

New Developments in Neuroscience

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Abstract. The human brain is the most complex structure known to man. The complexity of the brain can compete with that of the universe. Neuroscience, the study of the brain and other parts of the nervous system, developed first slowly and then at a rapid pace. Similar to research in many other areas, research in neuroscience is driven by people's curiosity and ingenuity. The brain is a giant information processor that can extract useful features in many forms of sensory signals. The brain is also a controller of complex motor systems and the site of human creativity and consciousness. It has enormous memory capacities, estimated to be in the size of 2.5 petabytes (2,500 terabytes)*(Reber, 2010). Understanding of some of these complex functions has enriched many lives and continues to do so with prospects of tangible public benefits from development of treatment of serious disorders of the brain and indeed the entire body. New hypotheses and serendipitous observations have contributed to many important discoveries. The increased knowledge and understanding of the functions of the nervous system acquired so far has already been beneficial to many people through the development of treatment of various diseases, and it has made it possible to devise ways to reduce the risk of acquiring many diseases. Research regarding organization and function of the brain continue to unveil fascinating aspects that were not imagined just a few decades ago. As stated in the Leonardo da Vinci quote "The noblest pleasure is the joy of understanding." Research requires resources, and the wider attention to the function of the brain brought by "The Decade of the Brain," spanning 1990 to 1999, had a beneficial effect on funding of research on neuroscience. The effect of the increased attention to the function of the brain, from governments and organizations that support research, can be expected to increase also in the future. The main purpose of this article is to describe, in a generally understandable language, some important new developments in neuroscience. The article discusses the implications and importance of recent finding for understanding some of the normal functions of the brain, and how brain functions are altered in some diseases where the symptoms are generated in the brain. The article also provides a brief history of the development of the science of medicine.

Keywords: Neuroscience, new developments, connectivity, plasticity for good or bad, diseases of the nervous system

1. Introduction

The brain is no doubt the most complex and best-designed biological structure, with the greatest adaptability known to mankind. Despite a tremendous increase in knowledge about the brain, that has been gained during the past three decades, our current knowledge about the general function of the brain and the spinal cord (the central nervous system) is still very limited.

Processing signals, which the brain receives from sensory organs, are extensive and to a great part unknown. For example, if the eye was assumed to work as a camera, we would see a picture with a black hole in the lower peripheral corner due to the absence of the photoreceptor cells where the optic nerve leaves the retina. The density of photoreceptors in the fovea of the retina is much higher than it is in other parts of the retina. The image would be distorted because of the uneven distribution of the photoreceptor cells in the retina where an image is projected by the optics of the eye. Little is known about the neural processing of the distorted picture that is produced by the eye, and that makes a person see an undistorted complete picture all the time.

In fact, it may not be productive to ask questions regarding the general function of the central nervous system. Instead, it may be more relevant to ask questions about specific functions of the brain. The fact that many more people are now engaged in neuroscience research than just a few years ago, has been an important factor in our increased understanding of the organization and function of many parts of the central nervous system (CNS - brain and spinal cord). For example, the creation of the Society for Neuroscience, founded 1969, has been beneficial in increasing the general interest in neuroscience. The Society for Neuroscience has dramatically increased its membership during the last three decades, from approximately 4,000 members 30 years ago to approximately 40,000 in 2014. The Society's annual meetings attract approximately 35,000 researchers with a diversity of specialties that covers the field of neuroscience.

2. Early studies of the brain

Our understanding of how the brain and the spinal cord are organized has changed over time, first slowly, then at a rapid pace. Early studies of the brain were first aimed at finding ways to treat diseases. Medical teaching and research was dominated by the work of Galen (Aelius Galenus or Claudius Galenus, (born AD 129, died 199 or 217) between year 200 and year 1543 (more than 1250 years). His studies and teachings were based on the dissection of pigs and monkeys (at this time, it was not permitted to dissect humans). Galen presented proof that the brain controls motion. Little else changed in the knowledge about the brain during that time.

Cartesius, commonly known as Renee Descartes (born 1596, died 1650), presented new hypotheses regarding the function of the central nervous system. Cartesius (Descartes) was a mathematician, a physiologist, and much more. He contributed to mathematics and gave name to the commonly used (Cartesian) coordinate system.

Cartesius envisioned the brain as having two main different parts: One part had functions that could be replicated by mechanical devices; he used the withdrawal reflex as an example of that. The other part was more complex; he called it the soul. His dualistic principle of the function of sensori-motor processes consist of a system that is predicable (mechanistic) and one that is not (the soul). He chose the pineal gland as the location of the soul because it is one of the few single structures in the brain while almost all other structures in the brain appear in pairs. This dualistic principle was the basis for discussions by many scientists for many years.

One of the first attempts to emulate bodily functions of an animal by mechanical devices was a mechanical duck, designed by a 29-year-old watchmaker, Jacques de Vaucanson (1709-1782). His mechanical duck was displayed in the gardens of the Tuileries, France, 1738.

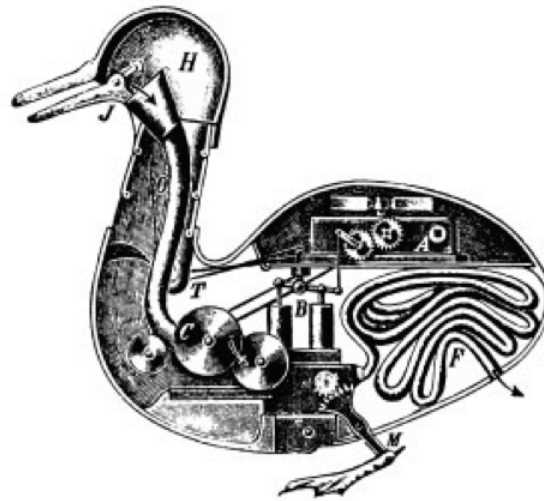


Figure 1. Vaucanson's duck, the first robot

More recently, many computer models have been proposed for emulating specific functions of the nervous system, and many computational models of specific functions of the CNS have been published.

3. A brief history of the development of modern neuroscience

It was not until experimental neuroscience (scientific study of the nervous system) was born, that important questions could be answered in neuroscience. That era of neuroscience, more or less, started with the work of Francis Bacon (1561-1626), who is credited for having introduced experiments in studies of biology. He advocated a critical view on old science. Among other important discoveries, it is worth mentioning that Francois Magendie (1783-1855) discovered that sensory information enters in dorsal spinal roots, while motor information exits in ventral roots. Later (in 1863), the Russian physiologist Ivan Sechenov (1829-1905) discovered inhibitory synapses. More recently, experimental work by Charles Sherrington (1857-1952) provided a major increase in knowledge concerning many basic functions of the CNS. Sherrington is often regarded to be the father of modern neurophysiology. Specifically, he studied spinal reflexes and described the action of the synapse. He also emphasized the importance of how different cortical areas of the brain interact with each other. The Hungarian anatomist J. Szentágothai (1912-1994) made use of the then newly developed electron microscope to describe the structure of the synapse. Later, the Australian neurophysiologist John Eccles (1903-1997), and the American neurophysiologist Eric Kandel (1929-) studied some of the basic functions of synapses, including the role of synapses in memory storage.

4. Recent developments in neuroscience

Modern neuroscience may be regarded as having two main parts. One part studies how systems in the brain are organized, work and interact, which is known as systems neuroscience. The other branch is the study of the biochemistry (molecular biology) of nerve cells and other cells in the central nervous system. In this review we will first discuss new development in systems neuroscience.

4.1. Systems neuroscience

During the past two or three decades, our understanding of how the brain is organized has advanced substantially. For example, it was earlier believed that the brain was generally compartmentalized with specific regions devoted to specific functions, such as that of motor and sensory systems (figure 2).

