Landmark Discoveries in Neurosciences

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The study of the basis of mental phenomena or the mind has always intrigued humans. Our current understanding of the functioning of the brain is the result of insightful research by many scientists, which has led to a detailed knowledge of brain structure and how this structure makes it possible for the mind to emerge from it.

1. Early Ideas About the Mind and Matter

As far as the recorded history goes, humans have wondered about the nature and basis of our own existence. Early thinkers seem to have realized that before they can answer the question 'Who am I?', they had to understand the origin of the thought process itself. They had to understand what is mind, and if it is different from the body. Gautam Buddha, as early as 500 BC, proposed that mental life is causally interconnected with matter. This view was radically different from that prevailing in the Vedic philosophy, which had existed for more than a thousand years.

In Western philosophy, the history of ideas about the mind started with the notion of duality; there are two fundamental kinds of substances: mental and material. In the early Greek and Western philosophical traditions, exemplified notably by Plato (circa 427–347 BC) and Aristotle (384–322 BC), the mind is contrasted with the body. However, the Greek physician Hippocrates[1] (460–370 BC) realized that the brain is the controlling centre for the body. In the book *On the Sacred Disease* it is written that "men ought to know that from nothing else but the brain come joys, delights, laughter and sports, and sorrows, grief, despondency and lamentations. And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear and know what is foul and what is fair, what is bad and what is good, what is sweet and what is unsavory…"

[1] See T Padmanabhan, The Healing Art, *Resonance*, Vol.15, No.10, 2010.

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Herophilus, a follower of Hippocrates, described the structure of parts of the brain, nerves and tendons and parts of the eye, since by then human dissection had become acceptable. Erasistratus had even done comparative studies across different species; he associated the size of cerebellum with the ability to run fast, and the complexity of the cerebral convolutions with intellect, thus beginning the ideas of the localization of function in the brain.

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However, these ideas were not pursued further for a long time to come because of the influence of great thinkers like Aristotle who believed that the heart, rather than the brain, is the seat of intelligence and emotions. Aristotle also believed that functions of the brain were localized in the cavities of the brain or ventricles, rather than the physical part of the brain. It took a long time before we arrived at the modern view of the brain structure and function. Here we briefly recount the history of the development of four landmark ideas that laid the foundation of most of our modern understanding of the brain function, recalling contributions of some of the pioneers, which lead to these developments.

2. Specific Functions are Localized in Specific Parts of the Brain.

After Hirophilus' time the idea that different functions are located in different physical parts of the brain was not developed further through the periods of later Greek rulers, the Roman Empire, the period of great influence of the Church until the end of the dark ages, the Renaissance and even early post-Renaissance years. During these times there were long periods of ban on human dissection hampering scientific investigations of brain structure and function. More specific ideas about the localization of function started to develop in the eighteenth century with experiments by a French physiologist Julien Jean César Legallois who showed a respiratory centre in a part of the brain called 'medulla', and that sensory and motor functions were ascribed to different spinal roots.

