From discovering to better understanding the relationship between brain and behavior.

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Abstract

This study reviews the relationship between brain and behavior, starting from its discovery through to the localization of various functions in specific brain regions and concluding with the specialized role of the basic neural networks. Delving into the journey of this relationship over the centuries, one can see the factors that hindered or facilitated its development, while gaining opportunities for further reflection and some guidelines for future research.

Keywords: Brain-behavior relationship, Encefalocentric theory, Functional localization, Hemispheric specialization, Cognitive functions, Neural networks

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Introduction

Humans have always had the tendency to observe events occurring in their environment and explain them. This systematic involvement and the development of investigative methods for various phenomena have led to the emergence of several scientific fields and the knowledge we possess nowadays.

The present study focuses on interpretations of behavioral phenomena over the centuries and on the factors contributing to them. Although the role played by the brain in behavior had been recognized since antiquity, it took a long time for this relationship to become widely accepted. Brain-behavior relationship was established as a result of accumulation of scientific evidence and has only recently been founded as an independent scientific field.

The phrase of German psychologist Hermann Ebbinghaus *''psychology has a long past but a short history''* [1] can also be applied to neuropsychology, as many centuries have lapsed between its birth as a concept and its establishment as a science. The purpose of this study is to describe the stages that brain-behavior relationship went though over the centuries, focusing on the knowledge revealed at each one.

The Origins of Brain-Behavior Relationship

Somatic and psychic phenomena were a common area of interest for ancient groups. The earliest interpretations involved supernatural forces, and treatments used to comprise herbs, prayers, and trepanation of the skull. Trepanation led to the exposition of dura mater outwards in order to release the evil spirit regarded as the cause of abnormal behavior. This practice constitutes the first human brain surgery and, according to archaeological findings from all continents, it dates back to the prehistoric period [2]. By conducting dissections, first the Ancient Egyptians and then the Greeks began to understand the function of body organs and introduced organic-based disease interpretations. The fundamental bases of western medicine were set at that time, in contrast to the medicine of the Asian world, which showed little interest in the morphology and function of organs, while maintaining an energetic and holistic perspective of disease through the centuries [3]. The differential point between the two approaches was definitely the role of the brain, since it was quickly recognized as a major organ of the body by the former, whereas it was ignored and excluded from body organs by the latter [4].

The first historical reference to the word ''brain'' is found in the Egyptian scroll of Edwin Smith, written in 1700 BC, though the texts date back to around 3000 BC [5]. It is the oldest medical text where a rational, scientific, and largely free from mysticism approach of traumas, injuries, and tumors is attempted. Forty-eight cases of patients are cited with detailed descriptions of examination, diagnosis, and treatment. However, although brain injuries are linked with kinetic symptoms, a systematic connection between brain and behavior was to happen much later by some pre-Socratic philosophers-scientists developing the encefalocentric theory (the word *''encephalon''* meaning brain).

Alcmaeon of Croton, a pupil of Pythagoras, was the first to research brain function [6]. By dissecting the *''pores''*, as he named the sensory nerves, he correctly predicted their role. In particular, with the phrases ''*the hegemonic is in the brain''' and ''all our senses are connected to the brain'',* he identified the brain as the central organ of intellect and sensory perception [7]. Later, Hippocrates of Kos agreed with Alcmaeon, but he additionally associated the brain with emotional and mental disorders. He examined epilepsy in animals and with the phrase ''*the brain is the cause of this disease, as well as other major diseases*", he demystified their nature [8]. Also, he observed that a wound on one side of the brain causes spasms on the opposite side of the body. Stating that *''intellect and emotion come from the same power''*, his contemporary, Democritus of Avdera, attributed intellectual as well as emotional function to the brain [9]. Therefore, the brain had been identified as the central organ of many functions since the 6th century BC. A novelty for that era was the separation of natural from supernatural and the adoption of scientific methods, such as systematic observation and experimental research, for investigating physical and mental phenomena. According to Kostopoulos, these bold ideas were developed in the wider geographic region of the Hellenic world (Southern Italy, Ionia, Thrace and later, Alexandria), where there was social tolerance for dissections of corpses, and not in the mainland**,** where only accepted sciences flourished. Thus, philosophical-scientific thought was divided between the encefalocentric theory and the already existing cardiocentric theory (the word *''cardia''* meaning heart).

The idea that the heart was the central organ of body control and the physical location of the soul was rooted in ancient Egypt and, more specifically in its mummification techniques. During mummification the heart was carefully kept, while the brain was cast out from the human body [10]. By combining the knowledge resulting from body dissections with their religious beliefs about reincarnation, the Egyptians attributed the greatest role to the heart. For them, it was linked to all parts of the body via canals called *''metu''* that carried blood, food, gases, tears, and other body secretions; the blockages within those canals constituted the cause of disease [11]. As the source of feelings, wisdom, memory, desires, and the entire personality, the heart was given back to the dead in the afterlife.

