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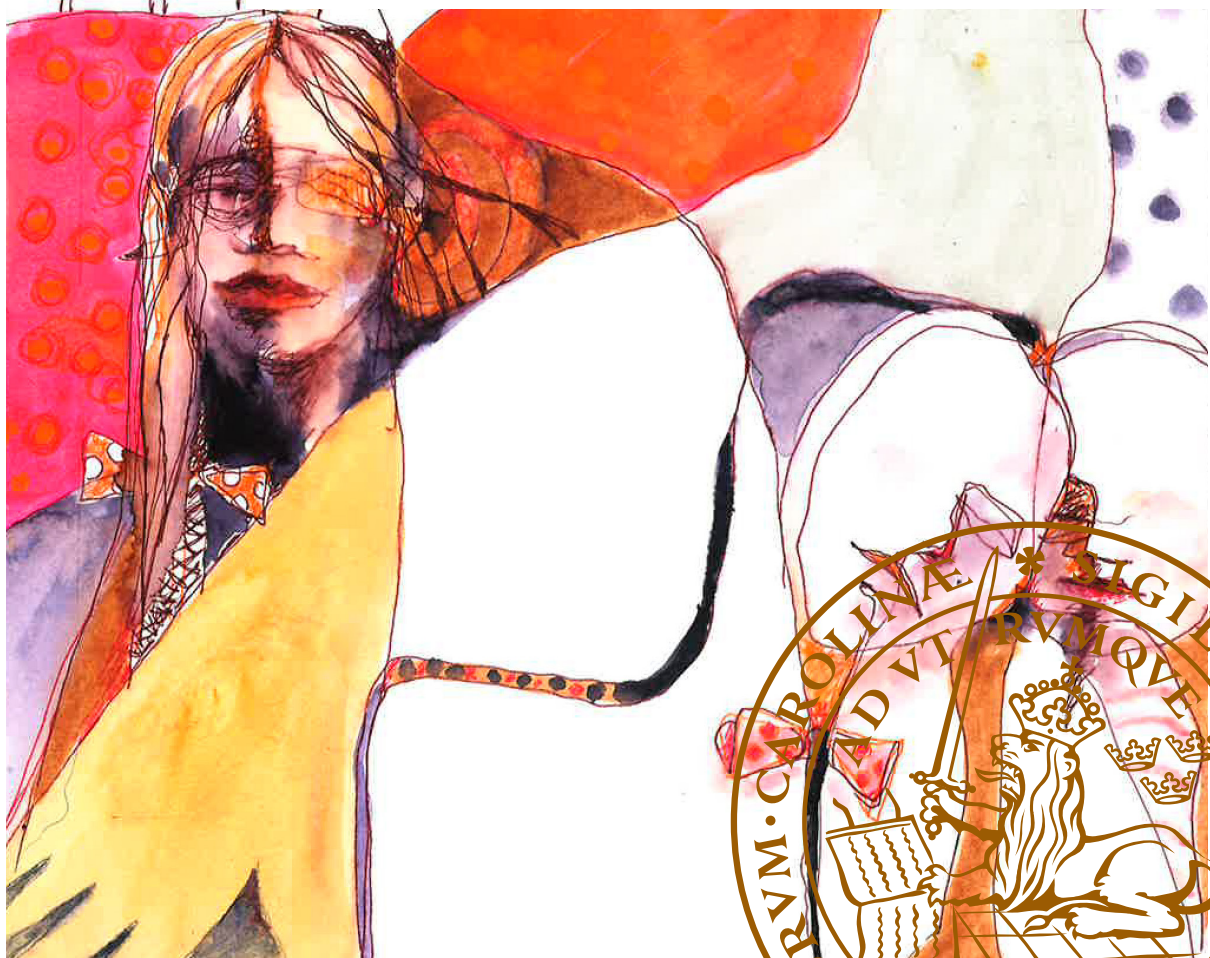


Information Processing in the Nervous System

On a Holistic Functional Organization Principle

JONAS M. D. ENANDER

NEURAL BASIS OF SENSORIMOTOR CONTROL | LUND UNIVERSITY



Information processing in the nervous system

Information processing in the nervous system

On a holistic functional organization principle

Jonas M. D. Enander



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DOCTORAL DISSERTATION

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Title and subtitle Information processing in the nervous system: On a holistic functional organization principle			
<p>Abstract</p> <p>This thesis is concerned with the nature of information processing in the nervous system. This issue has been investigated with animal experiments, using male Sprague–Dawley rats, and simulated touch generated by an artificial fingertip with neuromorphic tactile sensors. The processing of the tactile input from the artificial touch system has been analyzed in light of two opposing theories on information integration in the nervous system. The commonly accepted theory of functional localization, where distinct functions are believed to reside in localized clusters of neurons (e.g. the specific digit area of the primary somatosensory cortex); and the opposing holistic theory where function is seen as a result of the net activity of the nervous system, i.e. as an integrated whole. In addition to the experimental studies, a simulation study has been made to evaluate the validity of a self-organizational formative principle for the connectivity schemes seen in the spinal cord. Self-organization is a cornerstone for the holistic theory and hence the inclusion.</p> <p>The above outline has resulted in four papers. In paper I a dense interaction between the neocortical representations of individual digits was shown, questioning the discrete nature of historically popular cortical maps. In paper II this was further expanded when complex responses to tactile stimuli was found across the whole dorsal surface of the neocortex. The interdependence between these findings were implicated in paper III in which we showed that a stroke in a distant cortical area had a negative impact on the decoding performance of tactile stimuli in the primary somatosensory cortex, thus serving as support for the holistic theory of an indivisible neocortical modus operandi. Finally, in paper IV an initial argument was made for self-organization rather than detailed preprogramming as the formative rule for circuit formation. Paper IV also included the development of a novel interpretation of an artificial neural network as well as a model organism.</p> <p>The findings of the included papers are contextualized with a historical background looking back more than 2000 years and also with a theoretical background in neuroscience, genetics and mathematics. All in all trying to present a multifaceted but relevant discourse on the topic of information integration in the nervous system.</p> <p>The results of the included papers are in favour of the holistic interpretation. A holistic functional brain organization must thus be seen as plausible and with it follows consequences for how information processing can occur in the network of the nervous system and also how a functional decomposition might be possible, or impossible, to perform. One such consequence is that the neocortex should be seen as an indivisible unit of a dynamic system.</p>			
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On a holistic functional organization principle

Jonas M. D. Enander



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*To Moje
always curious*

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Preface

The organization of the thesis is intended to provide a structure upon which two competing theories of functional organization of the nervous system can be evaluated. The first section outlines the historical background relevant to the thesis. Then a description of the anatomical foundations of the nervous system follows as well as a theoretical consideration of the nature of different sensory experiences. This hopefully gives a relevant background to why the experiments in the included papers were designed as they were. Then a short introduction to network theory is presented as it contains one of the core observations upon which much of the discussion is built, the ‘small-world’ network. Finally, a short argument is given why this thesis on experimental neurophysiology is relevant to the medical professional.

The second major part of the thesis is a general description of the methods employed in the included papers. For an in-depth description the reader is referred to the appendix and each particular paper. The third major part is an overview of the results from each included paper, and once again the reader will be referred to the appendix for all the details.

Last are the discussion and conclusions. There the competing theories of functional localization and holistic organization will be pitted against each other in an attempt to clarify the explanatory potential they have in relation to the information given to that point.

Finally, I would like to ask for forgiveness if I have missed obvious references where due. Those inescapable mistakes stem from restrictions in knowledge and not intention. Furthermore, any ideas that are presented as the authors own may have been expressed before, and failure to honour the intellectual heritage is not intentional. Albeit, some ideas are the author's own, but he may certainly not be the first to have them.

List of original papers

I) Jonas M. D. Enander and Henrik Jörntell. (2019). Somatosensory Cortical Neurons Decode Tactile Input Patterns and Location from Both Dominant and Non-dominant Digits. *Cell Reports*, 26, 3551-3560.

II) Jonas M. D. Enander, Anton Spanne, Alberto Mazzoni, Fredrik Bengtsson, Calogero Maria Oddo and Henrik Jörntell. (2019). Ubiquitous Neocortical Decoding of Tactile Input Patterns. *Frontiers in Cellular Neuroscience*, 13, 1-17.

III) Anders Wahlbom* , **Jonas M. D. Enander***, Fredrik Bengtsson and Henrik Jörntell. (2019). Focal neocortical lesions impair distant neuronal information processing. *Journal of Physiology*, 1-15.

IV) Jonas M. D. Enander, Adam M. Jones, Matthieu Kirkland, Jordan Hurless, Henrik Jörntell, Gerald E. Loeb. A Model for Self-Organization of Sensorimotor Function: I. Spinal Monosynaptic Loop. *Manuscript*.

* Shared first authorship based on equal contributions

Introduction

This thesis is on the subject of how information is processed in the brain. To try to answer this rather imposing question experiments using simulated touch and recordings from brain cells (called neurons) has been performed and virtual simulations of developmental stages of the nervous system has been executed. However, before the particulars of the results and the ensuing discussion are presented the fundamental question needs some attention. What do we know about how the brain processes information? How does the brain work?

Many presentations, books, and discussions concerning the brain tells us that the brain has billions of neurons and it is often added that there are trillions of connections, called synapses, between these neurons. As a yardstick of comparison it is usually said that there are more synapses in the brain than stars in the universe. This is probably meant to inspire awe in the listeners and perhaps also in the speaker. Yet, as an isolated statement it is quite uninformative. The number of cells in the intestine is also in the billions and their connections with each other is also astronomical. However, when someone speaks about the number of neurons and their interconnections they hint at something more. It is an implication of complexity and of the almost mystical behaviour that somehow arises out of that complexity. It is a poetic way to ask the previous question: *how does the brain work?*

When studying the question of how the brain works it is often easy to start by searching the internet or picking up an introductory book on the subject of neurophysiology. Soon a picture of the brain is presented and upon the surface of the brain are colorful areas drawn with descriptions of which function each particular area serves. It seems very simple. Still there are comments that we do not know how the brain works. How can that be? There seems to be something missing if we can divide the brain into specific functional areas and still not know how they operate together. It begs the question how the subdivision of the brain came to be and how certain we are of the validity.