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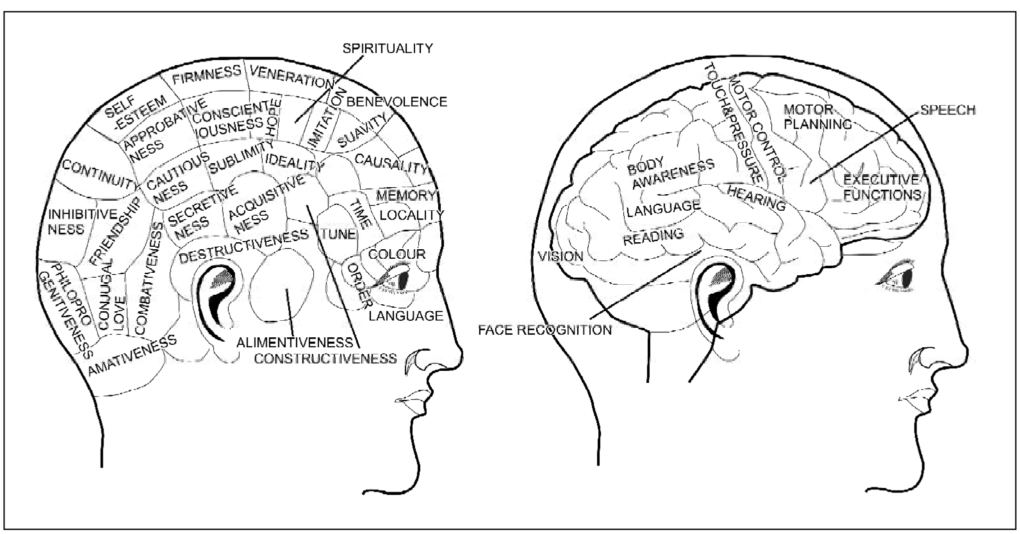
Ideas about the localization of function in the recent times initially came from the work of Franz Josef Gall, a German physician and neuro-anatomist who propounded a radical view in the 1800s that all behaviour and mental functions might be the result of specific processes in specific regions of the brain. He proposed that brain regions can increase in size with more usage, just as the muscle mass adds up with exercise. This increase in size, according to Gall, in turn leads to bumps and ridges on the skull. This view of mental functions based on the bumps on the skull has been referred to as phrenology. Although the idea of predicting mental abilities and personalities based on bumps on the head fell into disrepute, mainly because of its misuse by crooks to fool people and to justify continuation of the class and race based discrimination, it laid a foundation for ideas of localization of the brain function, which remains an active area of research in neuroscience till date. These ideas also started a debate between localizationists (Gall and his followers) and holists (scientists who believed that behavior is the result of the processes which are distributed throughout the brain) about the validity of this hypothesis. Major results in favour of localization of function were published by the French neurologist Paul Broca in 1861, who reported that damage to a particular area in the left half of the brain resulted in the loss of speech showing that there was a 'speech center' in the brain. Broca discovered this by studying a patient, Leborgne, also known as Tan, who could not speak. Postmortem examination of Leborgne's, brain showed damage to a specific region of the left frontal lobe. This speech area has been named after him as the Broca's area. Broca's meticulous note-taking with detailed descriptions of his observations helped in getting his ideas accepted by the scientific community. Around the same time a German physician, Carl Wernicke, described another area involved in speech comprehension which is now called Wernicke's area.

The next major breakthrough in cortical localization came a few years later from the experiments on dogs conducted by Eduard Hitzig and Gustav Fritsch in 1870. Their laboratory for these experiments was a dressing table in a bedroom of Hitzig's house in Berlin. They applied low currents to parts of the cortex and showed that stimulation of specific parts of the brain resulted in movements of specific body parts such as leg, face, neck, forelimb of the opposite side of the body. Thus, they not only localized a movement area in the brain, but also took it one step further to show that within the movement area there are different regions that produce movements of different parts of the body. Other main contributors to these ideas around that time included Robert Todd, Luigi Rolando and John Hughlings Jackson.

Hitzig and Fritsch's study unleashed a flurry of experimental activity to discover areas of the brain responsible for movement and sensation. Sir David Ferrier and Roberts Bartholow were most notable for their study of the motor cortex. Bartholow, a professor of medicine in Cincinnati, Ohio demonstrated existence of the movement area in the human brain in 1874.

Following the proposal of a language area by Broca's clinical studies and experimental demonstration of movement area by Hitzig, Fritsch and others, interest shifted to determining if there are specialized areas in the brain for different sensations. This required an entirely new set of techniques called electrophysiological recordings, i.e., recording electrical activity of neurons as they respond to sensory inputs coming from the sense organs.

Figure 1. This figure shows how ideas about the brain areas responsible for higher cognitive functions have changed from the time of Gall's phrenology (left) to the present day understanding of some of these functions inferred using modern techniques (right).



Richard Canton, Ernst Fleischl von Marxov, Adolf Beck and Hans Berger were the early pioneers who, during a period spanning more than six decades from 1870's to 1920's, showed that electrical current can be recorded from the brain, and that it varies with the state of the activity of the animal.

Richard Canton, Ernst Fleischl von Marxov, Adolf Beck and Hans Berger were the early pioneers who, during a period spanning more than six decades from 1870's to 1920's, showed that electrical activity can be recorded from the brain, and that it varies with the state of activity of the animal. The work of many great neuroscientists such as Hermann Munk, Edward Schafer, Ferrier and Sir Charles Sherrington over period of time led to the current description of areas of the brain that are responsible for different sensations.

