to 450 μm (and 2 mm section thickness), thus also increasing resolution of DTI images, and that can directly benefit resolution of fine anatomical structures such as hippocampal abnormalities in epilepsy. Novel contrast mechanisms are available to allow depiction of microvasculature, microbleeds and calcium and iron deposits, facilitating, for instance, detection and identification of tumors or pathologic increases in iron-deposit in multiple sclerosis. In MRS, greater SNR facilitates imaging of nuclei other than protons, such as sodium-23 or phosphorus-31 that can lead to study of novel metabolic pathways. Challenges at ultra high fields such as 7T include magnetic field inhomogeneity, which affects the stability of the images, cost including improvements in shielding and additional hardware development, transitory physiological effects such as heating and dizziness, and noise levels.

In functional brain imaging resolution limitations are affected by technology, but their primary cause lies in underlying signals. For instance in PET, in which coincidence detectors can measure data from the entire brain volume simultaneously, resolution depends on the size and quality of the detectors and on the processing speed at which they can record the data, both of which can be improved. This is also true for SQUIDs used in MEG. In EEG, spatial montages now exist to acquire data from 256 electrodes sampling most of the surface of the scalp. In fMRI, spatial resolution has traditionally varied inversely with the number of samples acquired. To collect data quickly enough to capture the 4–6 s BOLD response, the hardware would sacrifice spatial sampling to produce a resolution of 4–5 mm (relative to MRI at 1 mm), while only reaching a temporal sampling rate of 0.5–1 Hz (1–2 s resolution). However the development of multiband imaging sequences has improved the temporal resolution more than 10-fold to sub-second, making it comparable to the temporal resolution of fNIRS. Thus technological limitations on spatiotemporal sampling across these modalities are steadily being eliminated.

The primary constraints in resolution of functional images are characteristics of the signal measured. The BOLD signal measured using fMRI and the oxygenation-dependent hemoglobin signals measured by fNIRS are both limited by the time constant in the metabolic response to neuronal activity, which obscures neuronal dynamics regardless of speed at which this response is sampled. Therefore the network interactions that occur between cortical regions at the *sub-second timescale* are not directly accessible using fMRI or fNIRS, regardless of sampling rate, and can only be analytically inferred. In complement, in EEG the measured signal, generated by neuronal population in the cortex, spreads passively from its source, and is distorted by the dura, scalp and skull. As a result, the signal measured at any given EEG electrode represents a mixture of signals arising from, possibly, many cortical locations and the *location* of a neural signal in EEG, and to a lesser extent MEG, cannot be directly accessed, but can only be analytically inferred (**Fig. 2**). Furthermore, EEG, MEG and fNIRS, are preferentially sensitive to superficial cortical signals, with signals generated in deep nuclei largely obscured.

The resulting trade-off between spatial and temporal resolution in these functional techniques is unlikely to be addressed by technological innovations in existing neuroimaging modalities. Novel neuroimaging technology may be required to allow for measurement of whole-brain network dynamics occurring at sub-second time scales. An alternate and more immediate solution is to combine technologies either through simultaneously recording from different modalities, or by using the data from one modality to improve the interpretation of another. Spatially resolved MRI images can improve EEG spatial resolution by facilitating reconstruction of realistic head models to estimate conductivities throughout the scalp, skull and dura. Such models can then be integrated into deblurring algorithms designed to decrease the attenuating effects of these structures on the EEG signal. Due to the complementary nature of the signals recorded, simultaneous recording from EEG and MEG can improve the sampling and thus spatial resolution of the underlying neuronal activity. It is now also possible to acquire EEG data simultaneously with fMRI data. Although technically challenging, this strategy has shown success in providing correlational evidence to link sub-second visual processes with the activation of visual cortex and visual networks, as well as in localizing epileptic events of millisecond duration (eg, interictal spikes), readily visible in the EEG signals, to cortical sources, readily visible in fMRI data. Similarly, within the MRI modality integration across structural and functional data has been employed effectively to enhance information extracted regarding brain structure or function. For example, high-resolution MRI structural images are often used to localize the sources of activity in low-resolution fMRI images. Registration algorithms can align the two data sets in space and across time, allowing researchers to infer the location of a lower resolution (3–4 mm) BOLD signal on a higher resolution (1 mm) MRI structural image. Similarly diffusion MRI and fMRI can be combined to define the bounds on functional regions by comparing the parameter of activation in a given region as measured by fMRI, with the connections that it makes to another region as measured by DTI. As such, multimodal imaging, which currently broadly describes integration of data across imaging modalities (EEG versus MRI) or imaging categories within a technique (structural versus functional MRI), will continue to play a significant role in future developments in neuroimaging.