As it turns out, the debate on the nature of the function of the brain has been raging for a large part of modern, and not so modern, history. The exploration into how our behaviour emerges from our bodies began thousands of years ago and it has been a long journey. Working our way through trying to figure out from what behaviour emerges, which are the atomic parts and how these parts work together. The first part of the introduction will provide a thin outline of that history and a basis to evaluate how certain we are of the current state of affairs.

Historical background to the debate on cortical functional localization

The seed of a cerebrocentric neurophysiology

Naturally, the origin of human behavior has mystified us since our minds became powerful enough to formulate the question. For a large part of human history the organ that carried the burden of being the source of our behaviours was the heart. Exactly who first proposed the idea that the brain instead was the seat of origin is not clear and the difficulty of knowing inherently correlates with the amount of writings that has survived through time. Nevertheless, found in some of the earliest records of dissections, performed by the greek Alcmaeon of Croton (born c. 510 B.C.), are descriptions of the optic nerves and in Alcmaeons later writings he proposes that the brain is the central organ of the mind (Finger 1994; Smith 2013).

Contemporary to Alcmaeon of Croton were both Democritus (c. 460–370 B.C.) and Plato (c. 429–348 B.C.). They both believed in a triune soul where different behaviours were said to be rooted in different locations. One part was located in the heart, one part in the gut and one part in the head. The part in the heart was associated with higher passions such as anger, fear and courage. The part in the gut was associated with lower passions such as lust, greed and desire. Plato argued that these two parts perished whenever a person died, but the part that was located in the head, associated with intellect, was immortal. This inclination to parcelate behaviour and locate these in different locations indicated a greater degree of analysis than before. However, even with this intellectual seed it took almost five centuries before the cardiocentric paradigm started to give way to a cerebrocentric and the brain won over the heart.

The first real strides toward a cerebrocentric view was made by Galen of Pergamon (c. 130–210 A.D.). He refined a theory put forth by Herophilus (d. 280 B.C.) and Erasistratus (d. 250 B.C.) that stated that the machinery of the mind was due to animal spirits filtered from the blood and deposited into the ventricles of the brain (Smith 2013). These spirits could then through the nerves control the body. Galen suggested that these animal spirits could affect the brain itself since he had made the connection that an injury to the brain affected behaviour (Finger 1994). This theory became the intellectual foundation upon which the function of the nervous system was based on well into the Renaissance (Smith 2013).

Functional division of the brain

On May 5 1543 Andreas Vesalius (1514–1564) published his opus magnum *De humani corporis fabrica libri septem*¹. These books were concerned with human anatomy and were the results of numerous autopsies of humans performed by Vesalius. The neuroanatomical descriptions within marked a major advance of the subject from Galen's previous work, which had been primarily based on cadavers of cattle. Importantly Vesalius noted that the ventricles in humans were not unlike those of other mammals (Fig. 1), whereas the difference in reasoning power was. Thus, since the reasoning power was superior in humans but the ventricles were to a large degree similar to other mammals, he denied that the ventricles were the seat of the mind. However, he did not reject that it were animal spirits that were the core of the machinery of behaviour.

Further advances were made in 1664 when Thomas Willis (1621–1675) published his book *Cerebri anatome*². Within he divided the brain into functional parts and firmly placed the functions within the brain matter itself. Willis for example suggested that the cerebral gyri (the folds of the brain surface) controlled memory and will. This coupling of comparative anatomy, clinical and experimental material and theory was formative of the continuing development of neurophysiology (Finger 1994).

Still, it took until the beginning of the 18th century before the function of a specified brain area was widely accepted. Julien-Jean-César Legallois (1770–1840) was the first person to show through experiments on rabbits that respiration was only impaired when a cross-sectional lesion was performed at the level of the eighth cranial nerve³ (Legallois 1812). If the lesion, however, was performed caudally (above; closer to the snout) the respiration would continue. The location of the respiratory center was in 1851 defined to an even greater extent by Marie-Jean-Pierre Flourens (1794–1867), a highly respected French scientist and a professor of comparative anatomy in Paris.

Around the same time, two scientists, Charles Bell (1774–1842) and François Magendie (1783–1855), separately discovered that the dorsal roots of the spinal cord were sensory (concerned with the senses) while the ventral roots were motor (concerned with movement). This separation is nowadays known as the Bell-Magendie Law. The discoveries by Flourens, Bell and Magendie further established

1 The English translation is “On the fabric of the human body in seven books”

2 The English translation is “Brain anatomy”

3 The eighth cranial nerve is called nervus vestibulocochlearis and is in reality two nerves that partially runs in parallel (nervus vestibularis and nervus cochlearis). The first terminates in the vestibular system in the inner ear and relates to balance while the second terminates in the cochlea and enables hearing (F. Johansson 2015).

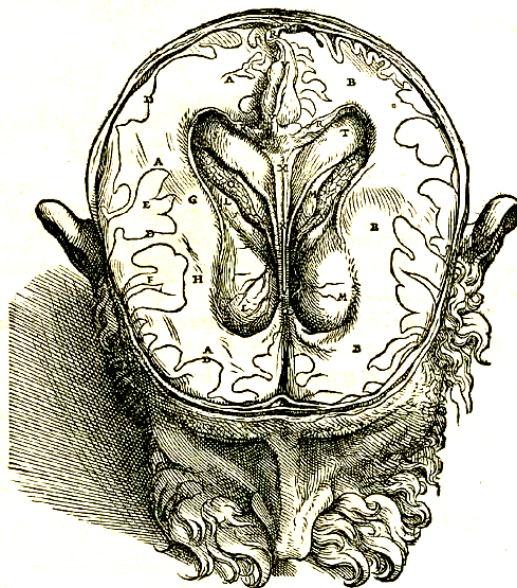
the idea that with thorough experimentation the concrete and specific functions of the nervous system could be defined. It also gave credence to the hypothesis that parts of the brain could be divided into sensory and motor systems. To some, it even suggested that this division could hold true for the outermost layer of the cerebrum (the brain); the neocortex.

QVINTA SEPTIMI LIBRI FIGVRA.

PRÆSENS figura quod ad reliquam in caluaria cerebri portionē attinet, nulla ex parte uariat: atq; id solū habet proprium, quod callosum corpus hic anteriori sua sede à cerebro primū liberauimus, ac dein eleuatum in posteriora refleximus, septum dextri ac sinistri uentriculorum diuellentes, & corporis instar testudinis extructi superiorem superficiem ob oculos ponētes.

Ab A, A, A, A itaq; & B, B, B, ac dein D, D, D, & E & F, & G & H eadem hic indicant, quæ in quarta figura. Sic quoque & L, L, & M, M, & O & P & Q eadem insinuant.

R, R, R Notatur inferior callosi corporis superficies. est enim id à sua sede motum, atque in posteriora reflexum.



S, T, V Super

Figure 1. Vesalius De humani corporis fabrica, figure on plate 609 depicting ventriculus lateralis dexter et sinister. Public Domain. Source: <https://commons.wikimedia.org>

Phrenology and equipotentiality

Herbert Spencer, an influential English intellectual, wrote in 1855 that “Localization of function is the law of all organization structure whatever: separateness of duty is universally accompanied with separateness of structure: and it would be marvellous were an exception to exist in the cerebral hemispheres” (The Principles of Psychology, Spencer 1855, 607). This eloquently sums up the zeitgeist of neurophysiological research during the 19th century.

One of the main figures promoting and developing these new ideas on localized cortical function was Franz Joseph Gall (1758–1828), physician and anatomist. He proposed that the brain were composed of different organs whose varying developmental degree and thus their performance would be reflected in bumps (if highly developed) and depressions (if moderately developed) in the overlying skull. He called the theory phrenology. Gall moved to Paris in 1808 and while living there he tried to publish his writings on the subject, albeit to no avail. However, he made a very good living by giving lectures on the issue and by doing so spreading his ideas (Finger 1994).

Gall believed that he could identify and localize 19 faculties in both man and beast and an additional 8 in humans alone. Among these faculties were for example destructiveness, acquisitiveness and veneration. Interest in this new theory of localization of function to the neocortex quickly grew and the Central Phrenological Society was established in Philadelphia 1822 by two physicians John Bell (1796–1872) and Charles Caldwell (1772–1853). Caldwell later published the first american textbook on phrenology in 1824 named *Elements of Phrenology*.

However, there were critics against phrenology as it was seen as a new theory without much concrete evidence apart from observational. The already mentioned Herbert Spencer discussed phrenology in his book *The principles of psychology* and chastised the followers of being indifferent to criticism and treating phrenology as a complete system of psychology (Spencer 1855, 609). Another scientist, John P. Harison, published in 1825 a paper with critique towards phrenology where he showed that it was not possible to predict brain size from the volume of space inside the skull (Harrison 1825). Therefore, to predict anything by measuring bumps of the overlying skull was futile. Another outspoken critic of Gall's phrenology was (the previously mentioned) Marie-Jean-Pierre Flourens. Flourens believed firmly in experimental science and animal studies using stimulation and lesions (Pearce 2009). He believed that the cortex of the brain was “equipotential”, i.e. that the cortex had to be seen as a whole and that the function was a result of the cooperation of all its parts. This was in stark contrast to the phrenologists view, something that Flourens wrote specifically about in his book *Phrenology Examined* (Flourens 1846):

“Grant,” says he [Gall, authors note], further, “to the animals certain fundamental faculties, and you have the dog that follows the chase with passion; the weasel that strangles the poultry with rage; the nightingale that sings with fervour beside his mate,” No doubt of it. But what sort of philosophy is that, that thinks to explain a fact by a word? You observe such or such a penchant in an animal, such or such a taste or talent in a man; presto, a particular faculty is produced for each one of these peculiarities, and you suppose the whole matter to be settled. You deceive yourself; your faculty is only a word, –it is the name of the fact, –and all the difficulty remains just where it was before. (Page. 39)

Flourens notion of equipotentiality of the cortex stemmed from his animal experiments where he had observed a recovery of function after removal of parts of the hemispheres, called restitution (Flourens 1824). This hypothesis of an equipotential cerebral cortex represented a holistic view of the functionality of the brain that clearly opposed the phrenologist view. However, as Gall died 1828 interest in phrenology had started to wane and the Central Phrenological Society had ceased to exist but by then the basic idea to functionally parcelate the cerebral cortex had been sown and would continue to spread.