But what about the other functions of the brain such as learning, memory, emotions, language, thinking and decision-making? Although the first brain area that was clearly identified was for speech, it became generally accepted that while sensory and motor functions could be localized in the brain, these 'higher' brain functions could not be.

The first researcher to answer the question of localization of memory in specific regions of the human brain was the famous Canadian neurosurgeon Wilder Penfield. Penfield was a student of Charles Sherrington. While operating the brain for treatment of intractable epilepsy in human patients, Penfield stimulated the cerebral cortex and found for the first time sensory, motor and language areas in the brain electrophysiologically. On rare occasions, while stimulating the temporal lobes, the patients reported experiencing a coherent recollection of an incident in their past showing that temporal lobes might be critical for memory.

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The progress in determining the brain areas involved in performing different cognitive functions was slow because the electrophysiological techniques and lesion studies could be done precisely only in animals. The experiments are hard to conduct, and the function could be deduced only by carefully controlling animal behaviour. In humans, data could be gathered only from those with brain injuries or with surgical lesions of the brain, where the extent of damage is usually uncertain. With the advent of modern neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), rapid advances are being made in understanding the brain areas involved in higher cognitive functions. PET visualizes the local changes in the cerebral blood flow and metabolism that occur during mental activities, such as reading, speaking and thinking. fMRI is based on detection of changes in the ratio of oxyhemoglobin to deoxyhemoglobin in specific brain areas, which occur because neurons in those areas are more active and therefore use more energy and oxygen. Using these imaging techniques experiments have been done to detect brain areas that are involved in language, identification of people and objects, emotions such as fear, anger, greed, and decision-making.

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3. The Brain is also Made Up of Cells

Cells as building blocks of plants were first described in 1653 by Robert C Hooke. By 1839 the cell theory, which states that tissues of all living organisms are composed of cells, was enunciated by Matthias Jacob Schleiden and Theodor Schwann. However, the cell theory had not been extended to the brain tissue. In the 19th century two competing ideas prevailed. One, called the reticular theory, postulated that the brain tissue was a continuous uninterrupted network in which information flowed freely. This idea got traction because the prevailing methods at that time failed to resolve individual cells as separate structures in the brain. The fine processes of the cells of the brain could not be traced to their ends and appeared to form a continuous network. This idea was also appealing because it viewed the entire brain as a single structure where all the thought processes had a diffused and mixed existence. The second theory postulated that the brain was composed of cells just like any other part of the body. This theory had roots in the idea of localization of function in the brain.

The fact that the brain is made up of cells was established by the work of two outstanding neuroscientists, Santiago Ramón *y* Cajal[2] of Spain and Camillo Golgi of Italy. Their work revolutionized the way we view and conceptualize the structure and function of the brain, and it forms the basis of all of the modern cellular and molecular neuroscience.

[2] See *Resonance,* Vol.5, No.11, 2010.

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Golgi, in 1873 developed a new staining technique, which is now called the Golgi technique. This technique, which uses silver nitrate, stains only a few cells in the brain. But these few cells get stained completely, down to their fine processes. Cajal's introduction to the Golgi staining technique happened in 1887, when he was 35 years old. That year Dr Luis Simarro Lacabra, a psychiatrist interested in histological research showed Cajal specimens stained by Golgi's silver impregnation technique discovered 14 years earlier. Cajal wrote in his autobiography – "it was there, in the house of Dr. Simarro...that for the first time I had an opportunity to admire...those famous sections of the brain impregnated by the silver method of the Savant of Pavia". 'Savant of Pavia' referred to Golgi, who was working in the University of Pavia.

Using Golgi staining, Cajal, who was the main proponent of the neuron theory, showed that the nervous system is composed of anatomically and functionally distinct cells. From 1887 to 1903, Cajal utilized the Golgi staining methods to document almost all parts of the nervous system. Based on his observations, in opposition to almost all contemporary neurologists, neuroanatomists and neurohistologists including Golgi himself, Cajal put forth and fervently defended the neuron doctrine to explain the structure of the nervous system.