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Gray Matter Analysis of MRI Images: Introduction to Current Research Practice

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Introduction

The neuroanatomical architectures that underlie function, cognition, and consciousness are at the foundation of neuroscience research. This includes research into neuroanatomical changes across the lifespan, from development through adulthood to aging. Magnetic Resonance Imaging (MRI), a non-invasive imaging method, enables in vivo studies into these core questions with humans. Different MRI sequences are designed and optimized to capture different structural properties of the brain tissues, brain morphometry, brain microstructure, and structural connectivity. Structural connections between brain areas are modeled by tractography through diffusion-weighted MRI (dMRI; Basser et al., 1994; Warach et al., 1992). Brain microstructures such as myelination, glia cell density, and free water content can be captured by a recent methodology, multi-parameter mapping (MPM; Weiskopf et al., 2013; Carey et al., 2018). Brain morphometric parameters including volume, cortical thickness, surface area, and gyrification index are calculated by T1-weighted imaging (Ashburner and Friston, 2001).

The brain morphometric parameters reflect local architecture such as the number of neurons, myelination, and synaptic density, which shape neural dynamics and functions. T1-weighted imaging is the most common approach in sMRI to extract such morphometric features of the human brain. Different concentrations of water, lipids, and other molecules affect the tissue responses to an energy perturbation of a radio frequency pulse. This results in different signal intensity which is measured by MRI.

Different brain tissues such as gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) contain distinctive compositions. In T1 weighted images, white matter is brighter than gray matter reflecting stronger signals. This is potentially due to the high concentration of the lipid-enriched substance (myelin) in white matter, while gray matter contains cell bodies of neurons and has a relatively higher concentration of water. GM mainly contains cell bodies of neurons, showing lower signal intensity compared to WM. Using these signal variations among brain tissues, the tissues are computationally segmented. Brain morphometric parameters are calculated with voxel-based morphometry (VBM) and surface-based morphometry (SBM); VBM estimates brain volume size, while SMB estimates cortical surface area and thickness by modeling cortical layers.

Morphometric analyses have been used to observe neuro-structural correlates of neurological and psychiatric disorders such as Alzheimer's Disease (Ferreira et al., 2011), major depressive disorder (Bora et al., 2012), and Parkinson's disease (Pan et al., 2012) as well as neuro-structural correlates of individual differences in aging (Fjell et al., 2009; Boller et al., 2017; Walhovd et al., 2016), intelligence quotient (IQ; Shaw et al., 2006; Narr et al., 2007; Schnack et al., 2015; Schmitt et al., 2019), executive functions (Weise et al., 2019), and personality traits (Riccelli et al., 2017; Vartanian et al., 2018). An interesting implication from morphometric MRI studies is that the relationship between brain morphometry and IQ varies across life-span. In early adolescent periods, higher IQ groups show a higher degree of cortical thinning (Shaw et al., 2006; Schnack et al., 2015). However, the relationship is reversed in older age, and a positive correlation between cortical thickness and IQ emerges (Schnack et al., 2015). Therefore, morphometric MRI analysis is useful to detect not only the association between brain structure and function but also longitudinal changes in the functions in brain structures.

Despite a large number of published structural MRI studies, some researchers pointed out that the replicability and the statistical validity in those reports are questionable (Open Science Collaboration, 2015; Boekel et al., 2015; Gray et al., 2018). Furthermore, the importance of pre-registration of experiments and data registration for open science is now increasingly recognized (Nature Human Behaviour, 2017, 2018; Nosek et al., 2018, 2019). Multiple groups such as open science framework (OSF; Foster and Deardorff, 2017), Openneuro (Gorgolewski et al., 2017), and the Brain Analysis Library of Spatial maps and Atlases

(BALSA; Van Essen et al., 2017) have started to support pre-registration and data registration. These practices are expected to enhance transparency in MRI studies. However, these practices are still under development, and some ambiguities become apparent in practical applications, including unbiased and justifiable hypothesis construction and determination of the expected effect size.

In this article, we describe two standard methods used in brain morphometry based on T1-weighted images. Then, we touch upon general issues of replicability, which is also pertinent to morphometric MRI studies, and discuss pre-registration and data registration as countermeasures.