Location of the faculty of articulate speech

The debate on whether specific areas of the cerebral cortex were the origin of specific functions continued throughout the 19th century and the most important dispute took place in France and concerned the faculty of articulated speech⁴. Gall and the phrenologists had already placed the faculty of articulated speech to the anterior lobes (the front of the brain, closer to the forehead) but the methods used by them had fallen into bad repute. However, the physician Jean-Baptiste Bouillaud (1796–1881) who stressed the importance of clinical material and autopsy studies, became an important figure in the dispute when his research on patients with speech disabilities agreed with the phrenologists conclusions regarding a location of the faculty of articulated speech. Bouillaud furthermore argued that damage to other parts of the cerebral cortex did not affect the faculty of articulated speech (Stookey 1963) thus fulfilling the need for a negative control.

However, Gabriel Andral (1797–1846) described in his opus magnum *Clinique médicale* 37 cases of patients with lesions in the anterior lobes but only speech impairments in 21 of these (Andral 1833). Obviously, parties from both sides of the discussion thought that they had evidence for their claims. It was, however, pointed out, concurrent to the debate, that a confounding factor for both sides were the limited amount of details in the reports that were presented as proof (Kusmaul 1877). This made it difficult for bystanders to form an informed personal opinion.

The tide turned in favor of the localists in 1861 when Paul Broca (1824–1880) presented his case of the recently deceased Monsieur Leborgne. Monsieur Leborgne was transferred to Broca's surgical ward a few days prior to his death. Broca observed that Monsieur Leborgne had no problem understanding when spoken to but could only utter the word “tan”. Broca deemed it to be a clear cut case of expressive aphasia (inability to articulate spoken words congruent with thought).

⁴ As opposed to the function of understanding of speech whose history won't be covered in this introduction.

Broca was informed of the current debate of cortical localisation and therefore took it upon himself to perform the examination of Monsieur Leborgnes brain directly after he had passed. The brain was subsequently presented to *Société d'Anthropologie* the day after (Broca 1861a, [b] 1861). The brain had a distinct lesion in the posterior inferior frontal gyrus (anterior lobe) in the left hemisphere. More or less the location predicted by phrenology and later theories. The case converted Broca to the localist view and with him many followed. The area where the lesion was found became known as Broca's area and was believed to house of the faculty of articulate speech. However, Broca decided not to slice the brain and could thus only make an external examination. Broca instead of slicing it decided to put Leborgnes brain in formaldehyde and save it to the after-world.

As a result, unknown to Broca, 146 years later the brain of Monsieur Leborgne was re-examined using high resolution MRI (magnetic resonance imaging). The examination showed significant damage throughout the left hemisphere both cortically (as observed by Broca) and subcortically (unknown to Broca due to his exclusively external examination). The subcortical damages included multiple subcortical structures such as claustrum, putamen, globus pallidus, head of the caudate nucleus, internal and external capsules, insula, superior longitudinal fasciculus and medial subcallosal fasciculus (Dronkers et al. 2007). However, history unfolded uninterrupted by these unknown damages.

Backlash of titans

Paul Broca's conversion to the localist view made the theory of cortical functional localization mainstream. Not all followed him however. Charles-Edouard Brown-Séquard (1817–1894), a Mauritian physiologist, neurologist and Fellow of the Royal Society, was an outspoken critic as evident in a paper he published in 1877 titled *Aphasia as an effect of brain-disease (Brown-Séquard 1877)*. Within, he outlined the stance by Broca to localize the “faculty of expressing ideas by speech” to the “back part of the left third frontal convolution” in the cerebral cortex. He continued by describing the publications of Professor William Rutherford Sanders of Edinburgh (1828–1881) and Theodor Hermann Meynert of Vienna (1833–1892), who both positioned the faculty of articulated speech to the insula (referenced to as “island of Reil” in Brown-Séquard's article).

“So that those facts which seem to show that the seat of the faculty is in one or in the other of these places are antagonistic to the other supposition. The facts relating to the third frontal convolution are in absolute contradiction with those relating to the island of Reil, and vice versa. Each series of facts destroys the value of the other.” (Brown-Séquard 1877 page 211)

Together with Brown-Séquard own empirical knowledge from the clinic where he had observed aphasia in patients and later localised lesions in their respective brains

to various locations both including and excluding Broca's area and the insula he concluded:

“My own view, as I shall have to say with more detail in a moment, is, that each function of the brain is carried on by special organs, but that those organs, instead of being composed of cells forming a cluster or mass in one part, are composed of scattered cells diffused in many parts of the brain, in communication, of course, one with the other by fibres, and forming a whole by this union of fibres, but still so diffused that a great many parts of the brain—I would not be bold enough to say all parts—contain the elements endowed with each of the various functions that we know to exist in the brain.” (Brown-Séquard 1877 page 212)

Another concurrent titan that opposed the theory of cortical functional localization was Camillo Golgi (1843–1926), an Italian biologist and pathologist who was awarded the Nobel Prize in Physiology or Medicine 1906 together with the Spanish biologist Santiago Ramón y Cajal (1852–1934) in "recognition of their work on the structure of the nervous system" ("The Nobel Prize in Physiology or Medicine 1906" n.d.). Through Golgi's histological work on nervous tissue he concluded that given the number of connections between neurons it was impossible to formulate a law that accurately captured the transmission of distinct information to localized groups of cells (Golgi 1883). Golgi even went so far that he in his Nobel lecture in 1906 stated that “although in various ways and to varying extent, every nerve element of the central nervous system contributes towards its formation” (Golgi 1906). However, next to Broca's case of expressive aphasia, one of the most important events during the debate of functional cortical organization was not the backlash of these titans but the Ferrier-Goltz debate.

The Ferrier-Goltz debate

Towards the end of the 19th century direct electrical stimulation of nervous tissue was developed as a new neurophysiological experimental method. Prior to this the common methodology had been to destroy a section of the nervous system and subsequently observe the effects thereof. In contrast it was now possible to stimulate a section of nervous tissue with a weak electrical current and observe the effects. Sir David Ferrier (1843–1928) used this new technology to create maps of the cerebral cortex of monkeys (Ferrier 1886) where the map indicated what kind of observable effect stimulation to that region generated (Fig. 2). By doing this he became recognised as one of the leading proponents of the theory of cortical functional localization.

Contemporaneous to Ferrier was Friedrich Leopold Goltz (1834–1902), professor of physiology at Universities of Halle and Strasbourg. He studied the effects on behaviour after removal of cortical tissue in dogs. He reported evidence that

supported the phenomena of restitution, i.e. the capacity of remaining brain tissue to restore lost functions. Goltz argued that lesions of the neocortex had effects but that the negative impact was towards higher cognitive functions and not towards more elementary functions (such as reaching and grasping, et.c., see caption of Fig. 2) as the proponents of cortical functional localization were suggesting.

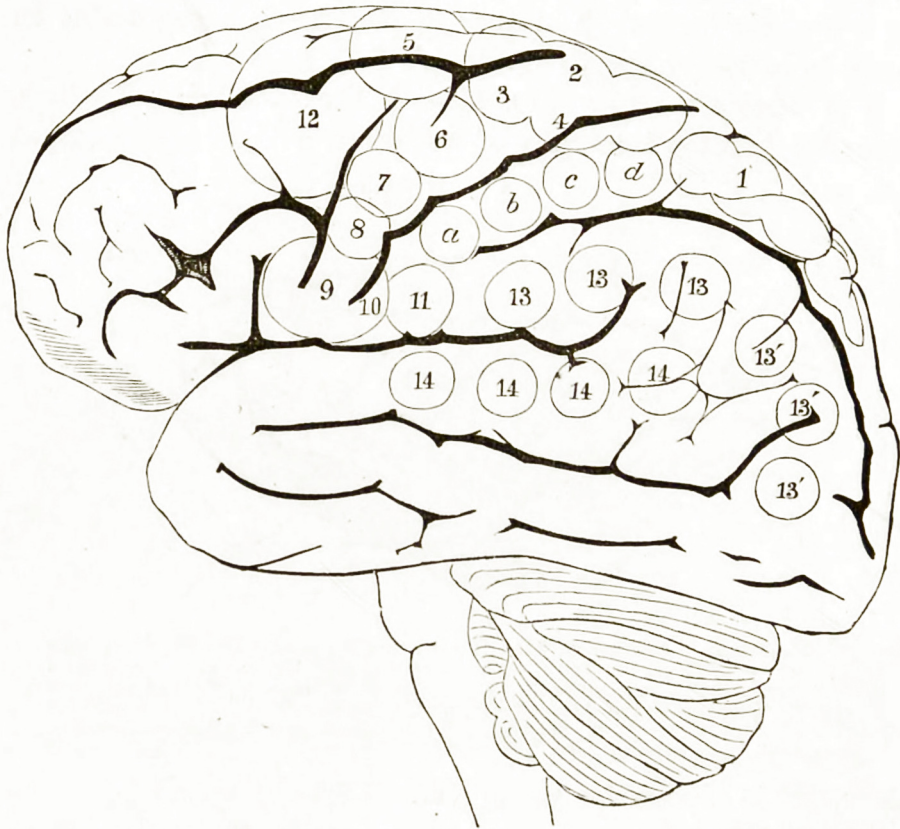


Figure 2. Functional map of the cortex. Figure 63, page 304, from Sir David Ferriers book *The functions of the brain* (Ferrier 1886). Examples of behaviours (quoted from same reference) associated with numbers are: 1) Advance of the opposite hind limb, as in walking; 4) Retraction with adduction of the opposite arm, the palm of the hand being directed backwards; 9 & 10) Opening of the mouth, with protrusion (9) and retraction (10) of the tongue.