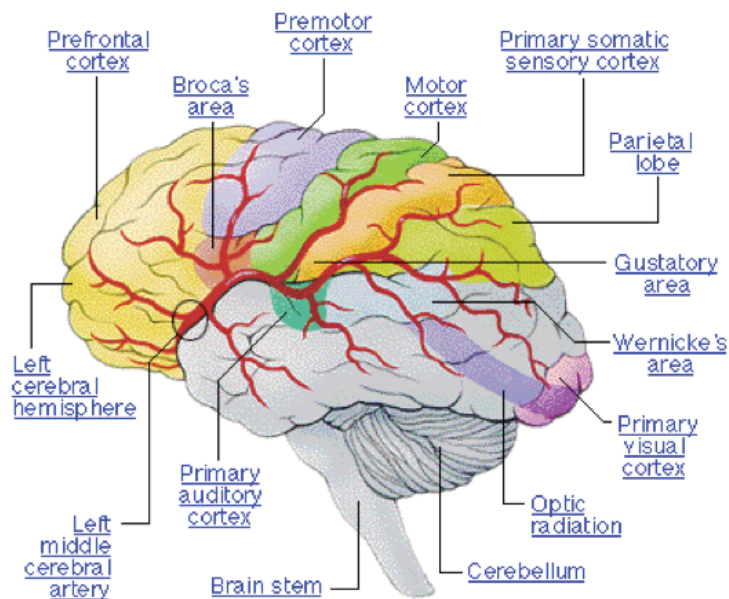


Figure 2. Old view of the organization of the brain showing compartmentalization.

It was believed that sensory processing and generation of motor commands occurred in specific anatomical parts of the brain. It is now understood that the brain is a distributed system, where a specific task is carried out in several anatomically different parts of the brain. It is generally accepted that the different parts of the brain do not operate independently, and that many parts of the brain participate in multiple functions.

The brain and the spinal cord control many systems of the body that was earlier believed to function independently. It is now known that the function of a certain part of the nervous system can be affected by other systems, including the inputs from the gut. For example, information from the intestines exerts some control over the immune system, and the immune system has some control over body functions such as pain.

4.2. Anatomical organization of the brain

Development of new technologies for anatomical studies aiming at identifying the course of nerve fibers (axons) in the brain and the spinal cord, have provided new insights into the anatomical organization of the brain. However, the function of the connections that axons make depends on the efficacy of the synapses that connect the axons from one nerve cell to another. Newly developed technologies have made it possible to identify which anatomical connections are functional, and to what degree (Schlee, *et al.*, 2012; Schlee, *et al.*, 2010).

Recent developments in neuroscience include new methods for studying the anatomy of connections (axons between cells in different structures), as well as the functions of these anatomical connections, with regards to the strength of the connections. Anatomical connections have been studied for many years, but studies of functional connections have had important contributions recently due to the development of new techniques.

Matteo Bastiani and Alard Roebroek, 2015 (Bastiani and Roebroek, 2015) have described some of the recently developed techniques for studies of the anatomical organization of the central nervous system. Earlier techniques for studying the neuroanatomy of the central nervous system were limited to histological staining and light microscopy. These techniques produced just a two-dimensional view. A recently introduced method, diffusion magnetic resonance imaging (MRI), makes it possible to study the structural organization and connectivity of the human brain in more detail (Bastiani and

Roebroek, 2015). Diffusion MRI and new tractography techniques (Qi, *et al.*, 2015), in particular, have been used to probe the architecture of both white matter (nerve fiber tracts) and gray matter (clusters of nerve cells) in three dimensions.

The technique of tractography (figure 3) offers 3-D modeling that can be used to visually represent neural tracts using data collected by diffusion tensor imaging (DTI), a special techniques that uses MRI, together with computer-based image analysis.

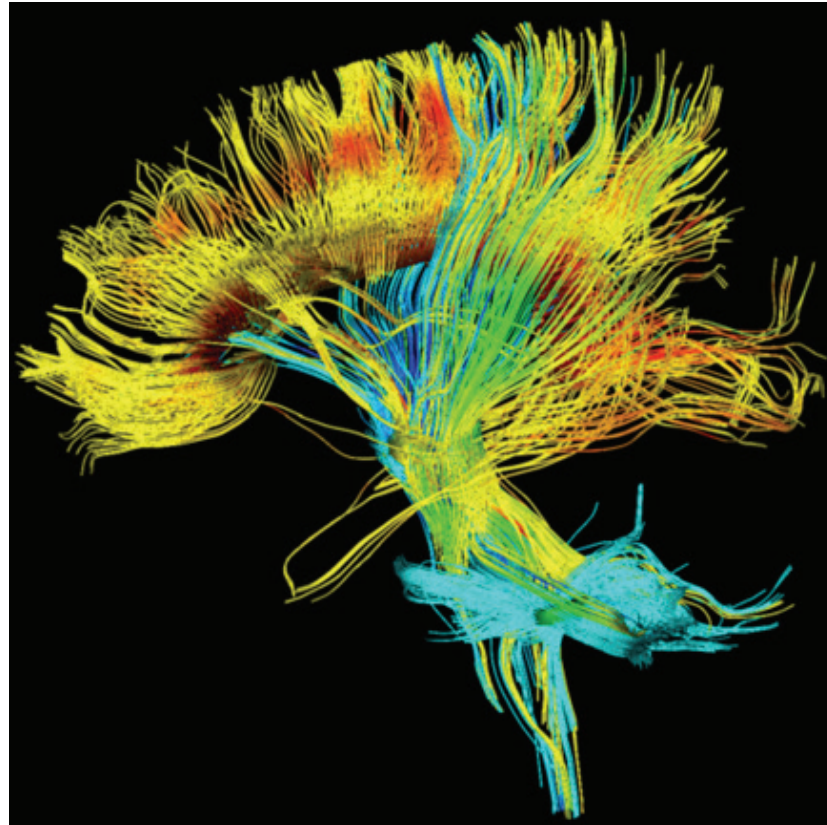


Figure 3. Receptors in the intestines influences the immune system, illustrating a result of tractography. From Siemens.com (Patent)

Since its introduction in 1994, the DTI methodology has been used to study the white matter architecture and integrity of the normal brains, and in the brain of people with diseases where the pathology is related to alterations in white matter (nerve fibers), such as in multiple sclerosis, stroke, aging, dementia, schizophrenia, etc. (Mori and Zhang, 2006).

Combined with mathematical network analysis, these techniques are increasingly influential in the investigation of the macro-, meso-, and microscopic organization of brain connectivity and anatomy, both in vivo and ex vivo. Other recently described methods for studying brain anatomy make use of a kind of detergent for removing surrounding material, making it possible to study details of nervous structure. After such chemical treatment, a whole organ can be made transparent. These new techniques produce beautiful pictures that may provide information not obtainable with other techniques (figure 4).

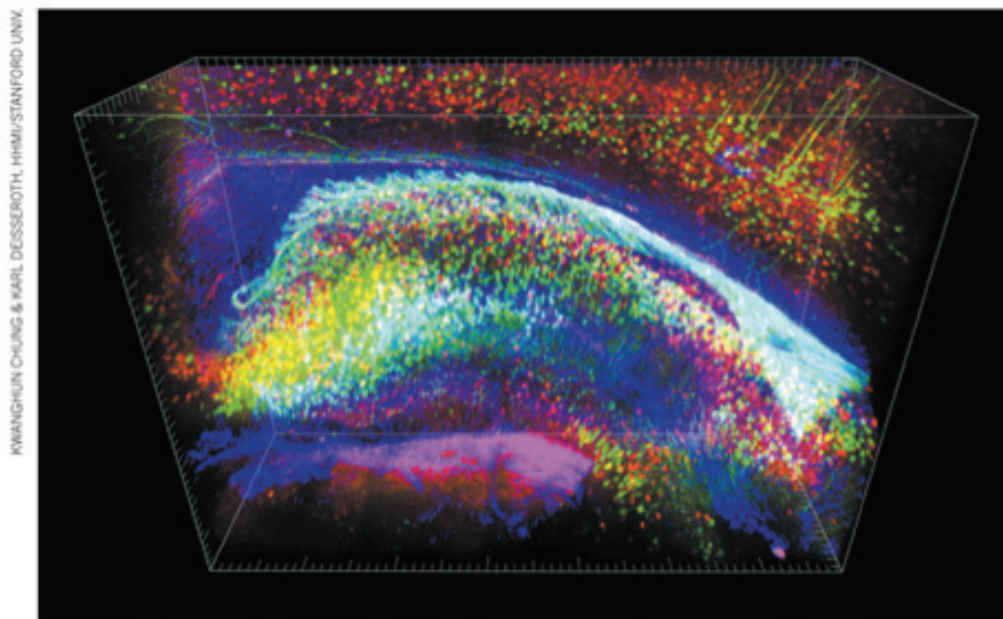


Figure 4. An example of a picture of neurons in an intact mouse hippocampus using CLARITY and fluorescent labeling, described by Karl Deisseroth.
(Chung and Deisseroth, 2013) From: Helen Shen 2013 (Shen 2013).