The Pythagoreans and Orphic philosophers embraced the Egyptians' beliefs about reincarnation and developed the cardiocentric theory [8]. But even earlier, in the Homeric era, references such as that in the Iliad *''bend, my Achilles, your strong soul, you should not have a hard heart''* denote an already existed connection of the heart with emotions and soul [12]. The main representatives of the cardiocentric theory were Empedocles of Acragas and Aristotle, who strongly connected the heart with the intellect [13]. According to them, blood was the carrier of the mind, while the heart, the organ with more blood, was its locus. Actually, the latter further developed the cardiocentric theory by suggesting three souls: the ''nutritive soul'' enabling growth and reproduction, the ''perceptive soul'' enabling senses and movement, and the ''rational soul'' enabling consciousness and intellect. The first two were found in all animals, while the third one only existed in humans [14].

Although Aristotle examined animal brains and made some important anatomical observations, such as the distinction of the cerebrum from the cerebellum and several nerves [15], his deep faith in the cardiocentric theory along with the avoidance of dissections of the ''sacred'' human body did not permit him to make any correlation between brain and behavior. The only role that he attributed to the brain was that of cooling the blood [14]. However, the Aristotelian theories were very popular in his era and Alexander the Great was one of Aristotles's students. These ideas were then passed down to the Stoic philosophers, who undertook their dissemination. There even were some anatomists, such as Diocles of Carystus and Praxagoras of Cos, who described the parts of the heart with their functions in detail, attempting to define the precise biological background of the cardiocentric theory. Nevertheless, Diocles finally revised his views conceding a part of the intellect to the brain. The significance of both theories at that period is reflected in Plato's theory about the three elements of the soul: the ''mind'' located in the brain, the ''spirit'' located in the chest, and the ''appetites'' located near the liver [16].

The Hippocratic medicine continued during the Hellenistic period in Alexandria, where dissections increased. The pioneers of that time were Herophilus of Chalcedon and Erasistratus of Ceos, who showed great interest in the brain [16]. The former distinguished the ventricles and indicated the fourth ventricle as the location of the soul, arguing that, along with the cerebellum, it controlled movement. The latter linked complexity with mental capacity through anatomical comparisons of gyri and fissures between animals and humans, while also demonstrating that each hemisphere controls the controlateral side of the body through lesion studies on animals.

During the Roman era, advances in medicine were limited, as a result of the prevalence of theocratic views and the prohibition of dissections. The continuer of scientific medicine and the encefalocentric theory was Galen of Pergamon, who thoroughly examined animal brains and described their anatomy in detail [17]. Among others, he distinguished the corpus callosum, the thalamus and the fornix. His experiments provided evidence for the connection of the brain with senses and movement, as well as the larynx with speech. Influenced by the Platonic theory, he suggested three types of spirit: the ''vital'' of the heart, the ''natural'' of the liver, and the ''mental or animal'' of the brain. According to him, the first two were related with growth, nutrition, and regulation of body temperature, whereas the third one was related with senses, movement, and intellect. In addition, he indicated an area at the base of animal brains, where the lateral ventricles connect with the third and fourth ventricle and a plexus of blood vessels, arteries and canals of cerebrospinal fluid exists, claiming that this *''rete mirable''* [wonderful network] was the location of the production of mental spirit. It is notable that, although scientific thought was critically influenced towards the encefalocentric theory by the Galenic theory for several centuries thereafter, it was still dominated by some remnants of the Aristotelian theory favoring the role of heart in emotional function.

After the 2nd century and during the Middle Ages, anatomical studies occurred sporadically and secretly in Europe. Even though Christianity advocated that the body would obtain its integrity during Resurrection, pre-existing prejudice against human dissections predominated in scientific thought [18]. Galen was the leading expert of this period and his anatomy was taught in medical schools. With the translation of his writings, his medicine was spread into the Arabic world, as was the case with Aristotelian writings. However, due to the same prejudice the Arabs did not engage in dissections. The main representative of the Arabic medicine was Avicennas, who attempted to reconcile the two theories [13]. With the book ''The Canon of Medicine'' he influenced the West for centuries. His theory is reflected in the drawings of German Albertus Magnus, known as *''Doctor Universalis''* (Universal Doctor) during the medieval period, depicting the three ventricles along with their functions. More specifically, the first was the ''common sense'' and served for receiving sensory stimuli, the middle was the ''imagination'' and served for perception, imagination, thinking, and reasoning, while, the posterior ventricle was the ''memory'' and served for storage of memory and intentions. On the other hand, the heart had a pivotal role in the formation of intentions that were transferred to the brain via the blood, so as to send the animal spirit to the muscles.

The obscurantism in medicine lasted until the 15^{th}-16^{th} century, when the Popes recognized the fundamental necessity of dissections and gave their official permission to their performance [18]. Thereafter, several anatomy theaters were founded under the guidance of Belgian anatomist Andreas Vesalius and lectures in anatomy began. He and Italian Leonardo da Vinci systematically performed dissections in the human brain, thus offering more accurate depictions of the ventricles [19]. Nonetheless, Vesalius openly questioned the doctrine of ventricle involvement in mental functions and the existence of *rete mirable* in the human brain, claiming that such correlations were not possible to reveal through dissections [20]. The influence of the ventriclocentric theory continued for several years and was apparent in the theory of French anatomist René Descartes, who identified a brain structure attached to the third ventricle, the pineal gland, as the "seat" of soul and cognition [20].