During the Physiology Section of the Seventh International Medical Congress of 1881 (Cormac 1881) Goltz and Ferrier held a discussion on the topic of “localization of function in the cortex cerebri” (Tyler and Malessa 2000). Goltz began with a presentation of the results from his studies, describing that the invariant deficit after removal of cortical tissue was a decrease in general intelligence and that particular functions such as movement and sensation seldom was permanently affected. He ended his presentation by announcing that he had brought one of his dogs with him

from Strasbourg. The dog, according to Goltz, had most of both hemispheres removed. He was willing to present it to the audience and then have it sacrificed such that the extent of the lesions could be verified.

Ferrier followed directly and presented the results from his studies. He presented, apart from his cortical maps (Fig. 2), results from cortical lesions in monkeys. For these experiments he had been using the newly invented technique of antiseptic surgery to make precise lesions with very low risk of infection affecting the extension of the lesion. He described, among other results, that after removal of the “leg center” in a monkey's cortex that the animal developed paralysis of the contralateral limb, as expected by localist theory. Furthermore, this deficit was only slightly improved over time, thus opposing Goltz argument of restitution. To the surprise of many Ferrier also ended his presentation by announcing that he had brought an animal to the congress. A monkey with the motor cortex of the left hemisphere removed. The animal was to be demonstrated to the audience and subsequently sacrificed such that the extent of the lesions could be verified. During Ferrier's presentation Ferrier also warned the listeners about extrapolating results from lower animals such as rats and dogs to higher animals such as primates.

Following the demonstration of both the relatively unaffected dog and the hemiplegic monkey their respective brains were removed and examined. The extent of the lesions in Ferrier's monkey matched the claim while Goltz dog exhibited preserved areas in the anterior lobe and lateral portions of both hemispheres, i.e. lesser extent than claimed. Thus, Ferrier emerged triumphant from the debate and combined with the improved surgical technique laid the path for a new dawn of neurosurgery (for a more in-depth account of the debate please refer to Tyler and Malessa (2000)). Goltz, however, continued to oppose the idea of cortical functional localization of sharply defined areas of function but he did concede to accept that a relative emphasis on different motor and sensory categories did seem to reside in the different lobes of the brain (Goltz 1888).

A cautious invocation of logic

Contemporarily with the debate regarding the particulars of cortical functional localization were also many scientists who were concerned with the nature of reasoning of how the brain could work. They pointed out that localization derived from symptoms were not necessarily identical to localization of function and the process of deducting function from cortical lesions was no trivial matter (Andral 1833; Jackson 1894). Morton Prince summarized the imprecise restrictions of the discourse in his address to the American Neurological Association in 1910:

“The doctrine of cerebral localization acquires a very different significance according to whether it means that the brain can be mapped out into a number of circumscribed areas in each of which can be located a definite psycho-physiological faculty or function; or whether it means only that these areas contain anatomical elements which are made use of for the physiological expression of a function; or that a given area is such an integral element of a functioning mechanism, widely distributed in the cortex, that an injury to the ‘center’ not only destroys the element but throws the whole of this function out of commission by means of dynamic influences upon other areas and thus produces a group of symptoms.” (Prince 1910)

Prince’s argument was that it is hard to verify whether the damaged area contained cells that defined the whole function, parts of the function, or if the damage affected other cells that in turn resulted in aberrant behaviour. Constantin von Monakow (1853–1930), a Russian-Swiss neuropathologist, reasoned along the same lines as Prince but moved closer to joining the two viewpoints of cortical functional localization and holistic function with his theory of diaschisis (Monakow 1914; Carrera and Tononi 2014). Diaschisis was used to denote the distant effects of a localized disruption of normal brain function. Meaning that the area for a lesion might not be directly involved with the execution of a behavior but the activity in that area might influence the activity somewhere else thus generating abnormal behaviour.

Another acclaimed scientist and Fellow of the Royal Society, Henry Head (1861–1940) had a fundamentally similar idea as von Monakows when he contrasted the function of a brain before and after the event of a lesion. Head described the function of the brain as to rely on schemas and the schemas that was formed prior to a damage might not generate an accurate representation of reality relative to the post-damage mechanics of the brain. These old schemas in the new mechanics would thus become associated with aberrant behaviour (Head and Holmes 1911). He reasoned that a damaged brain could not be seen as the old brain minus one or more discrete parts but rather as a completely new system. However, this integrative manner of reasoning did not gain any particular popularity.

Cortical cytoarchitectonics

Another aspect of cortical specialization was developed in parallel to the debate on cortical functional localization. It was cortical specialization as defined by cytoarchitectonics, i.e. the structure of the cells in nervous tissue, an idea already hinted at by Herbert Spencer (Spencer 1855). Several scientists studied the cellular structure of the brain and created maps where they argued that they saw discrete cortical areas with internally homogenous cellular structure. One of the most striking features that was used to subdivide the brain was distinct layers seen in the neocortex. The number, usually six, and thickness of these layers formed a large

portion of the further division. The most famous maps (Fig. 3) were created by Korbinian Brodmann (1868–1962) in 1909 (Brodmann 1909). As soon as these maps were available they became popular and it became common practice to try to relate a functional deficit after a lesion to a defined cytoarchitectonic area. Broca's area, for example, is still commonly accepted to be located in what is called Brodmann's area 44 and 45.

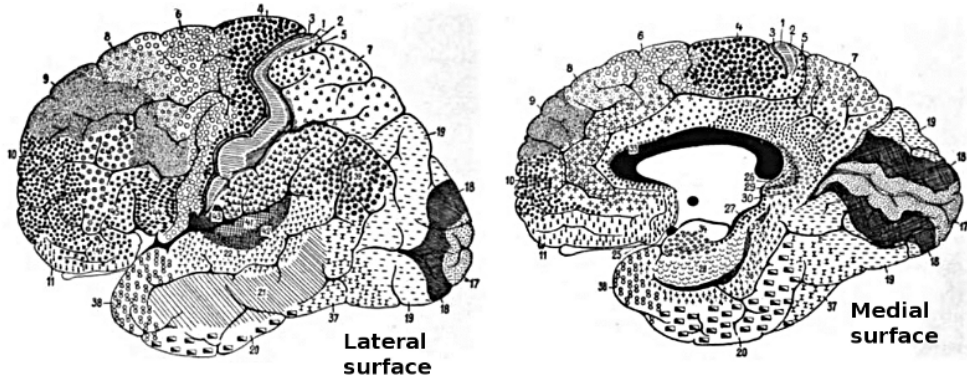


Figure 3. This drawing shows the regions of the human cerebral cortex as delineated by Korvinian Brodmann on the basis of cytoarchitecture. 1909. Public Domain. Source: <https://commons.wikimedia.org>

Karl Lashley (1890–1958), a psychologist who questioned the functional relationship between lesions and behaviour, also questioned these cytoarchitectonic maps. Lashley and a colleague separately remade one of the mapping studies that were published and later compared their results. The differences they found between their respective maps could not be described as a function of different experimenter but rather by quite large differences in the actual brains cellular anatomy (Lashley and Clark 1946). This suggested that the cytoarchitectonical maps had a weak explanatory potential since it appeared to be substantial anatomical variation within the same species.

However, the 19th century had started with an accepted Bell-Magendie law of spinal roots, seen the rise and fall of Gall's phrenology, felt the reverberations of Broca's case presentation and finally a heated debate between Goltz and Ferrier. As the 20th century came around, the established common idea was that there were sensory and motor areas of the cortex, with some more specific areas such as the area for the faculty of articulated speech. The exact definitions and demarcations, however, were still an open question. Furthermore, higher cognitive functions such as memory and general intelligence was still actively debated.

The last stand

During the 20th century the acceptance for cortical functional localization kept on growing while the advocates for a holistic viewpoint became fewer and their arguments marginalized. A prominent American scientist, Shepard Ivory Franz (1874–1933), described this, rather sarcastically, in 1917 when writing that the view that “the cerebrum as a collection of spatially related conglomerates of cells and fibers, each conglomerate having a certain function (perhaps mental) is easily apprehended by the instructor and easily taught to the student” (Franz 1917). Nevertheless, few new arguments was produced by the supporters for a more holistic view and their rhetoric became increasingly a synthesis of previous work. Franz, similar to previous scientists, summed up several cases where a deficit occurred after a lesion but where the deficit faded after rehabilitation. He concluded that if one admits to this fact that function can recuperate, then the structure of cerebral “organology” breaks down (Franz 1917).

Karl Lashley worked together with Franz and their collaborative studies focused primarily on maze learning in rats. Lashley and Franz concluded after several publications that they had no evidence that any particular part of the cortex was imperative for this kind of learning (Lashley 1929). Lashley summarized his findings and described two laws in his book *Brain Mechanisms and Intelligence* (1929). These laws were in essence a synthesis of the works from Flourens to Lashley and they were the *law of equipotentiality* and the *law of mass action*.

The law of equipotentiality was used to describe the capacity of any remaining neural tissue to carry out the function of the whole, original mass of tissue. Lashley admitted that this property varied relative to the location of the lesion and character of function observed and were only valid for the evaluation of complex tasks.