He wrote, "Our observations revealed, in my opinion, the terminal arrangement of the nerve fibres. These fibres, ramifying several times, always proceed towards the neuronal body, or towards the protoplasmic expansions around which arises plexuses or very tightly bound and rich nerve nest...[the] morphological structures, whose form varies according to the nerve centres being studied, confirm that the nerve elements possess reciprocal relationships in contiguity but not in continuity. It is confirmed also that those more or less intimate contacts are always established, not between the nerve arborizations alone, but between these ramifications on the one hand, and the body and protoplasmic processes on the other." His drawings, many of which are collected in his classic book *Histologie du Système Nerveux de l'Homme et des Vertébrés*, although made with a relatively primitive microscope, have all

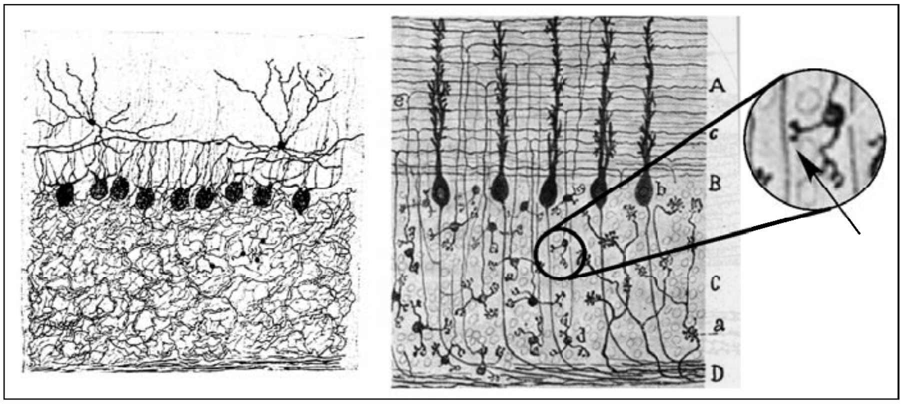

Figure 2. The reticular theory and the neuron theory. The drawings show organization of the nerve cells in the cerebellum as visualized by Golgi staining and drawn by Golgi (left) and Cajal (right). The diagram on the right was published as part of Golgi's Nobel Lecture. Golgi claimed that the nerve fibrils of different kinds of cells found in the cerebellum were interconnected *without a pause between two nerve cells* forming a dense nerve network. Cajal, looking at the same structure, observed a clear separation between individual nerve cells (see the gap pointed by the arrow in part of the magnified drawing in the circle).

been found to be accurate. Cajal noted, "… nervous element is an absolutely autonomous unit"; the term neuron was coined only in 1891 by Wilhelm Waldeyer.

Although we still do not know exactly how the Golgi's technique works, establishment of the neuron doctrine led to all the modern discoveries in neurosciences such as understanding of the structure and function of different types of neurons, their pattern of connectivity, properties of their junctions called synapses, transmission of information in the brain, biochemical analysis of the properties of neurons, neurophysiological characterization of function of individual neurons, and the understanding of how abnormalities of neuronal function leads to many brain diseases.

Although Golgi was a brilliant observer, ironically, he himself remained a firm believer in the idea of reticulate theory until the end. He wrote "If a method of preparation capable of demonstrating the anastamoses of different cells exists, it must be that of black staining…Thanks to this reagent one notes not only the cell body with its primary extension [the axon] clearly revealed, but,

Reticular theory – According to the reticular theory the cytoplasm of the cells of the brain is contiguous, forming a single large network. This theory, which is now abandoned, appealed to the notion of uninterrupted flow of information, thoughts and emotions in the brain.

Neuron theory – Neuron theory of the brain states that the brain is composed of distinct individual cells called neurons. This theory brings the microscopic structure of the brain in accordance with the structure of other parts of the body.

Luigi Galvani discovered that the nerve and the connected muscles of a dead frog twitched when they were touched by a charged electric device. He proposed that animal electricity flowed through the nerve to the muscle causing its contraction.

in addition, the most delicate ramifications. The use of the black dye can be limited to a small number of cells or to more extensive groups; occasionally one may even obtain a comprehensive view of an entire area of the central nervous system". However his many descriptions of the brain remain valid today. He described two kinds of neurons based on how far they send information, which are now called Golgi Type 1 and Golgi Type 2 neurons. He also gave an accurate description of the sensory organ in tendons, which are called Golgi tendon organs.