Morphometric Analysis of Structural MRI

There are two major methods for analyzing brain morphology: voxel-based (VBM) and surface-based morphometry (SBM). The former is based on a voxel-by-voxel comparison of T1 structural images and the latter on cortical surface models. These morphometries quantify regional brain volume, cortical thickness, and surface area. For sub-cortical regions, only volumetric measurements are available at the time of writing. Multiple research teams have been developing automated analysis tools for VBM and SBM (**Table. 1**). Although slight methodological variations exist across tools, the basic concepts and procedures are similar. The conceptual scheme is summarized below.

The analysis of structural images can be divided into two steps: preprocessing and statistical analysis. The preprocessing steps are aimed at cleaning and standardizing the dependent variable (e.g., the gray matter's feature examine). The measurement standardization ensures the values in each voxel are comparable across scanning sessions and/or participants. This is because MRI raw signal is a relative signal (depends on local variables of the scanning session, like temperature). The values need to be standardized to enable meaningful comparison across scans. A spatial standardization ensures that voxels are aligned in space. This enables comparisons across participants, as neuroanatomical structures are aligning to each other in the 3D space. Spatial standardization also enables comparison across studies and labs. There are two main standardized neuroanatomical spaces: the Montreal Neurological Institute (MNI space) and the Talairach space. The two spaces are similar but not identical (Laird et al., 2010). The formula can be used to convert coordinates between the two standard spaces. Statistical analysis is used to test for associations between the independent measures (i.e., experimental factors, like age, a personality trait, IQ, behavioral performances) and the dependent measure (gray matter's feature).

Preprocessing of sMRI

Voxel-Based Morphometry (VBM)

There are four main pre-processing steps to perform VBM: segmentation, registration, normalization, and spatial smoothing (**Fig. 1**A).

Step 1. In the segmentation step, GM, WM, and CSF are classified based on their relative signal intensity (Zhang et al., 2001; Ashburner and Friston, 2005). For example, in T1-weighted images, the strongest signal is measured in white matter (represented a light gray), gray matter omits weaker signal (depicted darker gray shades) and CSF is even weaker (depicted in dark gray/black shades). An automated algorithm classes the voxels to different tissues based on their signal intensity. In some software (e.g., SPM12, CAT) a unified-segmentation algorithm is used. This algorithm utilized the known architecture of brain anatomy structure of the brain (e.g., two hemispheres, gray matter is along the surface of gyri and sulci, white matter underneath, CSF is

Table 1 Available software for morphometric MRI analyses

Analysis methods	*Software (algorithm)*	*Affiliation*	*URL*
VBM	FSL (FLIRT and FNIRT)	The Analysis Group, FMRIB, University of Oxford.	https://en.wikipedia.org/wiki/FMRIB_Software_Library
	SPM12 (DARTEL)	The Welcome Centre for Human Imaging.	https://www.fil.ion.ucl.ac.uk/spm/software/spm12/
SBM	ANTs	Brian B. Avants, Nick Tustison and Hans Johnson.	http://stnava.github.io/ANTs/
	Brain Visa	CEA/NeuroSpin	http://brainvisa.info/web/index.html
	Brain Voyager	Brain Innovation B.V.	https://www.brainvoyager.com/index.html
	CAT12	The Structural Brain Mapping Group at the Departments of Psychiatry and Neurology.	http://www.neuro.uni-jena.de/cat/
	Connectome Workbench	Van Essen Lab at Washington University in St. Louis	https://www.humanconnectome.org/
	FreeSurfer	MGH Athinoula A. Martinos Center for Biomedical Imaging.	https://surfer.nmr.mgh.harvard.edu/

ANTs: Advanced normalization Toolboxes, CAT12: Computational Anatomy Toolbox 12, FSL: FMRIB software library, FLIRT: FMRIB′ Linear Image Registration Tool, FNIRT: FSL nonlinear registration tool, Statistical Parametric Mapping 12 (SPM12). Note: Connectome Workbench succeeds CARET, and also utilizes FreeSurfer for SBM.