The law of mass action described that the performance of a behaviour was proportional to the total quantity of available neural tissue, or as a contrast, that the reduction of performance was proportional to the extent of a lesion (Lashley 1929, 1930).

After Lashley's publications the distinct debate on cortical functional localization versus holistic function faded from the scientific stage, even though no definitive argumentative or logical winner truly emerged. However, the theory of functional localization have since become the theory to be taught in common educational material and as a consequence it is often the only known theory to students of neurophysiology. Nevertheless, the importance of a solid foundation for the continued understanding of the brain is obvious and the nature of functional brain organization is a cornerstone of this foundation. Therefore, in this thesis the available evidence for both cortical functional localization and the holistic theory will be reexamined, specifically in light of the results of the included papers.

Anatomical and connectionistic introduction

Evident from the *historical background to the debate on cortical functional localization* is that the view on the functional principles of the neocortex is a subject that divides the scientific community. Whatever function that is ascribed to the neocortex will however be dependent upon the function of the rest of the nervous system. This is of course since the incoming activity into the neocortex is from subcortical structures and outgoing commands from the neocortex targets yet other, or the same, subcortical structures. Having said that, the state of the discussion regarding the functional principles for many other of the structures of the nervous system is also defined by division and uncertainty.

Nevertheless, the division of distinct neuroanatomical structures is hard to question. Hence, these distinct neuroanatomical structures needs to be incorporated into any theory of brain organization regardless of stance in any meta-discussion. A knowledge of which structures that constitutes the parts of the relevant discussion is therefore needed. The complete list of possible distinct structures in the nervous system is, however, very long. If focusing on structures along the pathway for sensory information into the neocortex and motor commands flowing out from the neocortex the list is substantially shorter. While considering the distinct structures their relative interconnectivity will also be outlined. This interconnectivity, after all, is what positions them in the network that generates the observed behaviours. All in all, these aspects are necessary for understanding the results of experimental studies of the nervous system.

The sensory pathway

The origin of sensory information is the receptors of the skin (outlined in the coming section *The dimensions of experience*). The activity from these receptors are transmitted into the nervous system by axons called primary afferents, i.e. the first wires that conduct activity inwards. The classical description of the distinct structures and their connectivity along the way towards the neocortex would be that these skin receptor primary afferents terminate in a nucleus in the brainstem called

nucleus cuneatus. The outgoing axons from nucleus cuneatus then terminate in the important subcortical structure known as the thalamus. The thalamus is located deep within the brain at the top of the diencephalon and is commonly divided into a number of subnuclei. The axons from the nucleus cuneatus is said to terminate in a specific thalamic subnucleus and in primates this thalamic subnucleus is called nucleus ventralis posterolateralis thalami, often abbreviated VPL. In turn, the thalamic neurons are said to project towards the neocortex and to terminate in the cortical layer 4 (Gilbert and Wiesel 1979) of the primary somatosensory cortex where sensory processing can start.

However, albeit the structures might be distinct the connectivity between them has been shown to be less so. The efferent connectivity from nucleus cuneatus is supposed to have an isolated termination unto a specific thalamic subnuclei (VPL in primates) but has been shown to be quite diverse and include both a number of “non-VPL”esque thalamic subnuclei as well as other structures in the brainstem (Hand and Van Winkle 1977; Lan et al. 1994). Moreover, when investigating the efferent connectivity of thalamic subnuclei a similarly diffuse picture emerges where different subnucleus terminate in various cortical areas apart from whichever classical target they were “supposed” to have (Hunnicuttt et al. 2014; Cappe et al. 2009). The efferent thalamocortical connectivity from the thalamus is also supposed to terminate in layer 4 of the neocortex (Gilbert and Wiesel 1979; Feldmeyer 2012) but even this has been challenged in recent years when thalamic activity has been shown to have the comparable latency to layer 4, 5 and 6, implying a direct termination unto all of these layers (Constantinople and Bruno 2013).

Hence, the classical functional role for each distinct structure has been grounded on an assumed equally distinct connection scheme between the structures. This distinct interconnectivity has however been hard to find. This might explain, to some extent, the problems of reaching consensus regarding the functional role of the structures along the inward path for sensory information.

The spinal circuitry

Concerning distinct structures involved in the motor pathway from the neocortex the list is notably shorter compared to the sensory pathway. Most cortical pyramidal neurons simply project unto the interneurons of the spinal cord, which begs the question to what extent the spinal circuitry is understood. As already hinted at a consensus on the definitive function of the spinal circuitry does not exist. This might surprise readers as the spinal cord is often portrayed in general media as a simple structure mainly there as a reflex factory and relay station. The complexity of the spinal cord has, however, been well known for over a century.

“A simple reflex is probably a purely abstract conception, because all parts of the nervous system are connected together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts, and it is a system certainly never at rest. But the simple reflex is a convenient, if not probable, fiction.” (Sherrington 1906 page 7-8)

This fully integrated hypothesis of the spinal cord expressed by Sherrington is supported by the actual infrastructure of the spinal circuitry. By just considering this circuitry using a trivial neuronal categorization of neuronal motorpools⁵ and spinal interneurons it is difficult to unravel how a simple functional principle could preside. First, the motorpools of alpha-motor neurons⁶ (α MN) that forms the basis for the final common pathway of the motoneuron (Sherrington 1906) present a considerable overlap with each other (Fritz, Illert, and Reeh 1986; Fritz, Illert, and Saggau 1986). This overlap between different motorpools suggests a potential for spreading of activation outside and interaction between each particular motorpool. Furthermore, axons originating in the neocortex have broad termination territories within these motorpools (Jankowska 1992) suggesting a diffuse selectivity between corticospinal neurons and motorpool specificity. Moreover, the majority of corticospinal connections are made with spinal interneurons (Bortoff and Strick 1993) and not with α MN directly, arguing that any specificity in the corticospinal-motorpool connectivity will be challenged by the general corticospinal-interneuronal connectivity. This implied generality of the interneuron- α MN connectivity is further established by the high degree of distribution and convergence of the interneurons (Sasaki et al. 1996; Kitazawa et al. 1993).

Spinal interneurons receive, apart from corticospinal input, strong peripheral feedback from proprioceptive sensors such as muscle spindle primary afferents (Ia), Golgi tendon organs (Ib) and group II muscle spindle afferents (II) (see Fig. 16 panel B for a simplified overview of the proprioceptive muscle sensors) (Jankowska 1992). Thus, continuous dynamic movements cannot be left uncontrolled since it will be perturbed by the incoming sensory afferent feedback as well as the inherent kinematic “preflex” response (Brown and Loeb 2000). Meaning, that even if the corticospinal axons are supposed to be categorized as generating motor commands they will realise that command in a highly interconnected network with mixed types of activity from a multitude of proprioceptive and skin sensors. Thus, even if their activity might have a motoric intent the classification of their activity *per se* as motoric might be a stretch of the imagination.

5 A motorpool is a cluster of neurons defined by their shared singular target muscle

6 The α MN connects specifically to the extrafusal muscle fibres and do not affect muscle spindles.
Refer to Fig. 16 panel B for explanatory illustration.

The spinal connectivity furthermore fails to provide an obvious substrate for the neocortex to exert control over each muscle individually as if the spine was a simple switch board. This is probably a good thing since the human body has more than 600 muscles (Marieb and Hoehn 2007) and each muscle defines a degree of freedom or dimension in the “control problem” of controlling movement. The high-dimensional control problem posed by human biomechanics, or that of any organisms body, imply that any explanation that reduces the spinal cord to a reflex factory is too superficial to take seriously. Furthermore, this spinal complexity has important consequences for how the activity of the brain is interpreted.

Hence, even with the wildly simplified description written above, which for example totally ignores the connection schemes to and from the cerebellum, it is hard to see how the spinal circuitry could be reduced to a simple reflex factory and relay station. The known spinal circuitry fortifies this notion of complexity and successful analysis of the spinal cord as a fully functional motor system in its own right verifies this hypothesis to some extent (Arber 2012).

Cerebellum as some kind of neuronal machine

The last example, albeit a bit peripheral to this thesis, is the cerebellum whose internal crystalline cortical microcircuitry has been known for more than half a century (John C. Eccles, Ito, and Szentágothai 1967). This contrasts the cerebellum to the rest of the nervous system and suggests that the analysis of its function might be possible to perform with a higher level of certainty and thus warrants a consideration by that fact alone.

The highly regular cortical configuration of the cerebellum inspired the hypothesis that there had to be a general transformative function within this structure (Albus 1971; Marr 1969). This general function was, however, exclusively focused on motor control and this became formative for research into cerebellar function. However, after many experimental discoveries concerning cerebellar connectivity, physiology and cerebellar involvement in non-motor processing this has gradually changed. For example, Dean et al. (2010) suggested that the general transformative cerebellar function could advantageously be seen as an adaptive filter but that the cerebellar functionality *per se* could not be described to have any intrinsic inclination towards motor, or sensory, information. The particular function of a cerebellar microzone should in contrast be inferred by its defining external connections. Meaning, that if there is a general transformative cerebellar function it in itself only infers abstract transformation but the resulting observed function is defined by the input into and output from that function. This interpretation is, however, an elusive definition since approximately 98% of the defining parallel

fiber synapses are silent (Jörntell and Ekerot 2002) but plastic (Coemans et al. 2004). Therefore, any inferred function is transitory at best as it is dependent upon the invariant of input into a given microzone (even if that transitory functional definition is stable over time). Thus, a future unanimous definition of cerebellar function might not primarily rely on further descriptions of internal circuitry, but rather a clear definition of the input.

For example, important input into cerebellum arises from the spinal interneurons which by their important connectivity unto the motor neurons can be said to have a function in motor execution. Thus, by inheritance the cerebellum ought to be important for motor behaviour, which is the case but not due to any intrinsic cerebellar reason.