4.3. Functional connections

There are extensive anatomical connections between multiple parts of the brain, but not all connections are functional because of ineffective synapses (Wall, 1977). Only relatively recently has it become possible to study the functionality of anatomical connections. While anatomical connections between specific nerve cells either exist or not (are all or none), functional connections are graded, and the connections can be more or less strong.

New technology has made quantitative studies of the strength of connections in the brain possible. Techniques such as magnetoencephalographic (MEG) recordings, some form of electroencephalographic (EEG) recordings and measurement of very small changes in blood flow (Blood-Oxygen-Level Dependent, BOLD) contrast imaging, known as functional MRI (functional magnetic resonance imaging, fMRI) have made it possible to quantitatively determine the strength of connections between large groups of nerve cells in different parts of the brain.

Studies of functional connections have fundamental importance for understanding the organization of the central nervous system, and a new branch of neuroscience has evolved, known as the "study of connectivity" in the brain and the spinal cord. Studies of functional connectivity in the brain are possible because of the development of techniques such as MEG recordings. Studies of connectivity have developed into a quantitative method that is promising for understanding not only the normal functions of the brain, but also for the study of diseases, and what causes the symptoms of many diseases.

Studies of connectivity have revealed that the brain is a distributed system. The extensive functional connections that exist between most regions of the brain are often reciprocal creating loops, where information may circulate. That is probably the basis for the use of iterative methods in interpreting information in the brain.

Recent studies of functional connectivity have shown that most tasks, even simple ones, engage many parts of the brain simultaneously; several parts of the brain are involved in most tasks, and some parts of the brain can do more than one task.

Connections in the brain have similarities with the connections in modern communication systems. The connections between nerve cells in different brain systems have similarities to the connections made by airlines, that have a hub and spoke structure of their route maps (figure 5). The routes from a hub to different cities that are served by an airline have different number of travellers, and that can be expressed as the strength of the different connections from a hub. The connections between structures in the brain also have different strengths, and the strength can be expressed as the ability of axons to activate their target nerve cells. The strength of the connections in the brain can now be measured by using techniques such as MEG and EEG recordings; or by using BOLD contrast imaging a method used in fMRI.

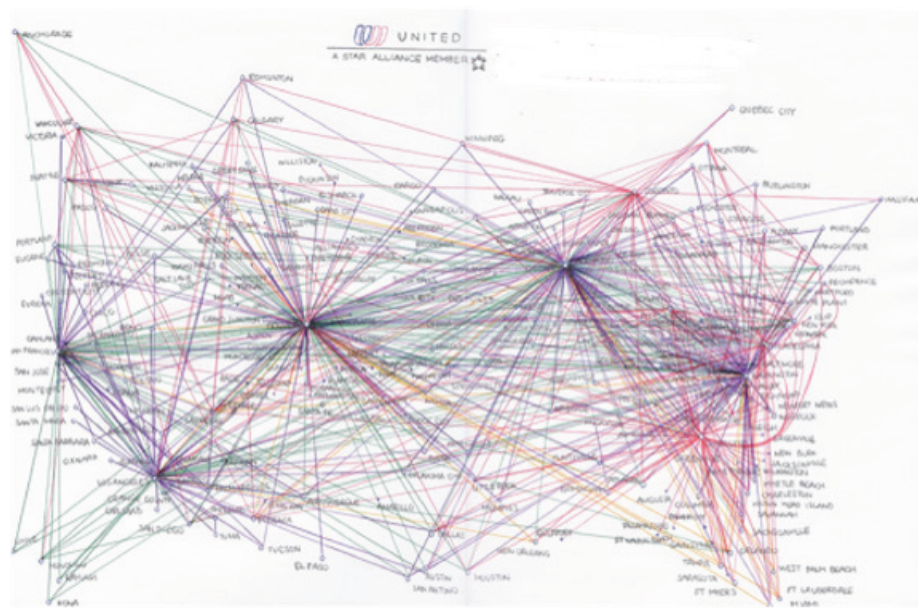


Figure 5. Route map of a large American airline (United Airlines). (From Schlee, 2011)

5. Neuroplasticity and its role in creating symptoms of disease

Neuroplasticity is the term used to describe the ability of the nervous system to change its function, mainly accomplished by changing the efficacy of synapses. Ineffective synapses can be made effective (Wall, 1977) by establishing functional connections, or effective synapses can be made ineffective, by blocking the function of anatomical connections. The brain is plastic, for the most part, and neuroplasticity can be beneficial in allowing for the creation of new learning skills, and restoring functions after damage. Neuroplasticity is important in the post-natal development of the nervous system (Møller, 2014). Neuroplasticity is also the basis for memory and making it possible to learn new skills. It has recently become evident that neuroplastic changes in the function of the central nervous system are also involved in creation of symptoms and signs of diseases, which means that neuroplasticity can also be harmful (Møller, 2014).

Neuroplasticity mainly involves changes of synaptic efficacy, but can involve changes in nerve cell protein synthesis as well. Activation of neuroplasticity can make synapses conduct better, it can make synapses that do not conduct at all conduct, or it can make synapses that conduct well stop conducting. Neural conduction in synapses is a graded process. The strength of connections depends on the efficacy of synapses. Since connections depend on synaptic efficacy, changes in synaptic efficacy through activation of neural plasticity, can also change connectivity in the central nervous system.

Changes in synaptic efficacy, such as the changes that may occur when neuroplasticity is activated, can open connections in the brain or the spinal cord that normally are closed, because the synapses that connect an axon from one cell to another cell cannot be activated. Symptoms from the opening of

normally dormant connections may result in a re-routing of information, and the subsequent activation of structures in the brain that are normally inactivated.

It has become evident that the redundancy in the brain is greater than earlier believed. This means that the same task can be done by several different parts of the brain. This has many important implications. One is recovery of functions after brain damage, such as from strokes and traumatic brain injuries where the parts of the brain that normally perform specific functions, such as control of muscles, are not functioning. For that to become possible, it is necessary that specific functions can be taken over by other system. The mechanisms for such switching of functions is neuroplasticity.

5.1. Change in connections in the brain plays an important role in many diseases

It is noteworthy that connections between different parts of the brain are not stagnant but dynamic. A change in synaptic connections may cause symptoms of disease, and may contribute to age-related changes in neural function. Altered connections in brain networks are involved in creating phantom perceptions, such as occurs in severe tinnitus, and in chronic neuropathic pain (Schlee, *et al.*, 2011).

It has recently been found that connections in the anterior cingulate and parahippocampus are stronger in persons who exhibited high degrees of long-time distress with tinnitus, than in persons who do not experience distress (Song, *et al.*, 2013). These findings indicate that neural circuits, which are not normally active, have become activated in these disorders. That has been assumed to be, at least partly, the cause of the ghost symptoms, and the suffering components of the disease.

Sensory deafferentation, or other forms of reduced input to the central nervous system, causes increased activation of specific structures in the brain, such as respective cortical regions in phantom pain and tinnitus (De Ridder, *et al.*, 2011a).

Studies of connections in the brain have helped to explain many features of diseases where the symptoms are caused by altered connections ("miswirings").

For example, it has recently been shown that the parahippocampus is involved in multiple networks that are active in different forms of expression of diseases such as neuropathic pain and tinnitus. (De Ridder, *et al.*, 2014; Schlee, *et al.*, 2009). Thus, a single hub can be involved in multiple overlapping networks (figure 6)

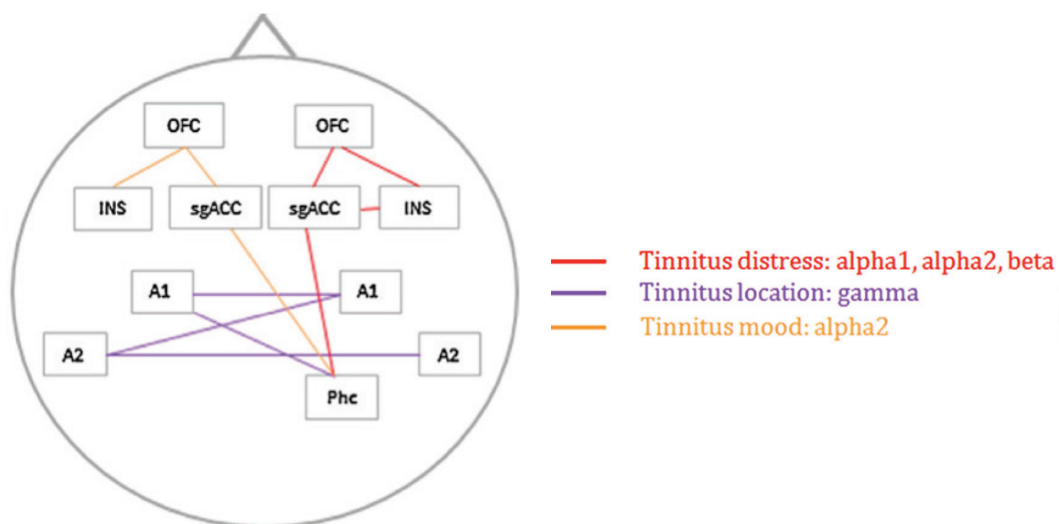


Figure 6. Illustration of how a specific structure, the parahippocampus (Phc) connects to many other structures. A1: left auditory cortex, A2: Right auditory cortex, sgACC: subgenual anterior cingulate cortex, OFC: orbitofrontal cortex (From: De Ridder *et al.*, 2014 (De Ridder, *et al.*, 2014)).