After the Renaissance, interest shifted from ventricles to the cerebral cortex. Specifically, English anatomist Thomas Willis published a book entitled "Cerebri Anatomie", in which he meticulously described the parts of the brain, associating higher functions, such as imagination, memory, and intentions, with the cerebral hemispheres, and physical functions and reflexes with the cerebellum. The striatum in his theory was associated with senses and movement [19]. Another scientist, Swedish Emanuel Swedenborg, placed greater emphasis on the distinction of functions stressing that it was the only way for various disorders to be understood [19]. He localized the motor cortex in the Frontal Lobe (FL), especially linking the upper gyrus with limp movement, the middle gyrus with corpus movement, and the lower gyrus with neck movement. Furthermore, by distinguishing intentional from reflective movements, he proposed that the former were controlled by the cortex, whereas the latter by the medulla. Regarding the higher functions, they were attributed to the FL as well. However, despite the great effort and progress of that time, the apogee of functional localization took place some years later with the phrenology of Austrian neuroanatomist Franz Gall [21]. Gall combined the method of systematic observation of behavior with cranioscopy, i.e., the palpation of the skull, as he believed that hills denoted excessive growth of underlying organs that were responsible for deviant behaviors; thus, he localized 27 functions in specific areas of the human brain. It is remarkable that he was the first who described aphasia in a case of a person with a fencing lesion in FL.

Evidence for Functional Localization and Hemispheric Asymmetry

In the early 19th century the discovery of the connection between medulla oblongata and respiration by French physiologist Julien Legallois and the distinction of sensory nerves from motor ones in the spinal cord by his counterparts, French François Magendie and Scotch Charles Bell, revived the use of experimentation in the study of functional localization [19]. The first step was taken by French physiologist Pierre Flourens, who induced brain lesions in animals so as to observe changes in behavior [22]. However, instead of specific correlations, he found that the greater the extent of damage was, the greater the deficits in all functions were, as well as that not all damages incurred impairments; consequently, he developed the holistic theory according to which the entire cortex was responsible for all functions and in case of brain damage spare areas controlled impaired functions. Meanwhile, his contemporaries in France, Claude Lallemand, Léon Rostan, Jean Bouillaud, Ernest Aubertin, and Gustave Dax, explored lesions in human brains and provided evidence for the connection of the left FL with speech [19,22]. In 1863, Gustave Dax first published a manuscript written by his father Marc Dax, in which he had already reported since 1836 that speech disorders were associated with lesions in the left hemisphere [23]. Notwithstanding, it was another French anatomist, named Paul Broca, who established functional localization, as he carefully examined the brain of people with impairments in speech production and identified alterations of neuronal integrity in the third left frontal gyrus. The loss of this function was named by him ''aphemia'' [24].

Additional proofs for functional localization emerged with the discovery of the motor cortex in the brain. In 1870, following the discovery of Italian physician Luigi Galvani of electrical stimulation of muscles and nerves [20], German anatomists Eduard Hitzig and Gustav Fritsch stimulated dog brains and detected specific areas in the FL that control the movement of body parts [24]. With their famous experiments, they also proved what their predecessors, such as Hippocrates, Erasistratus of Ceos, and Aretaeus of Cappadocia in antiquity, Domenico Mistichelli and Pourfour du Petit in the 18th century, and their contemporaries, such as Jackson, had already observed: that lesions in one hemisphere cause contralateral hemiplegia [25,26]. Five years later, Scot neurologist David Ferrier replicated those experiments in monkeys and confirmed the existence of motor areas in the FL and, also, in more posterior areas, while British physiologist Ritchard Caton provided additional support by recording the electrical activity in animal brains during movement execution [24,27]. Almost ten years later, other researchers, such as anatomists Victor Horsley and Robert Bartholow in Britain and the United States respectively, expanded Ferrier's experiments to humans and demonstrated the specialized role of several areas lying in front and behind Rolando's fissure in movement [28].

The discovery of the motor cortex discredited the view that the cortex was the seat of higher functions in the brain, which derived from phrenology, thus paving the way for investigation of its involvement in sensory control [20,29]. By conducting electrostimulation and lesion-induced experiments, Ferrier and two other physiologists, German Hermann Munk and Briton Edward Schafer, localized auditory and visual function in the Temporal Lobe (TL) and the Occipital Lobe (OL) respectively [24]. At this point, it is worth mentioning that Italian anatomist

Bartolomeo Panizza had preceded them in discovering the visual cortex in his studies of cerebral stokes, but he had not gained wide recognition. The same fate awaited the findings of Swiss ophthalmologist Louis Verrey, who had discerned lesions in the lingual and fusiform gyrus of a patient with color blindness after cerebral stroke with impressive accuracy for his era [30]. Subsequently, more evidence for the existence of sensory areas in the cortex emerged from Caton's and his Polish counterpart, Alolph Beck's, experiments using event-related potentials [27,31].

Broca conclusively demonstrated that the left hemisphere specialized in speech production; however, given that loss of speech wasn't accompanied with impairment in speech comprehension, he hypothesized that this function depended on the right hemisphere [32]. Moreover, he was the first to link hand dominance in writing with the contralateral hemisphere, typically responsible for speech production, assuming that there could be a hemispheric tendency regarding control of both functions. At this point, it is important to note that Broca presented revolutionary evidence against the pre-existing law of hemispheric symmetry and equality that had been put forward by French anatomist Xavier Bichat at the beginning of the 18th century and embraced by several eminent scientists, like Gall and Flourens. For this reason, he characterized his findings as an exception to this law [32].