In summary, it seems that many distinct structures of the nervous system has stood the test of time. The connectivity however has been constantly questioned, apart from the crystalline cortical microcircuitry of the cerebellum. However, the overall ordered nervous system that often was suggested initially has been forced to concede to an increasingly more interconnected network. This highly interconnected network is furthermore that within which the function of the neocortex realises itself, thus complicates any investigation of the function of the neocortex. Consequently, one might wonder how this complex interconnected network arises and if it possible to discern clues to the emergent functionality from this creation.

Genetically preprogrammed and emergent properties

The source of emerging behaviour in something that is not designed like a biological organism is often explained using a dichotomy, nature versus nurture. The nature versus nurture dichotomy splits the world into stuff that are innate, like genetic inheritance, and stuff that are external, like active experience or passive exposure. The aspect of nature versus nurture is of course a central aspect of any scientific inquiry into the physiology of a biological organ. The importance relates in large part to the aspect of manipulation. If we want to heal a damage committed unto an organ, can we do so by exposing the organ to something (pharmacological manipulation) or by rehabilitation (active experience)? Or is it possible, by prior exposure or experience to mitigate future consequences due to innate frailty? Obviously, the level of understanding needed to answer these kinds of questions is high.

No organ puts the question of nature versus nurture into such stark contrast as the nervous system. The perturbations of neuronal activity from any baseline is by definition a product of current experience and exposure. The continuous adjustments of synaptic weights are also dependent upon this experience. However,

to what degree the network formation and expressed functions depend on experience is uncertain, but the same can be said about the degree of influence the genetic code has on these aspects. Consequently, research into the genetic control over the nervous system is a very active research field.

Genetic techniques have evolved to be highly efficient and precise and the literature abounds with descriptions of genetic preprogramming and control over the nervous system. There are impressive accounts of temporal shifts of genetic expression during the spinal development determining the final neuronal identities (Delile et al. 2019) and complex arguments for spinal circuit formation based on these genetic instructions (Lai, Seal, and Johnson 2016; Osseward and Pfaff 2019; Hoang et al. 2018). Similar results and arguments can be found for the characteristics of the neocortex (Hofer et al. 2019) where highly detailed diagrams over the inter-areal hierarchy (Felleman and Van Essen 1991) has been proposed. These areal divisions has been seen as conserved within species in such a way that it has been suggested that there exists a genetic program regulating their emergence (Rubenstein and Rakic 1999).

Furthermore, apart from the proposed genetic control over macroscale characteristics such as areal division, control over microscale cortical circuitry has also been suggested. The neocortical layer structure observed by neuroanatomists has been confirmed to correspond to particular genetic expression profiles of the constituent neurons (Belgard et al. 2011; Kast and Levitt 2019; Gupta, Tsai, and Wynshaw-Boris 2002). These genetic identifiers has been used to target specific subtypes of neurons with optogenetic technology (Lima and Miesenböck 2005) when trying to tease out their hypothesized individual specific functional role in the neocortical network (Baker et al. 2018).

This hypothesis that each particular subtype or neuron has a particular functional role implies that there ought to be a difference in the nature of processing at different neocortical layers. It has also been suggested that this functional parcellation on a cellular level not only extends in a laminar fashion but also in a vertical direction. It was first suggested by Mountcastle (Vernon B. Mountcastle 1957; V. B. Mountcastle, Berman, and Davies 1955) that each neuron in a vertical organization relative to the cortical surface shared the same peripheral receptive field, thus creating an 'elementary unit of organization' called a column. This hypothesis provided the observed laminar cortical structure with a theoretical functional foundation since each vertical column could be segregated horizontally by layer and all of this has been implied to be orchestrated by complex genetic preprogramming.

There is, however, a conundrum within the investigation and contemplation of the ontogenetic origins of neuronal circuitry. If fetal and perinatal development depend on timed and genetically scripted sequences of events without leaving much room for later experience to shape the network, how much recovery will be possible in

the event of injury to either musculoskeletal or neural components later in life? If ontogenetic connectivity depended on the phylogenetic *a priori* ‘knowledge’ embedded in chemically hardwired connectivity loops between, for example, muscles, then that knowledge would be obsolete and potentially fatal with every new musculoskeletal mutation or injury. In direct contrast, an evolutionary lineage that utilized a general solution to the control problems facing the nervous system would gain a significant advantage in the evolution of new species.

Indeed, anatomical distinct structures, traced interconnectivity between these structures and defined genetic heritage does provide immense amounts of data that is in many cases interpreted from a functional localization perspective. However, it is not self evident that this mode of analysis has provided an increased understanding of the function of the nervous system. There seems to be properties of network behaviour that is not captured by neurophysiological techniques (Jonas and Kording 2017).

The complex relationship between the world and the brain

An important point in the previous section is the division between inherent neuronal mechanics, mostly defined by genetics, and emergent behavioural mechanics, due to experience. Thus, by extension, the question arises how different methods influences the results when mapping the functionality of different structures in the nervous system (Jonas and Kording 2017).

As already described (cf. *Cortical cytoarchitectonics*) a common attempt among neuroscientists to bring about order to the nervous system is the creation of maps. Many maps of the nervous system were created during the 20th century by categorizing the cellular structure and segmenting the tissue accordingly. A methodology that the reader now should be aware comes with numerous caveats. However, apart from this structural method of analyzing brain organization two additional methods have become commonplace in neurophysiological research.

In the first method activation of neural tissue creates a response elsewhere that is recorded and in the other method a peripheral sensory stimulation is applied and the response is recorded in the neural tissue. When performing the second method the kind of stimulation that is used depends on which modality that is to be mapped. Common modalities include auditory (Brewer and Barton 2016), tactile (Vernon B. Mountcastle 1957; Harding-Forrester and Feldman 2018), visual (Wandell, Dumoulin, and Brewer 2007) and motor (Mueller et al. 1996). The recording of

responses within neural tissue are typically done with EEG⁷, ECoG⁸, fMRI⁹ or recording electrodes inserted into the neural tissue itself. However, it can be noted that more often than not in the classical psychophysiological studies of perception passive sensations, like passive touch (Sur, Wall, and Kaas 1984), has been used as the peripheral stimulation. But, is it plausible to argue that the nervous system handles passive sensations in the same way as active exploration?

A common hypothesis of brain function is that the neocortex maintains internal models of its environment (Kawato, Hayakawa, and Inui 1993). A model here means an abstract representation of something else, e.g. whatever a neuron represents it is not equal to what generated the data that formed this representation in the first place, thus the representation has to be a model. These internal models have been shown to be optimally adapted to the statistics of the environment (Purves, Wojtach, and Lotto 2011) while not optimized for the processing of non-natural stimuli (Berkes et al. 2011). The optimization of these models have also been shown to gradually occur during development (Berkes et al. 2011), thus supporting the hypothesis of natural experience shaping the computational process of the neocortex. This also implies a strict relationship between the environment and the internal models in the brain, as mediated by the peripheral sensory organs. This strict relationship between the perceived function of the nervous system and the peripheral sensory organ was already pointed out by C. Golgi in his Nobel Lecture in 1906.

“As for the specific function of the central nervous system, I have, on several occasions, contested that it was correlated with a specificity of organization of the nerve centres, and I have come round to the idea that specific function is not associated with the characteristics of the organization of centres, but rather with the specificity of peripheral organs destined to receive and transmit impulses, or again, with the particular organization of peripheral organs which must receive the central stimuli.” (Golgi 1906)

More contemporary scientists have elaborated this idea by going beyond the peripheral organs themselves. They have asked if it is possible to formally define the full range of the dimensions of experience and not statistically infer them from the dynamics of particular biological receptors. Thereby gauging the **inherent** complexity of the sensation that is experienced or studied. Furthermore, such an understanding might serve as the basis for informed interpretations and predictions of the internal models of the brain and also provide an understanding of the possible

7 Electroencephalography

8 Electrocorticography

9 Functional magnetic resonance imaging

repercussions for an experiment of choosing a particular stimulation type over another.

The dimensions of experience

The first such estimation of the inherent complexity of a sensation was proposed for vision by Adelson and Bergens in their book chapter *The plenoptic Function and the Elements of Early Vision* (1991). This description of the strict relationship between light and the brain was aimed to be more informative than considering the particular receptors of the retina in an eye when exploring the question “what can be seen?”. This formal description challenged the notion that the fundamentals of vision were edges, peaks and corners (Hubel and Wiesel 1959) and suggested that these concepts rather were *things* extracted from the *substance* of vision and that the fundamental substance (or space) of vision was comprised of seven dimensions¹⁰. Adelson and Bergen did not, however, define what a certain organism could see since that would be restricted by the nature of the eye of that particular organism. Their work however defined that what was **possible** for an organism to see would be within the proposed seven dimensions.

Accordingly, the problem that the nervous system would need to solve would be to handle visual information within these dimensions. A theoretical argument thus followed that if the fundamental dimensions were not represented somehow in the nervous system then the subsets of the fundamental space would be distorted, thus affecting the presence of, for example, edges, peaks and corners since they are subsets of the fundamental space. Additionally, simplistic visual stimuli of the kind often used in classical psychophysiological research (Hubel and Wiesel 1959) would by this definition only sample a small subset of the complete fundamental visual space. Thus, for the particular case, only the eye and concerned neural tissue relative to the explored subset of visual space would be examined. Accordingly, the results and possible interpretations would be colored by this.

This line of thought inspired a similar exploration of the haptic¹¹, or tactile, domain in 2011 by Vincent Hayward in his article *Is there a ‘plenhaptic’ function?* (2011). Hayward noted a conceptual difference between vision and touch which was that the plenoptic function did not depend on the particular eye while, however, the nature of a haptic interaction would depend on the mechanics of the probe (probe

10 The seven dimensions of vision that were proposed were wavelength, time, viewing position (x, y and z coordinates, thus three dimensions), and two coordinates for positioning of the light ray (either x and y if calculated with Cartesian coordinates, or θ and ϕ if calculated with angular coordinates). These seven dimensions describe the intensity and quality of light for any viewing context.