Studies of connectivity have provided evidence that phantom sensations, such as pain and some forms of tinnitus, somehow involve parts of the old brain such as the nuclei of the limbic system, also known as the emotional brain (LeDoux 1996), in addition to sensory cortices. Especially, the nuclei of the amygdala and the anterior cingulate are now known to be extensively involved. There is also now evidence that the fifth lobe of the brain, the insular lobe, is involved in some of these diseases, but the functions of this part of the brain is still poorly known. Activation of these structures is at least partly responsible for the distress and mood symptoms such as depression that often accompany disorders of phantom sensations. Deafferentation is an extreme change in neural connections. Deafferentation caused by interruptions of peripheral nerves, or by fiber tracts in the brain, plays important roles in many diseases, especially chronic pain and tinnitus. Deafferentation may also be involved in creating the symptoms and signs of spasticity and the phantom limb syndrome (figure 7).

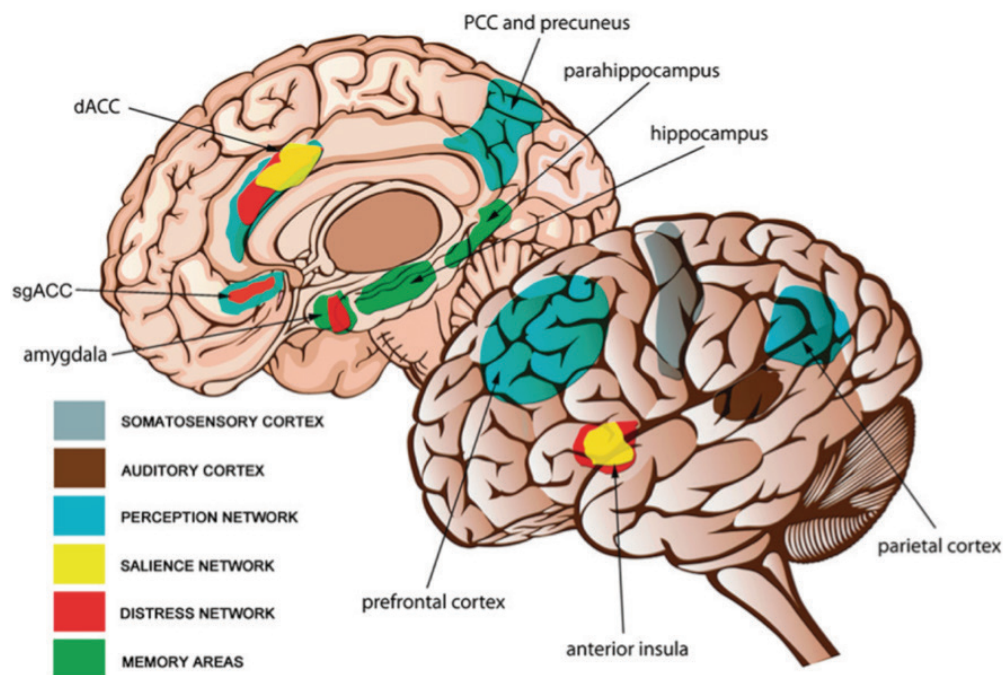


Figure 7. Brain networks involved in phantom perception. Sensory deafferentation causes increased activation of respective sensory cortices in phantom pain and tinnitus. Deafferentation may cause changes in many structures, such as the somatosensory cortex (gray in figure 7) in the case of phantom pain, and changes in the auditory cortex (brown) in the case of tinnitus. Perceptual network: subgenual and dorsal anterior (dACC) and posterior cingulate cortex (PCC), precuneus, parietal cortex, and frontal cortex (blue). Salience to the phantom percept is reflected by activation of dACC and anterior insula (yellow). Distress is related to activation of the anterior cingulate cortex (sgACC and dACC), anterior insula, and amygdala. The persistence of the phantom percept involves the parahippocampal area, amygdala, and hippocampus (green). From: DeRidder *et al.*, 2011 (De Ridder, *et al.*, 2011b).

6. Memory

Many efforts have been devoted to improving memory in general, and to restoring deficits, such as those that commonly occur during ageing. There are also situations where memory, or specifically memory consolidation, is enhanced. It is thus known that stress, in particular, can enhance memory. The reason for that is that adrenergic agonists can enhance consolidation of memory. In 1985, McGaugh (Roosendaal and McGaugh, 2011) showed memory enhancement from adrenergic activation, such as occurs during stress and in fearful situations. Memory consolidation and retrieval

are also affected by estrogen, testosterone, caffeine, amphetamines, and physical exercise that increases brain derived neurotrophic factor (BDNF).

Similarly, much effort has been dedicated to alleviate the symptoms of PTSD by trying to erase specific memories, such as memories related to traumatic events. Thus far, only a small degree of progress has been achieved. Drugs such as barbiturates and scopolamine can erase short-term memory, but not long-term memory. Since adrenergic stimulation promote consolidation of memories (Roozendaal and McGaugh 2011), adrenergic receptor blockers, such as propranolol, impair memory consolidation. Administration of beta-adrenergic blockers might then reduce the adverse effect of traumatic memories, but it seems to need to be given before the traumatic events to be effective.

The impairment of memory consolidation and retrieval from administration of beta adrenergic blockers is an unwanted effect, that occurs when these pharmaceuticals are used to protect the heart from overload. Only one of the available forms of beta-adrenergic blockers, atenolol, does not affect memory consolidation, because it does not pass the blood-brain barrier.

7. Large parts of the brain are involved in many functions

Earlier, the task of interpreting a spoken word was believed to be done in an area of the brain that is also used for production of speech, known as Wernicke's area (figure 8). The results of recordings of gamma activity in awake conscious persons show that much larger parts of the brain are involved in interpretation of spoken words, thus not only Wernicke's area seems to be involved (figure 9).

Recordings of gamma activity (EEG waves with frequencies between 80 and 100 Hz) have contributed to studies of functional connectivity, together with other components of EEG recordings, such as the alpha activity (waves in the frequency range of 7.5 to 12.5 Hz). Functional connectivity has also seen the contribution of what is known as functional MRI (fMRI).

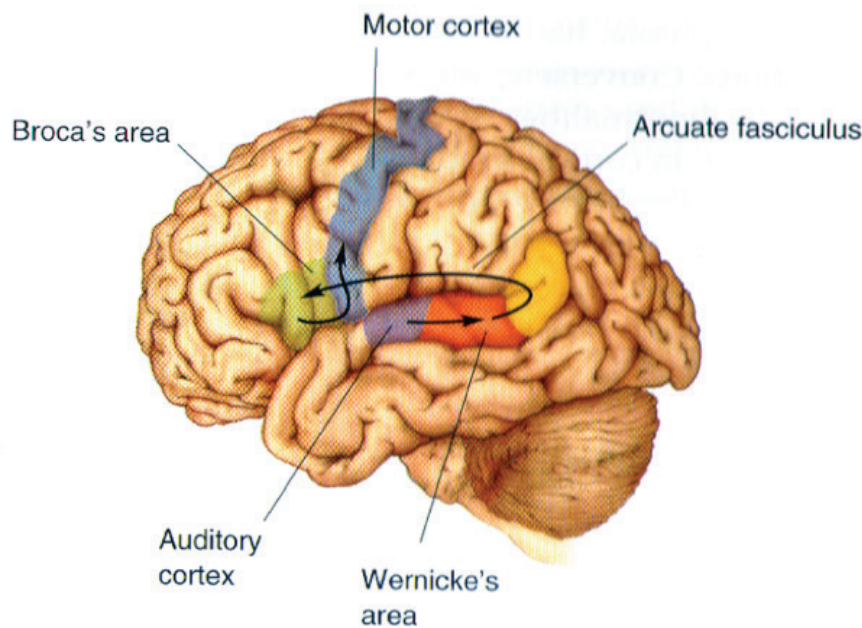


Figure 8. Old concepts regarding the organization of the areas of the brain that are involved in production of speech, and in the interpretation of speech.