The entire connection of the left hemisphere with language took place after the middle of the second half of the 19th century and was derived from the increasing recognition of the necessity for post-death brain examinations. German neurologist Carl Wernicke localized the ability of speech comprehension and conceptual usage of words in the posterior part of the left superior TL, and afterwards, French neurologist Jules Dejerine identified an area in the left Parietal Lobe (PL), the so-called angular gyrus, as responsible for reading and writing [22]. Furthermore, based on the findings of his mentor, German-Austrian anatomist Theodor Meynert, who had demonstrated that motor areas were located in the front part of the brain, while sensory areas in the posterior part, and especially the auditory cortex in the posterior part of Sylvius fissure, Wernicke explained Boca's aphasia as the result of loss of kinetic traces required for articulation, and the aphasia described by him as the result of loss of auditory traces required for speech comprehension [32]. However, his contribution did not stop there. Based again on Meynert's discovery of white matter connections, he explained a third type of aphasia, namely that of non-fluent speech repetition, later termed ''conduction aphasia'', as the consequence of disruption of the arcuate fasciculus which connects the third left frontal gyrus with the left superior temporal gyrus [33]. Obviously influenced by him, Dejerine, in turn, explained the reading disorder in which writing remains unimpaired, later referred to as ''alexia without agraphia'', as the consequence of disruption of the fibers connecting the visual center in occipital lobes with the left angular gyrus, proposing that it contained visual traces of words [34]. Therefore, the connectionism that had started with the assumptions of Scottish philosopher Alexander Bain about the existence of neuronal groups [35] was verified by Meynert's discoveries and acquired explanatory power with the models of disconnection syndromes.

Apart from the left hemispheric function, lesion studies also offered great insight into right hemispheric function. Involvement of the right hemisphere in visuospatial abilities was first shown by John Jackson, the father of English neurology [24]. Although Jackson was initially skeptical about the theory of functional localization, when he studied patients with right brain lesions, he noticed that left hemiplegia was accompanied by deficits in spatial orientation, visual perception, and disabilities in dressing, despite unimpaired vision [36]. He described the loss of these functions under the term "imperception" and, following the autopsy of a patient with tumor, he localized them in the posterior part of the right hemisphere. Soon afterwards, German neurologists Heinrich Lissauer described the disorder of visual object recognition later termed ''agnosia'' placing great emphasis on neuronal interconnections in the right hemisphere [33]. Based on his observations that only left hemiplegia was followed by negative emotional symptoms, such as irritability, hyperactivity, and mania, another researcher, French neurologist Jules Luys, inferred that the right hemisphere and, more specifically, the upper part of the TL was the center of emotional control [32]. In the light of his findings in the late 19th century, Luys promoted the idea that the left hemisphere was logical due to the close relation of language with reasoning, whereas the right hemisphere was emotional.

Furthermore, triggered by the accident of American foreman Phineas Gage in 1848, the connection of the FL with intelligence and personality was brought to attention [37]. While Gage was working on a railway construction, an explosion caused a steel rod to penetrate his cheek, rip through the front part of his brain and come out through the skull. Although Gage survived and physically recovered, after 20 years of monitoring him, his physician, John Harlow, published an article reporting that Gage had become inconsistent, irreverent, obstinate, irritable, and impatient, and his intelligence had decreased [38]. This case urged several researchers to study the effects of FL lesions and particularly those of the Pre-Frontal Cortex (PFC) in behavior. Significant data were produced by the experiments of Hitzig and Ferrier, who showed that after FL excision animals become apathetic, impulsive, and unmotivated, attributing these changes to loss of intellect or loss of attention respectively [39]. Another researcher, the Italian neurologist Leonardo Bianchi, noted that PFC excisions were associated with social and emotional disturbances ascribing them to the dissolution of personality [39].

Towards the end of this section, it should be mentioned that in the late 19th century some progress was made in memory function, as French psychologist Théodule Ribot distinguished anterograde from retrograde amnesia stressing that recent memories are more vulnerable to brain damage than remote ones; also, Wernicke and Russian psychiatrist Sergei Korsakoff described the amnesic syndrome that took their name [40]. Nevertheless, some evidence connecting memory with TL, obtained in the context of Schafer's and his American colleague Sanger Brown's examination study of hearing after TL excision in a monkey [41], and particularly with the hippocampus, produced by the Russian's neurologist Vladimir Bekhterev's lesion-detection study in a patient with amnesia, were rapidly forgotten [42].

Brain-Behavior Relationship in Depth

Although functional localization became the key issue in the scientific dialogues of the 19th century, it failed to convince all the scientists of that time. The main source of controversy lay in the experiments of German physiologist Friedrich Goltz, from which no evidence was emerged for the existence of the motor and sensory cortex in the dog's brain. A characteristic of this controversy was the debate between Ferrier and Goltz, the main representatives of localizationism and holism respectively, at the 7th International Medical Conference in London [43].