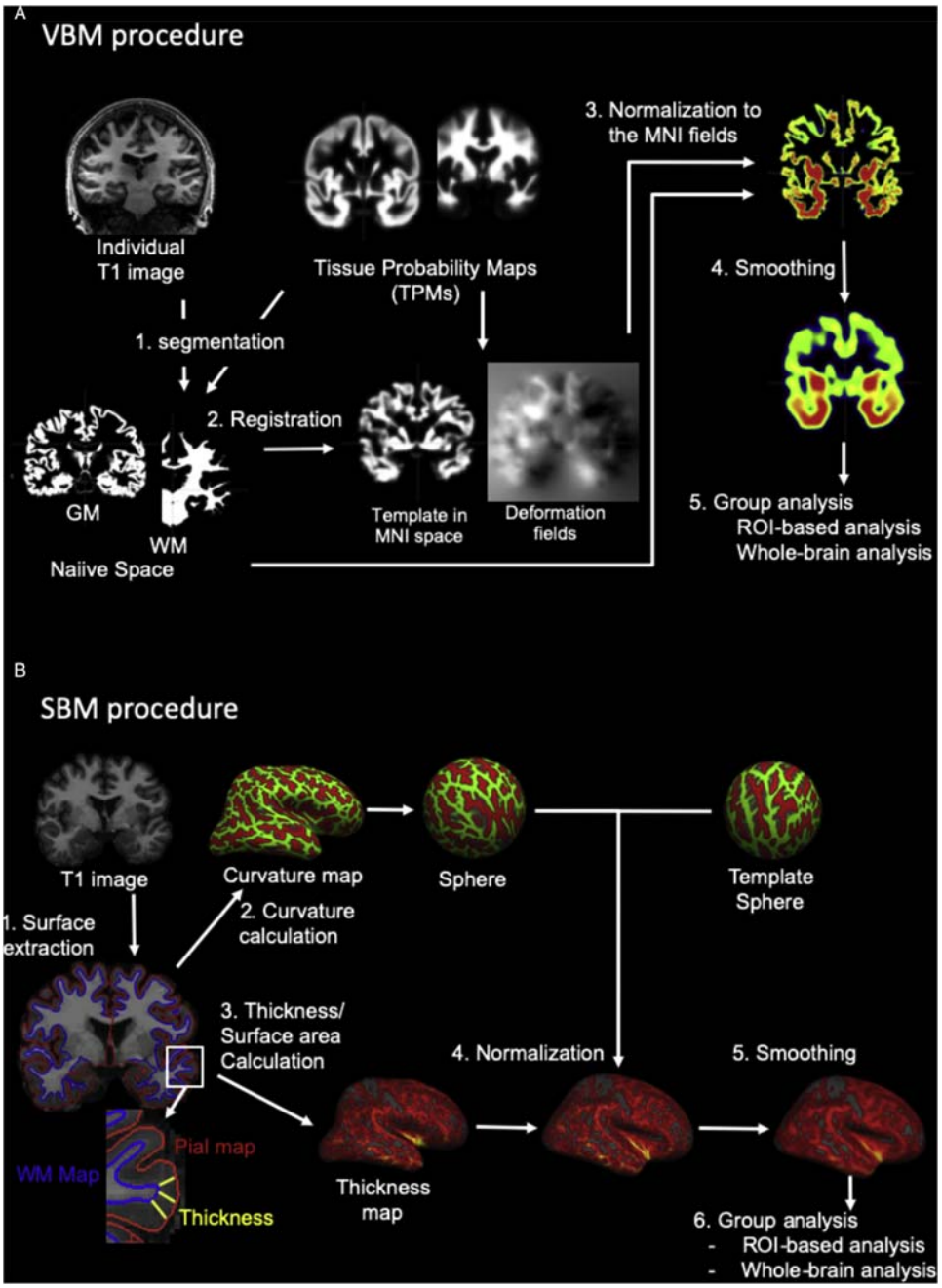

Fig. 1 (A) VBM preprocessing. Step 1: A T1 anatomical image is first segmented into gray matter (GM) and white matter (WM) with tissue probability maps (TPMs) in the naive space. Step 2: Segmentized images are secondly registered to templates with affine linear transformation. Additionally, deformation fields are calculated to fit the T1 image to the templates in the template space. Step 3: In doing so, the T1 image is normalized with the deformation fields. Step 4: The normalized T1 image is smoothed with a Gaussian kernel. Step 5: After the completion of pre-processing, group analysis will be performed. (B) SBM pre-processing. Step 1: A T1 image is graphically modeled as a pial map and a WM map. Step 2: A cortical folding pattern, curvature, is calculated and mapped on the original space. Furthermore, the curvature map is deformed into a sphere for the normalization. Step 3: Cortical thickness between the pial and WM maps and surface area are estimated using the models. Step 4: Using estimation of Jacobian determinants of the sphere in the original space onto the template sphere, normalization is performed to deform thickness and surface area maps. Step 5: Surface smoothing is executed with the normalized image. Step 6: Finally, the smoothed image is further processed for group analysis.

in the ventricle and around the surface). This information is presented in anatomical templates, known as a-priori tissue probability maps (TPMs). An iterative process of segmenting and matching to the a-priori template is used to optimize the segmentation process. The unified segmentation algorithm can also be used to normalize the images to the standard spatial space.