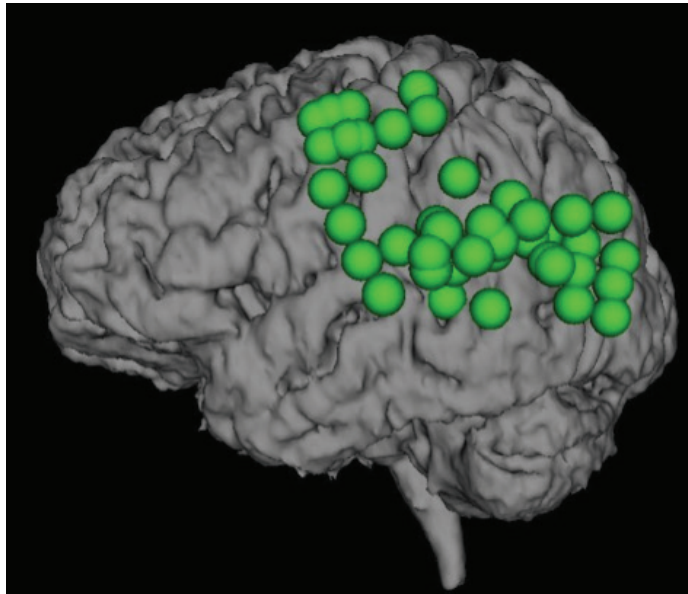


Figure 9. Regions of the cerebral cortex with high levels of gamma activity in people who are interpreting a spoken word. High level of gamma activity is regarded as a strong sign of neural activity. The picture is a composite illustration from studies of approximately 30 people. It shows the locations where recordings of the gamma activity from the exposed lining of the brain (dura mater), in conscious people, had high values. (From V. L. Towle, 2008 (Towle, *et al.*, 2008)).

8. The mind can influence the body

It is not only signals from the environment, and from organs in the abdomen, that can influence the function of structures in the brain. Also the "mind" can control many functions, such as how muscles contract. There are examples of how just thinking can affect basic functions of the body. Figure 10 shows an example of how just thinking can alter the strength of contraction of muscles on the hand elicited by the same electrical stimulation of the motor cortex.

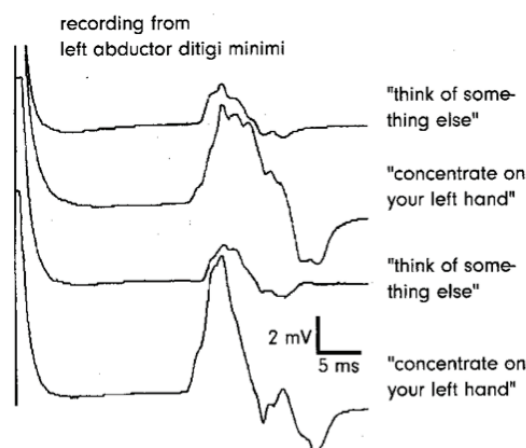


Figure 10. Illustration of how the mind can modulate motor functions. The graph shows electrical activity recorded from a muscle on the hand, elicited by magnetic stimulation of the motor cortex, in an awake person (From Rösler, 2001 (Rösler, 2001)).

It can be seen from the recordings in figure 10 that simply thinking about the hand can increase the strength of the muscle contraction. This is a sign that the mind can control the excitability of the motor system. In the experiment illustrated in figure 10, the electrical activity from muscles of the hand were recorded when the motor cortex was stimulated by electrical current induced by magnetic impulses applied through the skull to the brain (figure 11).

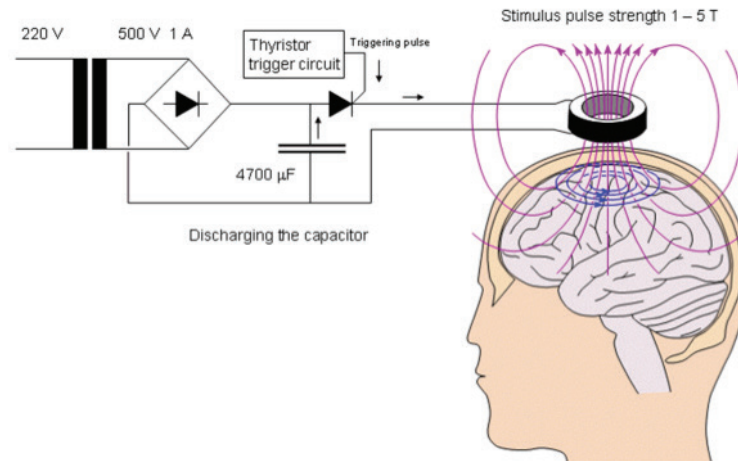


Figure 11. Transcranial magnetic stimulation (TMS) can be used to activate brain structures by inducing electrical current in the brain. It is painless, and does not cause any other noticeable inconvenience.

Physical exercise has been known to increase the production of BDNF and, more recently, it was found that physical exercise also facilitates the recycling of organelles in nerve cells. This means that the voluntarily contraction of muscles can affect many systems in the brain. This is just another example of how extensive and complex interactions between widely different body and brain systems are.

Breathing deeply can reduce stress, thus another example of how brain functions can be affected by muscle activity.

9. New techniques in studies of brain functions

Technology developed for diagnosis of the location of epileptic foci has made it possible to study the function of different structures in the brain. For example, studies of the insula lobe (the fifth lobe of the brain), which is often the site of epileptic foci (Stephani, *et al.*, 2010 ; Stephani, *et al.*, 2009), have introduced new valuable methods for studying many different aspects of brain function. These methods use electrical stimulation and recording from multiple locations within the region of the brain, where the epileptic foci are expected to be located (figure 12). The purpose of these studies is to provide information about the anatomical location of epileptic foci, so as to provide direction of surgical treatment of severe epileptic seizures.

In addition to the value for diagnosing the anatomical location of the start of epileptic seizures, these studies also provide much information about the normal function of the structures in the brains where this technique is used.

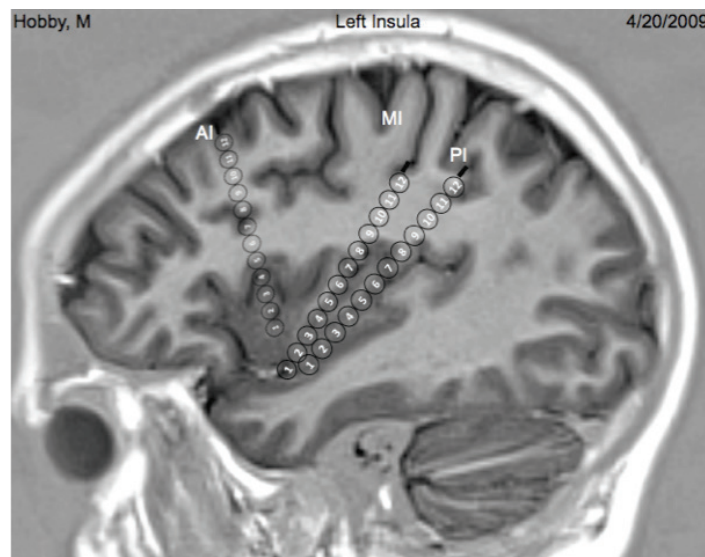


Figure 12. Implanted electrodes for stimulation and recording from different locations in the insular lobe. In this study, 123 electrodes were implanted. From: Casper Stephani, 2009 (Stephani, *et al.*, 2009).

The studies by Stephani (Stephani, *et al.*, 2009) provided important information about the function of the insular lobe. Since the person undergoing such diagnostic studies is conscious, he/she can communicate what he/she experiences when specific locations are stimulated. This diagnostic method allowed studies of the basic function of specific region of the insular lobe. Previously, little was known about the insula lobe and its functions but, as a byproduct of these diagnostic studies, much has been learned about the function of the insular lobe. Similar methods would be suitable for studies of other regions of the human brain.