The solution came with increasing recognition of the importance of cytoarchitectonics and myeloarchitectonics initiated, as mentioned above, by Meynert. However, although Meynert proposed that the motor and sensory cortex were separated in the brain, he ignored what his contemporary, Ukrainian anatomist Vladimir Betz had discovered, i.e., the existence of a large number of giant pyramidal cells in motor areas in comparison to sensory ones [32,44]. The discovery of Betz cells inspired several scientists to explore the physical boundaries of motor and sensory phenomena in the brain and develop anatomical-functional maps in the early 20th century. This was accomplished by combining data obtained from histological, electrophysiological, and surgical studies. For example, British physiologists Sir Charles Sherrington and Albert Leyton created the first anatomical maps of motor skills of primates [45]. Soon after, Australian neurologist Alfred Campbell published a more comprehensive map of motor and sensory functions as well. Based on his histological observations, he confirmed that motor areas were dominated by giant pyramidal cells, unlike sensory areas which were dominated by small granular cells [46]. Meanwhile, there was a consensus among histologists that the Rolando fissure separated the anterior motor areas from the posterior sensory ones.

Given that these findings supported the existence of distinctive motor and sensory centers in the brain, what was the neural background of higher functions? Since the beginning of the 20th century, German neuroanatomist Paul Flechsig had discovered some cortical areas outside the motor and the sensory areas (primordial areas) and described them under the term ''association areas'', arguing that they served for the intellect [47]. The basis of this theory was his myelination studies during growth and, more specifically, the observation that primordial areas were myelinated before birth, in contrast to association areas that were myelinated after birth, reflecting, as he explained, associations between various stimuli. Four years later, Campbell distinguished multiple neuronal connections within association areas and regarded them as the physical depository of integrated information, as well as the source of abstract thought [46]. Even though the above-mentioned and other famous histologists, such as Korbinian Brodmann, Oskar and Cecile Vogt, Constantin von Economo, and George Koskinas, had constructed several brain maps promoting functional localization [48], it was the holistic view that eventually prevailed into the first part of the 20th century. A pivotal role was played by American psychologist Karl Lashley's unsuccessful attempt to localize the ''engram'' (trace) of memory in the rodent frontal association cortex, to which his contemporaries attributed intelligence [19]. Indeed, Lashley examined the consequences of brain lesions in conditional learning, but rather than finding a precise locus, he showed that memory depended on the extent of the lesion or in other words on the ''mass action'' of the brain [49]. However, despite rejecting localization of higher functions, he and other supporters of holism at that period, such as neurologists Pierre Marie, Henry Head, Constantin von Monacow, and Kurt Goldstein, appeared less rigid towards localization of primary functions [19,36,50].

In addition to the revival of the holistic model, two other factors contributed to the limitation of functional localization studies during the first half of the 20th century. Firstly, the prevalence of the Gestalt, Behaviorist, and Psychoanalytic movements led to interpretations of behavior without direct references to the brain [22]. Secondly, the postulation of the neuron doctrine, which began with the discovery of the structural components of the neuron (body, dendrites, and axon) by Italian histologist Camillo Golgi, was further elaborated with the discovery of the synaptic gap between neurons (the synapse as later named) by Spanish Santiago Ramon y Cajal, and established with their being awarded the Nobel Prize in physiology/medicine in 1906, shifted scientific interest to neuronal communication triggering a series of studies that brought to light its chemical and electrical nature [51].

On the other hand, some factors that had previously acted on the field of psychology paved the way for the birth of neuropsychology and the systematic exploration of brain-behavior relationship. The first was the foundation of laboratories dedicated to psychological research and the adoption of experimental and test-administration method. Thereby, psychology was distracted from philosophy and biology and became an experimental science. Wilhelm Wundt is considered the father of experimental psychology, as he founded the first laboratory in Germany in 1879, while contributions by Gustav Fechner, Hermann von Helmholtz, Hermann Ebbinghaus, Georg Elias Müller, William James, Stanley Hall, and Ivan Pavlov were significant for the development of this field. The second factor was the emergence of psychometrics. Specifically, influenced by Darwinian theory two British researchers, Frances Galton and James Cattell, focused on the definition and measurement of intelligence, placing special emphasis on statistical concepts, such as individual differences and correlation [52,53]. Subsequent criticism of the existing anthropometric tests (e.g. sensory acuity and body part size) as oversimplified measures of intelligence, along with the development of a humanistic approach for children with mental retardation, stressing the need for their distinction from psychiatric children and induction into special schools, played a determinant role in the development of the first modern intelligence test by French psychologists Alfred Binet and Théodore Simon at the beginning of the 20th century [54]. Thereafter, conceptualization of intelligence as multifaceted rather than single and unitary, and as including a group of higher functions (memory, attention, visuospatial abilities etc.), which were distinct and measurable, in conjunction with increasing demand for mental testing in education, immigration policy, military, and medical practice (psychiatric, neurological, neurosurgical), led to the production of numerous standardized cognitive tests [54-56].

Since scientists realized that mental testing can be useful in diagnosing brain damage (organic brain syndrome) and especially its localization, the field of neuropsychology was established and modern functional localization began [56]. At this point, a significant role was played by American psychology professor Ward Halstead, who founded the first neuropsychological laboratory in 1935 and put forward a comprehensive cognitive assessment in focal brain lesions over a single or unifactorial-intelligence test administration, so as to allow for the potential for specific correlations [57]. This suggestion was the outcome of his long-term engagement with neurological populations that permitted him to record a suite of symptoms, and was practically expressed with the construction of the first multifactorial-intelligence test by him and his student Ralph Reitan [58]. From then on, the foundation of neuropsychological labatories in several places all over the world was enhanced by availability of focal brain lesions due to wars and development of surgical techniques for treatment of tumors, epilepsy, and mental disorders. At the same time, further emphasis was placed on the improvement of tools for cognitive assessment (standardization, psychometric properties, normative data) and research methodology (between-group comparison, statistical analysis, sample quality). After 1940, these laboratories conducted systematic research producing a large amount of sound knowledge on the brain-behavior relationship.