11 Haptics is the name of the concept of sensing an object or surface by active exploration.

here refers to the thing that performs the touching, like a finger). This was due to the mechanics of the probe; which defines the parameters of the function of force transformation, resulting in fields of deformation in the probe. The fields of deformation refer to mechanical gradients in the skin, which as a consequence turn tactile sensing into a nonlocal phenomena, i.e. the tension that arises in the skin when something indents it is projected outwards and beyond the point of contact.

Furthermore, the dependence on the mechanics of the probe was due to the fact that a haptic interaction potentially changes the thing that is perceived, which is not true for vision. For example, touching a pile of sand deforms the pile while watching it does not. This deformation changes the nature of interaction between the probe and the environment (a pile of sand in this example) since the thing that is the source of the field of deformation has changed. Hayward explored what could potentially be haptically measured and concluded that to describe a field of deformation at least nine dimensions were required. Thus, suggesting that the inherent complexity of a haptic interaction was at least of that order.

If moving a step closer to a concrete organism classical studies of the tactile system has often been focused on the different skin receptors that each define a tactile submodality. The most commonly listed skin receptors are Merkel cells (indentation), Ruffini (stretch), Meissner corpuscles (skin movement), Pacinian corpuscles (vibration) and free nerve endings (pain) (Review by Abaira and Ginty 2013). A consequence of the suggestion by Hayward (2011) is that apart from the specific receptor dynamics of each skin receptor the thing that defines the responses of each particular receptor to a haptic interaction is the biomechanical context in which it is located, i.e. the particulars of the field of deformation. Thus in a concrete example, the biomechanical context is at least comprised of at which depth the receptor is located, the mechanical properties of the surrounding tissue, and the current state of deformation. It can be noted as a side note that the specificity of the submodalities defined by each skin receptor can be questioned as studies have shown little difference in the spike output under dynamic conditions (Jenmalm et al. 2003; R. S. Johansson, Landström, and Lundström 1982).

However, consider a Merkel cell, for example, that is commonly seen to react to indentation of the skin. The degree of compression that is transferred to the receptor during a haptic event will be defined in one way if the cell is located in skin that is thin, with minimal amount of surrounding adipose tissue and hard bone beneath, like the knuckles of your fingers. Compare that to a point below your bellybutton where most of us have a certain degree of subcutaneous fat, and no bone directly beneath. These different biomechanical contexts are commonly collapsed to differences in what is called a receptive field, i.e. the area of the skin that the receptor reacts to when stimulated with a punctate stimuli (Kaas et al. 1979; V. B. Mountcastle 1997). These receptive fields can be arbitrarily complex and by their

respective configuration facilitate extraction of tactile features (Pruszynski and Johansson 2014). However, it is seldom considered that the receptive fields themselves might be a phenomena emerging from the individual dimensions of the biomechanical possibilities, as hinted at by Hayward (2011).

Sadly, a clearly defined plenhaptic function has not yet been created. Nevertheless, the synthesis of differing mechanics of probes, the time-dependent potential deformation of interactions and the high-dimensional state of an elementary characteristic such as deformation suggests an astronomical fundamental space of haptic interactions. This also suggests that the processing of haptic information would, in the natural setting, run across submodalities and receptive fields, indicating the necessity for a significant integrative process.

This implied need for a complex integrative process can be contrasted to what is seen as the current understanding of the functional basis of nucleus cuneatus, the nucleus where primary afferents from the skin from the upper trunk terminates. It is argued that information from single primary afferents from the skin is sufficient to be relayed through the cuneate nucleus to the thalamus (Zachariah et al. 2001). This suggests little contribution of cuneate neurons in means of processing of tactile information and disregards the haptic complexity outlined above.

However, more recent studies of contact mechanics has found that cuneate neurons encode a finite set of haptic dimensions extracted from the incoming primary afferents and that these dimensions are high-level composites rather than discrete representations of the skin receptor submodalities (Jörntell et al. 2014). All in all, lending credence to the hypothesis that the internal representation in the nervous system of tactile interaction is not based on individual skin receptors but rather samples from a high-level and high-dimensional haptic space. Thus, when probing the function of the nervous system concerned with touch, for example, a simple stimuli will only illuminate a deceptively small space of the complete haptic space and the related functionality.

This abstract notion of inherent complexity of the external world together with the not obviously helpful analysis of neural connectivity further the growing concern that the properties of network behaviour has to be analysed as an isolated phenomena.

Network analysis

Evident from the previous sections is that a huge amount of work has been put down by neurophysiologists over the course of centuries when trying to tease out the function of the nervous system. However, where the boundaries are between categorization of various constituents of the nervous system, definitive concrete end-results of activating particular neurons and theoretical abstract functions are sometimes difficult to tell. Thus, true definitions of functional localization or holistic function are seldom to be found.

Nevertheless, it is maintained that the defining trait of the holistic theory is that in order to understand the brain it has to be seen as a single working unit – and not several discrete independent centers. However, does the known connectivity between neurons of the brain provide the necessary foundation for the whole brain to work as a single unit? Given that the number of neurons in a human brain is around 89 billion (Herculano-Houzel 2009) the propagation of activity from one neuron to another neuron on the other side of the brain could potentially involve millions of intermediary connections. If only considering synaptic transmission delays, with a duration of approximately 0.5 millisecond and ignoring any additional delays in the neuronal machinery, the time to complete a million synaptic transmissions exceeds 8 minutes. That is too long to facilitate any kind of adaptive and positive behaviour across large sections of the neocortex and implies that the only viable computational option is to perform local calculations.

However, this argument of transmission duration is more than a straw man as it will lead us to a very important discovery. Arbib et al. (1998) estimated that any neuron in the neocortex connects to any other neuron with synaptic linkages involving no more than five neurons on average. Indicating that somehow the neuronal network is interconnected in a manner that makes it possible for the 89 billion neurons (Herculano-Houzel 2009), with on average 7000 connections between each cell (Pakkenberg et al. 2003), to be quite close to each other. If this estimation would be true it would mitigate the transmission duration problem and open up for the possibility of a holistic integrative principle. The explanation to this paradoxical possibility did, however, not come from the neurophysiological community, but from mathematics.

Small-world networks

In 1998 Strogatz and Watts published a letter in the scientific journal *Nature* called *Collective dynamics of 'small-world' networks*. Prior to their letter, studies of networks had been made into two extreme versions. On one hand, the completely regular network, comprised of n vertices (or nodes) with k edges (or connections) per node. Each node only connecting to other nodes closest to the originator. The regular network is also known as a ring lattice (Fig. 4 panel A) and have the characteristic that they have a high number of what is called 'cliques'. A clique is a mathematical concept that refers to a subset of nodes where every two distinct nodes are adjacent to each other. In other words, the nodes are locally highly interconnected. A related characteristic that is often mentioned is *clustering* (*the degree of cliques comprised of three nodes, denoted as C*). On the other hand, in a regular network the average number of connections that one has to travel to go from a randomly selected starting node to a randomly selected destination node is high, this distance is often called *average path length* (*denoted as L*). Meaning, if data originates from a certain node and it is needed somewhere else the travel distance is on average high.

In contrast to the regular network is the completely random network where the connection from each node can go to any other node, i.e. not necessarily the closest (Fig. 4 panel C). In these networks the clustering is often very low but the average path length is also very short. They are in many senses the inverse of the regular network.

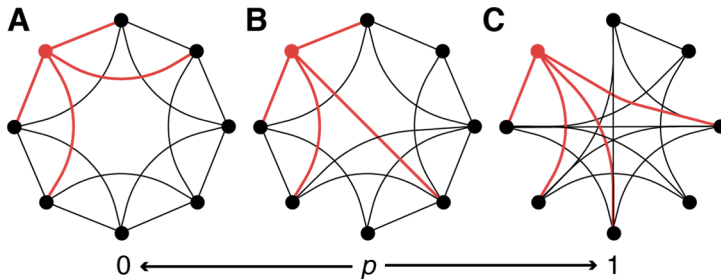


Figure 4. Adapted from Strogatz and Watts (1998), different network topologies with different probability of rewiring from 0 (left) to 1 (right). A) Regular ring lattice network. Example node and connections to closest neighbors marked in red. B) 'Small-world' network. Example node and connections still marked in red, note that one connection has been rewired due to the process described by Strogatz and Watts. C) Random network. Each node connects to any other node in the network.

Strogatz and Watts novel idea was to explore the middle ground between these two extremes. They achieved this by starting with a regular ring lattice network (like the one shown in Fig. 4 panel A). They then progressed by considering each connection

of the network and randomly rewiring it with the probability p . The rewired connection could end anywhere in the network. The parameter p was in the range of $0 < p < 1$, and could thus gradually progress a network from completely regular ($p=0$) to completely random ($p=1$).

As an objective comparison for their networks they calculated the clustering coefficient given p (using the notation $C(p)$), and average path length given p ($L(p)$). They found that the clustering coefficient (C) continued being high for a large interval of p , while the average path length (L) quickly decreased (Fig. 5). Meaning that, a few shortcuts left most cliques intact but the average distance between the nodes quickly became short (Fig. 5).

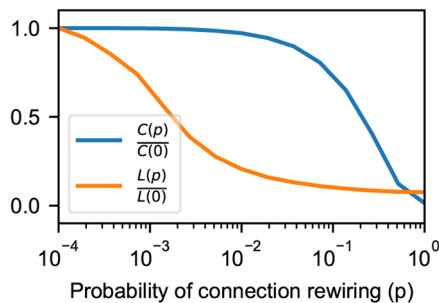


Figure 5. Normalized relationship between average path length (L) and clustering coefficient (C) with respect to probability for a connection to rewire (p , x-axis). Generated as described in similar graph in Watts and Strogatz paper (1998, fig. 2). Note that the clustering is high for a broad range of p , while average path length drops quickly (thus the use of lognormal x-scale).