9.1. The vagus nerve

The vagus nerve, the tenth cranial nerve, was traditionally known for supplying autonomic (parasympathetic) innervation of the heart and to organs in the abdomen including sexual organs. It is only recently that the ascending fibers of the vagus nerve have attracted noticeable attention from neuroscientists. These ascending vagus nerve fibers send signals to the brain from sensors in abdominal organs, such as receptors in the small intestine. These influences are generally reciprocal, and the brain can influence the function of organs such as the liver and the pancreas, kidneys, and sexual organs, mainly through the vagus nerve, or by substances secreted from cells in these abdominal organs. The gallbladder, pancreas, and the stomach can influence the brain through the vagus nerve, and also through a hormone, cholecystokinin (CCK). It has recently become evident that the vagus nerve also influences the immune system.

There is now considerable interest in the use of artificial (electrical) stimulation of the ascending part of the vagus nerve. Electrical stimulation of the vagus nerve is commonly used for breaking and reducing the risk of epileptic seizures (FDA approved). Similar methods are now being used for treating depression (FDA approved), and studies are in progress regarding its possible use in treating diseases where maladaptive plasticity plays an important role, such as chronic neuropathic pain and severe tinnitus (Engineer 2013; Engineer, *et al.*, 2011).

The axons of the vagus nerve terminate on cells in the nucleus tractus solitarius, and these cells send axons to many parts of the brain. That means that the vagus nerve can activate cells in many parts of the brain (figure 13).

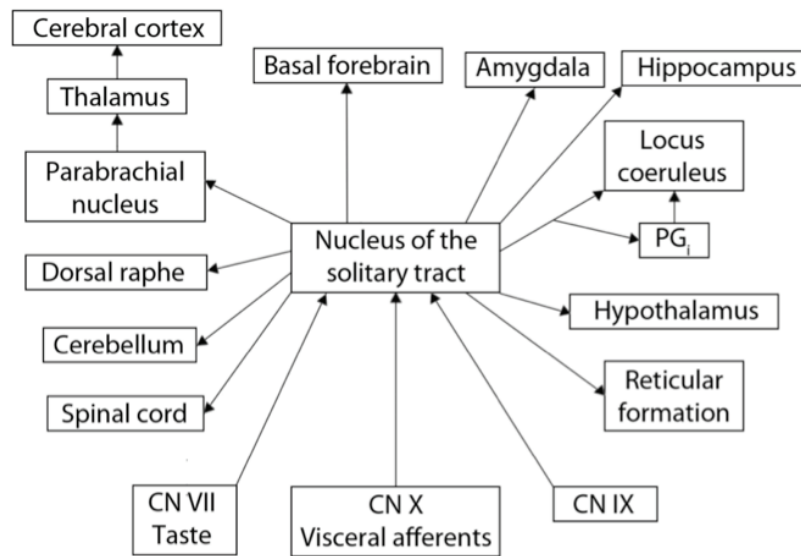


Figure 13. Illustration that shows how many structures can be reached by activity in the vagus nerve, that terminate in the cells of the nucleus of the solitary tract.

In addition, there is evidence that the ascending fibers in the vagus nerve play the role of redundant sensory pathways from lower abdominal organs, that exist in parallel with the better known spinal cord pathways (Alexander and Rosen, 2008; Komisaruk, *et al.*, 2004). The vagus nerve can also control the ability of the nervous system to change its function through enhancing neuroplasticity. This has opened a possibility to reverse some diseases that are believed to be caused by activation of bad plasticity.

Electrical stimulation of the vagus nerve, together with appropriate sensory stimulation, is now being tried for treating disorders that are believed to be caused by bad plastic changes (maladaptive neuroplasticity), such as chronic pain and tinnitus (De Ridder D, 2014; Engineer, 2013). There are also indications from studies in animals that vagus nerve stimulation, together with stimulation of the sensory system, can make recovery from strokes faster (Khodaparast, *et al.*, 2014).

Stimulation of the vagus nerve can be accomplished by placing electrodes on the vagus nerve where it travels on the neck, thus a relatively easy and safe way of activating many structures in the brain.

9.2. What is the language of communication between nerve cells?

The language of communication between individual nerve cells is the discharge pattern in axons, and in some axons, it is secretion of molecules that have been transported in the axons. Earlier, it was believed that the rate of discharges of individual nerve cells was a measure of the level of excitation in specific parts of the brain. However, many thousands of nerve cells are involved in creating messages, and it is now becoming evident that the neural activity in individual nerve cells is not a valid measure of the excitation in structures of the brain such as sensory systems. Instead, studies have indicated that the coherence of impulse activity in ensembles of nerve cells is a better measure of neural excitation than the discharge rate of individual nerve cells (Eggermont and Tass, 2015; Møller, 1984; Møller, 2003). However, there are tremendous obstacles in studying the coherence in the discharge activity of large ensembles of nerve cells.

10. Diseases of the nervous system

It is not only progress in understanding the normal function of the nervous system that has advanced, but also understanding the pathologies of the nervous system has advanced considerably over the past two or three decades. It was previously assumed that disease symptoms were caused by (pathological) changes in the function of specific parts of the nervous system, and that the symptoms were related to detectable morphological changes. That was the reason imaging techniques came to play dominating roles in diagnostics of many diseases of the central nervous system. There is now considerable evidence that altered connections in the brain play an important role in many diseases. Initiation of neuroplasticity going wrong (maladaptive plasticity) can contribute to the development of symptoms of diseases.

It has become evident recently that neuroplasticity going wrong can cause symptoms of diseases. We call such diseases "plasticity diseases". It is now evident that symptoms of some diseases are caused by functional changes in the brain or spinal cord that are not associated with morphological (structural) changes that can be detected by available imaging techniques. The harmful plastic changes, induced by activation of "maladaptive neuroplasticity" that is involved in more diseases than earlier assumed, are examples of diseases that have no detectable morphological correlates.

It is now generally agreed upon that harmful (maladaptive) plasticity is the main cause of chronic neuropathic pain, severe tinnitus, spasticity, and some forms of muscle spasm. Phantom limb syndrome is perhaps the clearest evidence of the involvement of harmful plasticity in generating symptoms.

Earlier, it was believed that symptoms were mainly caused by pathologies of specific parts of the nervous system. It is now evident that many neurological diseases have signs of malfunction of more than one part of the nervous system. Whether and how such different parts of the central nervous system contribute to the symptoms is not always known. Some parts of what was earlier known as the motor system, such as the supplementary motor areas, are also now known to be involved at least in some forms of chronic neuropathic pain (Tsubokawa, *et al.*, 1991). The basal ganglia, that were regarded to belong to the motor system, are also involved in creating the symptoms of the plasticity diseases. The nucleus accumbens also plays a role in chronic neuropathic pain (Chang, *et al.*, 2014). The nucleus accumbens is mainly regarded to be involved in addiction and reward matters.

The symptoms of many diseases of the nervous system have two distinctly different parts, one is a ghost sensation. The other is less distinct, and can best be described as causing distress and suffering. To further complicate matters, diseases such as tinnitus and chronic neuropathic pain are not a single disease but a group of different diseases (Møller, 2010b; Møller, 2003).

Diseases that are caused by harmful plasticity are often referred to as "plasticity diseases". There is a general consensus that neural network dysfunctions are related to many disorders of memory, including age related diseases such as dementia, specifically Alzheimer's disease.

Diseases such as severe and chronic neuropathic pain are classified as phantom (ghost) sensations due to the absence of physical stimulation. Such sensations are caused by the activation of neural circuits, which normally are activated by physical stimulation; that is the reason for the perception of ghost sensations such as pain and tinnitus.

10.1. The immune system

While the role of the immune system has earlier been assumed to be restricted to fight intruders of various kinds, such as virus and bacteria, it is now evident that the immune system has a much wider importance than earlier believed, and that it controls many neural functions. There are therefore several reasons to discuss the immune system from a neuroscience point of view. It is also now evident that the immune system plays an important role in neurological diseases, such as chronic neuropathic pain (Marchand, *et al.*, 2005; McMahon, *et al.*, 2005).

It is also now known that the nervous system controls many aspects of the functioning of the immune system. For example, receptors in the gut can affect the immune system mediated through the vagus nerve.

Humans have two different immune systems: The innate immune system and the adaptive immune system. The innate immune system cannot “learn”; it is programmed to respond to different kinds of intruders, such as bacteria and virus, but also abnormal cells, such as cancer cells, are assumed to be the targets of the innate immune system. The adaptive immune system is plastic, and can “learn” to exhibit a stronger response to repeated exposures. The adaptive immune system is slower to respond than the innate immune system.