Golgi and Cajal shared the Nobel Prize in Physiology and Medicine in 1906.

4. Communication Among Brain Cells

Interestingly due to advances in the field of electricity, investigations into the nature of signals that flow in the nerves to communicate with the muscles preceded our understanding of the structural and functional organization of the brain. Luigi Galvani (1737–1798), an eminent professor from the University of Bologna, Italy discovered that the nerve and the connected muscles of a dead frog twitched when they were touched by a charged electric device. He proposed that animal electricity flowed through the nerve to the muscle causing its contraction.

With the original insights of Galvani, electrophysiology in modern times was advanced substantially by three German physiologists – Emil DuBois-Reymond, Johannes Muller, and Herman von Helmholtz, who were instrumental in the characterization of electrical activity in nerve cells and determination of the speed at which the information travels through the nerve. The idea of mind/soul acting on the body through some mysterious force was being challenged more and more by these discoveries in which the electrical nature of the brain–body interaction was emerging.

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With the establishment of the neuron doctrine the immediate question was how neurons communicate with each other. The sharp observer that Cajal was, he also proposed that axons and dendrites, and the processes of the cells, which had earlier been described in accurate detail by Otto Friedrich Carl Dieters, might have specific roles in carrying information to and from neurons. The point of junctions between neurons, where they exchange information was called 'synapse' by Sir Charles Scott Sherrington. The initial clues about how neurons might communicate with each other came from the famous experiments by a German pharmacologist, Otto Loewi.

Neurotransmitters are a family of chemicals that transmit electrical signals from a neuron to a target cell at the synapse.

The vagus nerve, arising from the brain stem, innervates a patch of tissue of the heart, which is responsible for the maintenance of the normal rhythm of the heartbeat. Loewi, who received the Nobel Prize in 1936, dissected out an intact beating frog heart along with the vagus nerve and stimulated the vagus nerve to slow the heartbeat. He then took the fluid bathing this heart and placed another frog heart without the vagus nerve into it, which resulted in the slowing of the heart-beat rate in this second heart. This showed that some soluble chemical released by the vagus nerve was controlling the heart rate. This chemical was later found to be acetylcholine, the first neurotransmitter to be discovered. Neurotransmitters are a family of chemicals that transmit electrical signals from a neuron to a target cell at the synapse. A large number of neurotransmitters have since been discovered each with a specific function. The role of neurotransmitters in neuronal communication and control of information flow is an active area of research. Chemicals that enhance the action of neurotransmitters or mimic their role, and chemicals that block their action are already used in treating many of the brain diseases and symptoms, from pain due to injury to depression.

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5. Adult Brain is Plastic

The cells of the brain generally do not divide in adults. Therefore, the adult brain cannot easily repair itself after injuries, but does it also mean that the adult brain is structurally and functionally incapable of any change? That was the belief until about the 1980's for most areas of the brain, except for those involved in learning and memory. The most recent and the last landmark discovery in the brain sciences discussed here is that the brain

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retains remarkable ability to change even in adulthood, a phenomenon called brain plasticity. Jon Kaas at Vanderbilt University, Tennessee along with Mike Merzenich and colleagues were among the first to show conclusively that after nerve injuries, neurons in parts of the brain that cease to receive sensory inputs acquire novel inputs from other parts of the body. Later, Tim Pons and colleagues showed that the primate brain is capable of a very large-scale reorganization, perhaps due to some underlying new neuronal growth. Initial results on organizational plasticity in the somatosensory or the touch system of the brain were later extended to the other parts involved in vision, hearing and movement. The discovery that the brain can undergo these changes has opened up new avenues for research for recoveries from peripheral nerve, spinal cord and brain injuries, not only by inducing growth, but also by directing appropriate rehabilitative therapy. These findings show that the adult brain is 'trainable' as that of a child, although possibly in a more limited manner.

With the collective efforts of many neuroscientists, many of whom have not been mentioned here, over many centuries the brain has emerged from being a keeper of the soul to a complex electrical organ, which is composed of neurons communicating via electro-chemical signals. The mind can be thought of as the sum of all the electrical and chemical activity in the brain, which also defines the sum of our being.

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Suggested Reading

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