In France and England, neurologist Henry Hécaen and psychologist Oliver Zangwill respectively explored almost simultaneously the existence of hemispheric specialization. After its connection with language, the left hemisphere was additionally connected with skilled movements (e.g. copying gestures, using tools, dressing) by Hugo Liepmann, the loss of which named ‘’apraxia’’ [59], and later its role was extended to all higher functions; hence, it was described by the majority of scientists as ‘’superior’’. In contrast, some scientists, such as John Jackson, Donald Hebb, and Katherine McBride, provided data that implicated the right hemisphere in the visuospatial function and somatosensory perception of the left side of the body [60]. In view of this controversy, Hecaen and Zangwill undertook examination of the effects of unilateral brain lesions and, by using the new available method of testing mental functions, demonstrated the specialization of the posterior part of the right hemispheric in visuospatial abilities [61,62]. As a result, the doctrine of left hemispheric dominance was replaced with the concept of hemispheric asymmetry, thus reintroducing focus on the role of the right hemisphere. Consequently, as representatives of its function, visuospatial tasks acquired significant role in neuropsychological assessment.

In Russia, based on data comparison between healthy and unhealthy people and, also on his colleague’s**,** psychologist Lev Vygotsky’s, theory about multiple systems of mental function, psychologist-neurologist Alexander Luria developed the theory of the three principal functional units of the brain [63]. The first unit includes a broad plexus of neurons, the so called ‘’reticular formation’’, which runs through the stem and the thalamus and acts as regulator of instincts, reflexes, tendencies, muscle tone, and alertness. The second one includes a network of temporal, parietal, and occipital areas responsible for receiving, recognizing and integrating sensory information. While the third one consists of frontal areas and controls voluntary actions. Specifically, the PFC, which has neural connections with almost all parts of the brain, forms a person’s intentions and goals, as well as planning and regulating behavior in order to achieve them. Given that higher functions rely on collaboration of all brain units, but each of them maintains a particular role, Luria’s theory can be regarded as a synthesis of localizationism and holism and as the first unitary theory of brain function [64,65].

In the United States the first studies aimed at localizing intelligence, but failing to demonstrate a consistent relationship, ended up as an argument in favor of mass action theory [66-70]. The main reasons for that were the lack of a standard definition for intelligence, the employment of inadequate tools for its measurement, and the usage of insufficient or non-representative samples. Following efforts, though, yielded more positive results. Halstead eventually demonstrated that frontal lesions were associated with loss of intelligence [69]. Also, Reitan’s studies produced specific correlations between left hemispheric lesions and decline in verbal performance, in contrast to right hemispheric lesions and decline in practical performance [71,72]. Special mention should be made of psychologist Hans-Lukas Teuber, as he created a wide network of colleagues and provided evidence for specialization of the posterior part of the right hemisphere in visual perception and visuospatial function [73-75], as well as specialization of the left hemisphere in auditory perception and verbal function [76,77]. With his model of double dissociation he influenced future researchers towards conducting comparisons between groups of patients with different brain lesions, thus leading to more accurate correlations between functions and brain areas, as well as between symptoms and syndromes [78]. The name of another psychologist, Arthur Benton has been linked with the connection of the posterior part of the right hemisphere with spatial orientation and face recognition [79,80]. Finally, two other scientists deserve mention here, as they shed more light into the specialized roles of both hemispheres and their interconnections. The first is neurologist Norman Geschwind, who, apart from reviving the study of disconnection syndromes and verifying previous well-documented knowledge of function localization, also indicated a region in the inferior PL (angular and supramarginal gyri) into which all associative areas project, proposing that this is the location where various information is combined [81,82]. According to him, disconnection syndromes are caused by neuronal disruptions in that specific region. For example, visual agnosia reflects the disconnection between the visual areas of the right hemisphere and the language areas of the left hemisphere. Almost concurrently, biologist-psychologist Roger Sperry conducted his famous experiments in people with commissurotomy (split brain) and proved that the two hemispheres are largely independent in processing visual and verbal stimuli, while the corpus callosum serves for their communication [83]. He was awarded the Nobel Prize in medicine/physiology for these findings in 1981.

In Canada, neurosurgeon Wilder Penfield systematically applied the method of intraoperative electrical stimulation in order to accurately distinguish functional areas from epileptic focus, and preserve them. As stimulation of different brain areas elicited various types of behaviors, Penfield was able to make specific correlations and construct precise anatomical-functional maps. He localized the primary motor cortex in FL and the primary somatosensory cortex in PL, pinpointing the exact areas within them that are related with movement and sensation of body parts [84]. Moreover, he confirmed that language is localized in the left hemisphere. Nevertheless, his major contribution to neuropsychology is considered the repeated observation of the connection between memory and TL [85]. As this new relation required further exploration in temporal lobectomies, it was psychologist Brenda Milner (born in 1919), a PhD student at that time, who was assigned with that task**.** In collaboration with Penfield and other neurosurgeons, Milner managed to localize learning in the middle TL and, particularly, in the hippocampus [86]. The key to that discovery was the case of Henry Molaison, a patient who suffered from anterograde amnesia, i.e., inability to acquire new memories after bilateral medial temporal lobectomy [87]. Afterwards, by examining more cases, Milner explained that anterograde amnesia involves memories of events and faces based on conscious recollection, in contrast to memories of skills and procedures, which are stimulated unconsciously. Also, she demonstrated that left hippocampal lesions impaired verbal memory, whereas right ones impaired visual/visuospatial and face memory [88,89].