It is now known CCK plays a role in the activation of an anti-inflammatory pathway from sensors in the small intestine to the immune system (Raybould, 2007). This means that what happens in the small intestine may influence (decrease) the risk of getting sick.

Many organisms have immune systems that are similar to that of humans. For example, recent studies of the basic functions of the innate immune system in a 1mm long worm (nematode) show that the worm’s immune system has many similarities with the human’s immune system (Tracey, 2011). The worm’s immune system is controlled by the nervous system; it is balanced, not too strong and not too weak. The immune system in this worm that uses the same molecules as is in use in our immune system (acetylcholine) can control many functions of the nervous system.

The human brain and spinal cord have their own immune system, where microglial cells have a similar function as T-cells in the body.

10.2. Childhood development

Many diseases, especially autism spectrum disorders, spina bifida (a birth defect that includes incomplete closure of the spinal canal), and many craniofacial anomalies (such as cleft palate), are now believed to be a result of fault occurring during the development of the nervous system early in pregnancy (Kelly, *et al.*, 2012; Møller, 2007; Schanen, 2006).

Recent developments have made it possible to reduce the risk of giving birth to a child with spina bifida, autism, and possibly other serious diseases such as malformations of the bones of the face, such as cleft palate. Studies published in the early 1990’s showed evidence that the risk of giving birth to a child with spina bifida could be reduced substantially if the mother takes folic acid, a B vitamin, before and during pregnancy (Chitayat, *et al.*, 2015; Surén, *et al.*, 2013). More recently, it was shown that the risks of giving birth to a child with autism could be reduced by as much as 50% by taking folic acid before and during pregnancy (Surén, *et al.*, 2013).

This indicates that autism and spina bifida are caused by faults in the neural programming that controls development before birth (DeVilbiss, *et al.* 2015). This is naturally of great practical importance, but it is also of theoretical importance in that it supports the hypothesis that diseases, such as autism and spina bifida, are caused by faults (defects) that occur early in pregnancy. This may explain why it has not been able to correct the pathology by treatment after birth, when the symptoms become evident.

The sensory nervous system must receive input early in life in order to develop normally. Studies in animals have shown that depriving light to the eyes causes morphological abnormalities in the visual cortices (Wiesel and Hubel, 1964). The results of other animal studies indicate that other senses, such as vision, can take over the unused hearing cortex (Horng and Sur, 2006). Sur and Leamey 2001 (Sur and Leamey, 2001) showed in studies in animals that, if the auditory nervous system was deprived from input immediately after birth, a miswiring of the brain occurred. The nerve fibers from the visual system were seen to connect to cells in the auditory thalamus, and from there connect to cells in the auditory cortex. When the animals matured, cells in their auditory cortex responded to light stimulation as an indication of misdirected visual information. These experiments showed that cells that are not active might be invaded by input from other systems.

Lack of activation of any system in the brain of young individuals may therefore have serious consequences, because of this attempt to fill voids in the nervous system. This is one reason why it is important to give deaf children some input to their auditory nervous system.

10.3. Age related changes

The understanding of the causes of the typical signs of old age, such as memory loss and other signs of dementia including Alzheimer's disease, has changed recently. Recent studies seem to indicate that dementia can be delayed, and perhaps avoided, by being active both physically and intellectually (Martinez de Villarreal, *et al.*, 2006). Dementia, including Alzheimer's disease, exhibits similar risk factors to cardiovascular diseases. It has been known for some time that physical exercise, and intake of sufficient amounts of Omega-3 fatty acid, folic acid, and other vitamins (Das, 2008), increases synthesis of brain derived neurotropic factor (BDNF), which is an important substances in the central nervous system (Gómez-Pinilla, *et al.*, 2002; Wu, *et al.*, 2004). Meditation is regarded to be beneficial for its ability to decrease stress by cultivating a beneficial internal state in the brain.

It has been shown recently that autophagy ("self eating") in cells in the brain is facilitated by physical exercise (Levine, *et al.*, 2015). More recently, it was shown that autophagy of organelles of nerve cells is important for normal functioning of cells, and impaired autophagy has been linked to diseases such as cancer.

In general, recent research in neuroscience has emphasized the importance of a person's lifestyle for longevity and quality of life. It was earlier believed that loss of nerve cells in the brain was the cause of memory loss, but it has recently been shown that there is little to no loss of nerve cells in the brain of an older individual. Age-related shrinking of the brain must therefore have other causes than nerve cell loss. Loss or shrinking of glial cells may be one of the causes of the shrinking of the brain that normally occurs with aging (see table below). While the average number of nerve cells remains rather stable during adult life, at least until 80 years of age, there exists a considerable loss of nerve fibers in the brain (Marner, *et al.*, 2003).

The strength of some connections in the brain may increase, while the strength in other connections may decrease, as a person ages (Schlee, *et al.*, 2012). Specifically, changes in functional connections between specific parts of the brain are correlated with decrease in the ability to retain visual information (figure 14). It is seen from figure 14 that stronger connection to the temporal lobes is associated with decreased cognitive performance, as shown by the Benton test, which measures the ability to retain information. There is, at the same time, a reduced inflow to the medial temporal lobe system, reduced input to the posterior cingulum/precuneus region of the brain, a stronger connection to the temporal lobes, and a stronger inflow to the posterior region (Schlee, *et al.*, 2012).

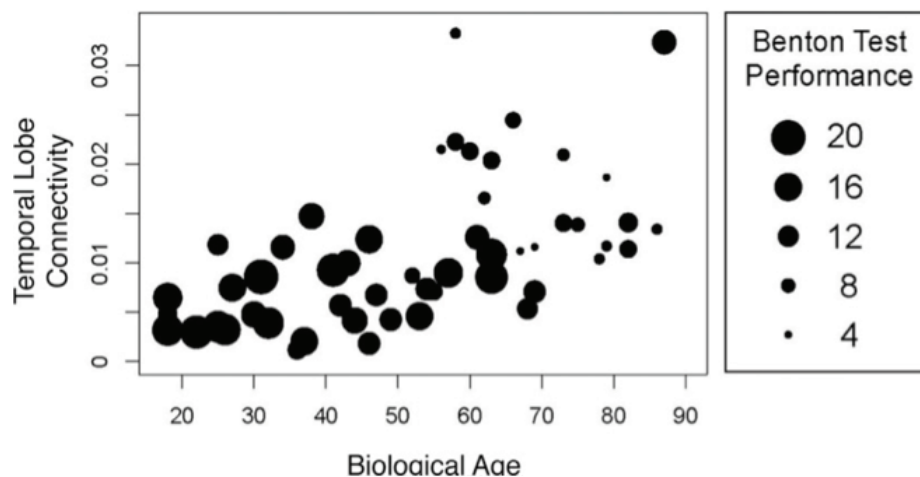


Figure 14. Graphical illustration of the association between biological age, temporal lobe connectivity, and performance of the Benton test. The vertical axis shows mean partial-directed coherence (PDC) values for the left and right temporal lobe connectivity as a function of age. Advancing age leads to stronger connectivity of the temporal lobes (from Schlee *et al.*, 2012 (Schlee, *et al.*, 2012)).

The association between biological age, temporal lobe connectivity, and performance of the Benton test is particularly interesting because it links important performances, such as memory, to specific measurable changes in the brain.

11. How do diseases develop?

It has also been shown in recent studies that stress has an adverse effect on the nervous system. Development of disease is often complex, and it is rarely possible to link a single cause or event to the development of a disease. For this reason, the likelihood of a disease is described by risk factors, rather than a single cause. Very different diseases, such as cardiovascular diseases and neurological diseases like dementia, share the same or very similar risk factors. It was shown recently that the pathology of chronic neuropathic pain and severe tinnitus has many similarities (Møller, 2010a). These two seemingly very different symptoms engage some similar parts of the brain (De Ridder, et al., 2014; De Ridder, *et al.*, 2011a), (figures 6 and 7). This means that it is possible to learn valuable essentials about one of these diseases from studies of the other one.

It has become evident that what is known as stress has many more different effects on body functions than earlier believed. Stress affects many brain functions, and causes increased release of several important substances, mainly norepinephrine and corticosterone (Selye, 1956). Stress may increase the likelihood of diseases such as virus infections, and some forms of cancer. Recent studies have shown that stress suppresses immune reactions, which may be how it affects the risk of infectious diseases and some forms of cancer.

Stress also promotes hypertension, which is the primary risk factor for cardiovascular diseases and for stroke. High blood pressure is a risk factor for many diseases; it is the most important risk factor for stroke. It is therefore of great importance to treat high blood pressure. Hypertension is currently defined as blood pressure of 140/90. A recent study showed great benefits of lowering the systolic blood pressure further (Group, 2015).

Norepinephrine and corticosterone affect many basic functions, such as the cardiovascular system and alertness. Epinephrine (adrenaline) and norepinephrine (noradrenaline) are important for consolidation of memories. Now it is known that these substances affect many more neural functions. For example, it was recently shown that stress through the release of epinephrine and corticosterone increase the duration of acute pain. Epinephrine and corticosterone also promote the conversion of acute pain into chronic neuropathic pain (figure 15).

Mechanisms underlying stress-induced pain chronification after surgery:

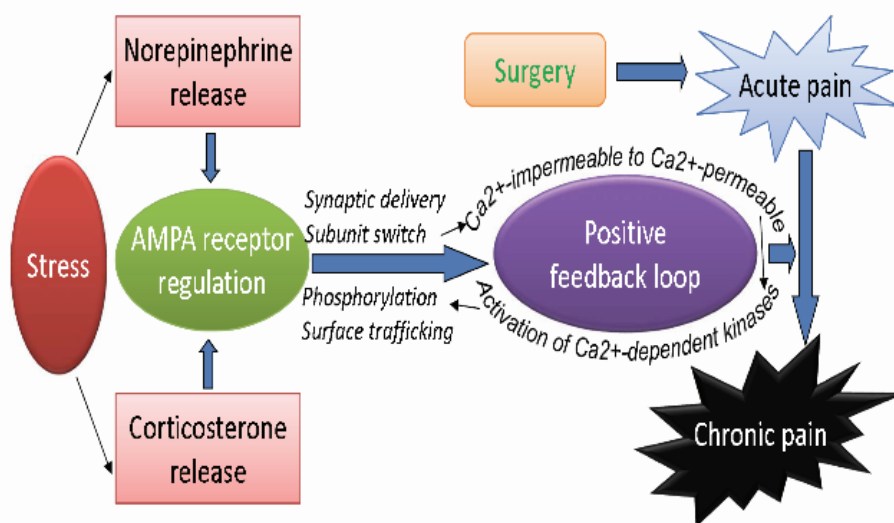


Figure 15. Mechanisms underlying stress induced chronification of pain after surgery. The model shows the role of stress on acute pain and in the development of chronic neuropathic pain. Courtesy Dr. Feng Tao, 2015 (Li, *et al.*, 2014).

It has been estimated that most incidences of chronic neuropathic pain are in fact caused by poorly treated acute pain, such as resulting from surgery and other forms of bodily trauma. This means that the commonly given advice by healthcare professionals that patients should be careful by not taking too much pain relievers is, in fact, promoting the development of chronic neuropathic pain, which is difficult to treat successfully.

What a person eats is also important, and there has been much progress in understanding the role of food in causing diseases. In particular, the knowledge about the role of food in reducing the risk of many diseases has increased recently. In studies of the effect of different kinds of food on the risk of contracting certain diseases, it has again become evident that different systems of the body interact in many complex ways. Less attention has been given to the beneficial effects of some kinds of food in reducing risk factors of diseases. Examples are many forms of food that contain antioxidants. There is increasing evidence of the benefit from supplements, such as vitamins and omega-3 fatty acids.

It has been known for some time that severe head injuries (closed head injuries) often lead to the occurrence of dementia earlier in life. However, it has only recently been known that what was earlier regarded as light head injuries, such as concussions, also increase the risk of dementia occurring many years later.

The role of environmental factors on the development of diseases has become more and more obvious. One of the most recent studies shows that walking in nature can have more positive effects on a person, compared with walking in a city environment (Bratman, *et al.*, 2015).

12. Recent discoveries regarding biochemistry of the brain

The biochemistry of the brain has been studied intensively, specifically regarding the chemicals that mediate transfer of information in chemical synapses (transmitter substances). These transmitter substances play important roles in the general function of the CNS. It is also believed that neural transmitters play important roles in many diseases, and that the correction of such faults could alleviate the symptoms of, and even cure, many diseases. Many modern medications have been based on basic research involving neurotransmitters. The importance of neuronal transmitters and errors (faults) in neural transmitters is evident from the fact that, discoveries of many neural transmitters and their role in diseases, have been awarded the Nobel Prize and many other prestigious awards. In 1970, three scientists were awarded the Nobel Prize in Physiology and Medicine for their work on neural transmitters. These were Julius Axelrod, Bernard Katz and Ulf von Euler. The 1994 Nobel Prize in Physiology and Medicine was given to Alfred G. Gilman and Martin Rodbell for their discovery of G-protein coupled receptors, and their role in signal transduction. Arvid Carlsson, Paul Greengard and Eric Kandel shared the year 2000 Nobel Prize for their discoveries concerning signal transduction in the nervous system.

Some of the medications developed have been highly beneficial, and changed the way certain diseases are treated; other new medications have had severe side effects or limited beneficial effect, thus emphasizing the complexity of biological systems.

Elevated blood pressure can have many causes, stress is one common cause, and reducing stress can be beneficial and even life saving. There is now a family of drugs available (beta adrenergic receptor blockers) that is effective in preventing or reducing the effect of these adrenergic substances on blood pressure and heart rate. The first beta-adrenergic blocker was propranolol, developed by James Black, who was awarded the Nobel Prize 1988. With the exception of atenolol, these drugs pass the blood-brain barrier and cause impairment of memory.

Angiotensin, that is synthesized in the body and increases blood pressure, can cause hypertension if excessive. The level of active angiotensin can be reduced by blocking the enzyme that converts one

form of angiotensin, angiotensin I to the active form, angiotensin II. A drug that can inhibit this enzyme, angiotensin converting enzyme (ACE) inhibitor, was discovered 1975 and approved for use in treatment of hypertension 1981. There is now a family of drugs with this effect, and these drugs have been very successful in treating severe hypertension.

Findings that the common neurotransmitter, serotonin, is low in people with depression, initiated attempts to restore the level of serotonin by drugs of various kinds. Available drugs do that by inhibiting reuptake of serotonin (selective serotonin re-uptake inhibitors, SSRI). SSRIs are believed to increase the level of serotonin by preventing its reuptake in the presynaptic cell, thereby increasing the amount of serotonin available for the neurotransmission. Prozac was the first in a series of drugs that were expected to restore normal levels of serotonin. Prozac was introduced in 1987 as a wonder drug, especially for treatment of depression. Other drugs followed Prozac with similar effect, such as Paxil and Zoloft.

After many years of extensive use of the various different kinds of SSRIs for treatment of various forms of depression, Fournier, *et al.*, 2010 (Fournier, *et al.*, 2010) found that the benefit from the administration of SSRIs increases with the severity of depression symptoms. These investigators found that the benefit of administration of SSRIs is substantial compared with administration of an inactive substance (placebo) in people with very severe depression, but on average the effect may be minimal or nonexistent in patients with mild or moderate symptoms.

Recent studies have shown that the hormone cholecystokinin (CCK) has many functions, including potential clinical applications. CCK type A is secreted from the first segment of the small intestine, and causes the release of enzymes from the pancreas and bile from the gall bladder. There is now considerable evidence that most of the CCK-mediated intestinal feedback involves activation of extrinsic neural pathways, such as the vagal afferent pathway inhibition of food intake in response to the presence of food in the small intestine (Raybould, 2007; Strader and Woods, 2005).

This hormone is also active in the brain where it is both a neurotransmitter and neuromodulator, and it has also been shown to suppress hunger. Recent evidence has suggested that the hormone CCK also plays a major role in inducing tolerance to opioids, and that it is involved in creating the pain hypersensitivity some people experience during opioid withdrawal (Raybould, 2007).

New evidence has revealed other important actions of CCK that are mediated through the vagus nerve and which are involved in general body functions, such as regulation of food intake.

13. Conclusions

The complexity of the brain is overwhelming, and only comparable with the universe. Despite our accelerated increase in knowledge about the brain, we have only scratched the surface. In studies of the universe, and in physics in general, hypotheses have played a much greater role than what they do in biology and, indeed, in neuroscience.

Many seemingly basic questions regarding the functions of the central nervous system are still unanswered. For example, when a person hears a sound, the person's awareness has been activated but it is not known where in the brain that occurs, and it is not known what specific neural activity causes the awareness of sensory signals. Something is known about the procession of sensory information, but it is not known which parts of the brain are activated and what processes produce the awareness. Which structures are involved in creating the perception (feeling of) "self"?

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