Near the end of this section, it should be mentioned that during the attempts to define and localize intelligence and higher functions similar queries emerged about emotional function and animal experiments were carried out for that purpose [90,91]. It was the American neuroanatomist James Papez who reviewed this topic, proposing that the hypothalamus, thalamus, hippocampus, and cingulate gyrus, participate in emotional expression [92]. Some years later, his compatriot physiologist Paul McLean added the amygdala, septum and PFC to Papez's circuit, and coined the term ''limbic system'' to describe the neural substrate of emotional function [93].

After 1960, some advances gave new impetus to the study of brain-behavior relationship. Firstly, associations and journals were founded, spreading neuropsychological knowledge worldwide and fostering the emergence of new research questions [94,95]. Secondly, cognitive psychology was born and introduced the concept of ''mental processing'' as a response to the simplistic behavioristic approach of functions on the basis of the dipole ''stimulus-reaction'' [96]. Thirdly, technological progress placed neuroimaging techniques at the disposal of brain research, thus enabling precise detection of lesions and *in vivo* exploration of anatomo-functional relationships [97]. As a consequence, the disengagement of neuropsychology from lesion localization, along with the increasing data denoting the existence of specialized neural networks, highlighted the need for redefinition of its scope. Therefore, neuropsychology incorporated concepts of cognitive psychology and new attempts began to develop cognitive tests and apply them to neurological and psychiatric populations in order to uncover the sub-processes and reveal the neural networks underlying them.

Cognitive neuropsychology and cognitive neuroscience constitute the most recent branches of science for the study of the brain-behavior relationship, differing in the extent of the emphasis they place on the two parts of the dipole, processes or neural substrates respectively [98]. This section would be incomplete without a reference to the basic neural networks either been proved or speculated that underpin different types of behaviour.

The division of visual processing in two streams, the ''ventral'' and the ''dorsal'' or the ''what'' and the ''where'', which diverge from the striate cortex projecting into the inferior TL and inferior PL respectively, was put forward by Ungerleider and Mishkin [99], who suggested that the former analyzes features (shape, pattern, texture) and the latter spatial location of a visual stimulus. Afterwards, Goodale and Milner [100] modified this model, arguing that the dorsal stream guides visually reaching and grasping actions, and so, it is the ''how'' system that undertakes visual-motor integration. More recent approaches focus on the potential for collaboration of the two streams in producing visuo-motor actions, and especially examine the likelihood that the ventral stream is involved in the visual analysis required for grasping an object at the appropriate side and the dorsal one in performing the appropriate gesture, executed via dense connections with the frontal motor areas [101,102].

An analogous dual-stream model for auditory processing was introduced by Hickok and Poeppel [103]. The ''ventral'' auditory stream, one hand, is comprised of the superior and the middle TL bilaterally, and is responsible for speech recognition that includes segmental, syllabic, and lexical analysis of the auditory input, entailing access into the mental lexicon. The ''dorsal'' auditory stream, on the other hand, is left dominant and consists of the posterior portions of the superior TL and the inferior PL that constitute the temporal plain (the heart of Wernicke's area), as well as the posterior portion of inferior FL (Broca's area). Similarly to the visual dorsal stream, it undertakes auditory-motor integration or, in other words, translation of phonological information into gestures required for speech articulation.

Alexander et al. proposed a model of five parallel basal ganglia-thalamocortical circuits. The first two are the ''motor'' and ''oculomotor'' originating in the pre-central motor fields and the eye fields. The second two are the ''prefrontal'' ones originating in the dorsolateral PFC and the lateral Orbitofrontal Cortex (OFC). Finally, the last one is the ''limbic'' circuit originating in the medial OFC and the Anterior Cingulate Cortex (ACC). They especially focused on the function of the first two, attributing the movement of body and eyes to them respectively. Movement is executed with the contribution of an additional pathway made up of the upper motor neurons that spring from the motor areas and end up either to the brainstem or the spinal cord, carrying motor information required to stimulate nerves and muscles. Then, by reviewing the function of non-motor circuits, other scientists [71,104-106] concluded that the ''dorsolateral PFC'' circuit is related to attention, working memory, decision making, planning, and reasoning, the ''lateral OFC'' circuit is related to outcome appreciation (punishment versus reward) in decision making under uncertain situations and, particularly, preference for rewarded or socially appropriate behavior and inhibition of opposite ones, while the ''medial OFC/ACC'' circuit is related to stimulus-reward-emotional value association learning, decoding, and monitoring, as well as to motivational behavior. More specifically, the dorsolateral PFC circuit receives inputs from the dorsal sensory streams and the OFC circuits receive inputs from the ventral sensory streams. In particular, the lateral OFC receives visual, auditory, somato-sensory, and taste inputs, in contrast to the medial OFC that receives olfactory and visceral inputs. Both have multiple connections with other limbic areas, such as the hippocampus and the amygdala; however, recent experimental data have shown functional dissociation between them in emotional function with the medial part being involved in processing and the lateral part in regulating emotions [107].

LeDoux examined emotional function by focusing on fear [108,109]. He identified two different circuits related to amygdala. The ''direct'' circuit permits the transmission of sensory information from thalamus to amygdala, so that dangerous stimuli can be detected immediately and the person can respond quickly. The ''indirect'' circuit involves the mediation of the cortex, so that fearful stimuli can be analyzed and appraised in detail. During such situations, the amygdala either rapidly arouses ''fight or flight'' responses derived from fear conditioning, or after receiving the output of memory activation and cognitive processing, it encodes the emotional status of the experience and triggers emotional responses.

A recently described and accidentally discovered network is the default network that is activated during undirected thinking, but conversely, deactivated during goal-directed tasks [110]. When individuals are not focused on external environment, their brain is not actually at rest [111]. Rather, it is engaged with internal tasks, such as recollecting autobiographical memories, considering other people's perspectives, making hypothetical social interactions and, generally, envisioning the future and imagining alternative scenarios for upcoming events, so as to predict the respective outcomes and prepare individuals. Neuroimaging studies have shown that self-referential processing is associated with consistent activation of the medial PFC, posterior cingulate cortex, retrosplenial cortex and precuneus, while the supplementary activation of sensory and limbic areas permits encoding of the content of the imagined event [112]. Increased activation of the medial PFC in depression and anxiety may reflect the existence of intensive negative self-referential thoughts that distract attention from another loci of focus, probably as a consequence of failure of the dorso-lateral PFC and lateral OFC to inhibit and reappraise them [107,113-116].

Finally, based on the discovery that memories consist of neurons being connected after simultaneous excitations caused by sensory or movement experience [67,117], Fuster developed a theoretical model of two broad networks for the formation and storage of sensory and motor representations or ''cognits'' [118]. In respect to him, cognits are hierarchically organized according to their complexity. The ''sensory'' network departs from sensory areas and ends up in posterior associative areas [119]. Specifically, the concrete visual, auditory, and somatosensory cognits of a given sensory modality lie in the inferior TL, superior TL, and anterior PL respectively. The more complex polysensory cognits and cognits of events including time and location (episodic memory) lie in the upper areas, one above the other. Still higher, where occipital, parietal, and temporal lobes converge, the cognits of facts and abstract concepts (semantic memory) are located [120]. The ''executive'' network is comprised of the primary motor, premotor, and prefrontal cortices and is symmetrical to the sensory one as each of these parts subserves different level of motor function, i.e., simple movements, goal-directed motor actions, and action plans with more distant goals respectively. In particular, the cognits of speech articulation are located in the premotor cortex (Broca's area), whereas the cognits of abstract forms of language required for conceptual reasoning and creativity are located in the lateral prefrontal cortex [31]. Fuster, indeed, gave more theoretical explanations highlighting that the more connections there are between a cognit and other cognits, the more abstract and widely distributed it is in the brain [121]. More or less complex sensory-motor actions produced on the basis of reciprocal connections between sensory and motor structures. In any case, the hippocampus mediates the synaptic modulations underlying cognit formation and the amygdala attaches the emotional and motivational information of the experience [122].

Discussion and Conclusion

A series of changes in some people's way of thinking prepared the ground for the production of current knowledge. Amongst them there were rejection of superstitions in disease interpretation, elimination of prejudices about the human body dissections, and challenge of the cardio-centric theory that was well-rooted in religious and philosophical thought [123]. Notwithstanding, without the adoption of scientific methods, such as systematic observation and experimentation, the relation between brain and behavior would not have come to light.

The development of brain-behavior relationship depended thereafter on interdisciplinary collaboration, and scientists' ability to formulate new experimental questions and designs, but mainly on the methods devised for studying both parts of this dipole. The more investigative methods of the brain, such as cell staining and electrophysiological techniques, as well as neurosurgical techniques, were developed, the more evident the localization of language, motor, and sensory functions in specific areas of the brain became [124]. On the other hand, the localization of less overt functions was parallel with improvements in definitions and construction of assessment tools. Ultimately, neuroimaging techniques provided the key to accurate correlations between cognitive processes and neural networks.

Studying the journey of brain-behavior relationship since its beginning more than 2500 years ago, one can amass a wealth of information about how the brain works. However, this journey will continue until no more questions can arise [125]. For the puzzle of this relationship to be completed, one of the fundamental lessons offered by the study of the past must be fully understood: more emphasis should be placed on optimizing the methods of brain function investigation and on developing new ones. Nowadays, computers are widely available and computerized cognitive assessment has already proven more advantageous than traditional paper-and-pencil methods. For example, it is more objective and accurate, as it provides automatic administration and scoring [126,127]. Also, it is more sensitive, allowing for precise measurement of reaction time and error type (omission and commission). Moreover, it permits simultaneous presentation of several stimuli and thus, evaluation of more complex behavior. Last but not least, it facilitates cognitive assessment with the concurrent usage of the second method available by technology, that is, neuroimaging [128]. Since the benefits of both these computer-based methods have been shown [129-132], especially when they are combined [133,134], it can be assumed that computerized functional localization is now a reality and that the brain-behavior relationship has already moved on to the next stage of its development.

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