They then calculated C and L for three real-world networks: collaborations between film actors, the power grid of the western United States and the neuronal network of the worm *C. Elegans*, which at the time was the only completely mapped neural network of a biological organism. For each network they calculated the actual C and L , and also C and L if the network would have been completely random. Comparing the results from these calculations they found that the actual C was higher than expected (high local clustering), while still reporting a low L (short average path length). The conclusion they arrived at was that these three real-world networks exhibited the characteristics of high interconnectedness and short average path lengths, a combination they called “*small-world*” networks (Fig. 4 panel B).

Apart from currently more relevant aspects, the wiring principle that emerges in small-world networks minimizes the number of long-range connections needed to optimize the network performance (Karbowski 2001). Long range connections are from an energy perspective expensive and evolutionary pressure would remove them if not critical for the behaviour of the organism.

Further exploration of small-world networks revealed that not only did they provide an explanation of how the connectivity of the brain could align itself with the estimations of Arbib et al. (1998), but also provided a theoretical foundation upon which the debate on cortical functional localization could be projected. Since small-world network topology supports distinct information processing in local clusters while also facilitating global integration of information (Bassett and Bullmore 2006). This seminal observation thus functions as a potential keystone bringing multiple observations across the varying neurophysiological disciplines together under one holistic theory. However, from this point the discussion will be more speculative and will accordingly be continued in the appropriate section (cf. *Discussion*).

Examples from the clinic

Finally, retreating from abstract theory and esoteric high-dimensionality one might wonder if the discussion presented previously has any relevance to users of biological information, such as medical professionals.

For any medical professional there is always a tug-of-war between what is known theoretically and what works empirically. For anyone working with neurological pathologies this is probably most true for lesions located in the neocortex and the resulting symptoms. While every trained physician knows the location of many brain areas such as Broca's area and the primary sensory and motor cortices, alpha and omega when assessing deficits in a patient is the clinical examination. Lesion localization is not paramount for the acute phase since the possibility of reparation of nervous tissue is currently non-existent. For example, a thorough examination, correct handling of failing vital parameters and efforts to minimize any additional damage are the focus points to achieve a good outcome when a patient with a stroke enters the emergency room.

Yet, it is not uncommon for clinically oriented studies to incorporate some kind of neuroimaging into their data (Maldjian et al. 1999; Desmurget and Sirigu 2015). This is of course reasonable, no matter if you believe that the functional relationship between lesion and symptom is established or not, since the data collected can be used, if not now, in the future. Moreover, the data from imaging can be used for other highly relevant clinical questions, for example predicting upcoming need for critical care (Faigle et al. 2015).

Notwithstanding, the cortical functional dogma is the general notion in the clinic, thus linking the location of a stroke¹² with specific symptoms. In the introduction of a paper by Corbetta et al. investigating the relation between behavioral deficits and stroke locus it is even stated that “a cornerstone of clinical neurology is that focal brain injury causes specific behavioral symptoms or syndromes that reflect the functional specialization of different brain modules” (Corbetta et al. 2015). The

¹² In the strict sense a stroke is a cortical infarction that results in a symptom. In everyday clinical lingo it is often talked about “silent strokes”, thus referring to a cortical infarction without overt symptoms. This is an indolent action, albeit an incorrect use of the term by definition. Here stroke retains its original meaning. The difference between cortical infarction and lesion however is that the first indicates the reason behind the damage while the latter only indicates damage.

paper, however, ends up showing that the number of deficits from stroke is a few multi-functional clusters, supporting the integrative paradigm rather than one of distinct modules.

Turning the design around and instead of including any patient with a stroke, including patients with a specific symptom and subsequently investigating the location of the lesion leads to similar results. A recent study included patients with the not uncommon symptom of expressive aphasia and found that it was not predominantly paired with a neocortical lesion in Broca's area but rather with lesions in the nucleus caudatus (Grönholm et al. 2016). In the more general sense, studies on deficits in patients after unilateral stroke include observations of bilateral sensory deficits (Kim and Choi-Kwon 1996; Brasil-Neto and de Lima 2008).

The strict relationship between functional output and neocortical areas are also confounded by the observation that many incidents of stroke pass unnoticed (Wardlaw, Smith, and Dichgans 2013). Thus, even though stroke is a leading cause of global disability and mortality (Benjamin et al. 2019) the linkage between characteristics of the lesion and the impact on the clinical care is murky. As a consequence, a deeper understanding of the functional mechanisms of the nervous system could have a profound impact not only in an academic sense, but also for the patients of the medical practitioner.

Methods

This thesis includes two categorically different papers relative to the methods employed when acquiring the data upon which the results have been derived. Paper I, II and III employ a classic experimental design with animal experimentees, neurosurgery, electrical stimulation and neuronal recordings. Paper IV outlines a model of an artificial neuron and subsequent artificial neural network with results from the subsequent simulations.

Below are the methods employed in the included papers. The methods are described in a general sense and for the particulars the reader is referred to each individual study that is available in the appendix.

Experimental methods

Anesthesia

The animal experimentee, male adult Sprague–Dawley rats, were prepared and maintained under anesthesia with ketamine (100 mg/ml) and xylazine (20 mg/ml) mixture with a concentration ratio of 20:1. Prior to the induction of anesthesia the animal was sedated with isoflurane (3% mixed with air) and followed by an intraperitoneal injection (ketamine (100 mg/ml):xylazine (20mg/ml) concentration ratio of 15:1, 1.5 ml/kg). Anesthesia was maintained with a continuous infusion through an intravenous catheter inserted into the right femoral vein at approximately 5 mg/kg ketamine per hour (end concentration 20:1). The absence of withdrawal reflexes to noxious pinch to the hind paw was used to characterize adequate anesthesia until the brain surface was exposed. After that the level of anaesthesia was additionally monitored using a ball electrode resting on the brain's surface, thus acquiring an electrocorticogram (ECoG). The ECoG signal was monitored for irregular occurrences of sleep spindles indicating deep sleep (Niedermeyer and da Silva 2005). The duration of experiments did not exceed 8 hours, after which the animal was sacrificed.

Surgery

Prior to initiation of neurosurgery procedures the head of the animal was fixed in a stereotactic frame. In order to access the surface of the brain a craniectomy was made. The location and extent of the craniectomy differed between the individual studies. However, the already mentioned ECoG ball electrode was placed on the surface of the exposed brain at a suitable location relative to the planned recording locations. For additional recording stability a cap of agarose (0.03 g/ml dissolved in physical saline) was made to cover the exposed surface of the brain.

Recording

Recordings were made exclusively *in vivo* in the right hemisphere. The exact locations varied with the hypothesis of the study. Individual neurons were recorded with patch clamp pipettes extracellularly in loose-patch current clamp recording mode. Patch clamp pipettes were pulled from borosilicate glass capillaries using a Sutter Instruments (Novato, CA, USA) P-97 horizontal puller, and back-filled with an electrolyte solution. The composition of the electrolyte solution in the patch pipettes was (in mM) potassium-gluconate (135), HEPES (10), KCl (6.0), Mg-ATP (2), EGTA (10). The solution was titrated to 7.35–7.40 pH using 1 M KOH.

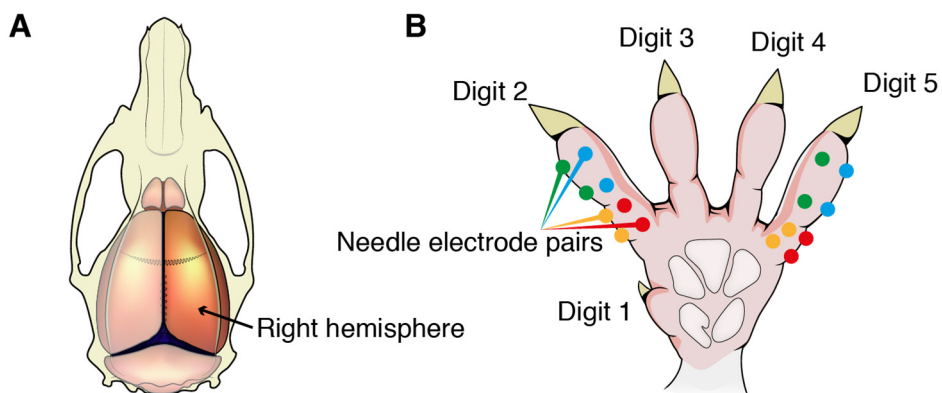


Figure 6. Experimental method setup. A) Illustration of rat skull with superimposed brain, at low opacity. The right hemisphere is opaque. B) Caricature illustration of a rat forepaw with digit numbering written out. Predetermined needle electrode insertion points marked with dots in pairwise colors.

The pipettes were inserted into and extracted from the brain under inspection with a microscope for detection of signs of deterioration of the state of the brain, such as bleeding. The pipettes were advanced slowly (approximately 0.2 $\mu\text{m/s}$) perpendicular to the brain surface using an electrical stepping motor. Any neuron encountered was recorded if possible and in some cases a number of neurons were

recorded in sequence in the same electrode track. In most experiments, the recorded signal was output on a loudspeaker at the same time as it was displayed on an LCD computer screen for monitoring of the signal by the experimenter. The screens were therefore at a remote location to the animal (>2 m away on the lateral side) in an otherwise normally lit room with a humming background noise from fans in the electrical equipment.

All data was digitized at 100 KHz using CED 1401 mk2 hardware and Spike2 software (Cambridge Electronic Design, CED, Cambridge, UK). Spikes were identified using in-house software, where spike identification was based on matching to manually constructed templates. All spike detection was carefully controlled by visual inspection of raw data traces throughout the recordings (Fig. 8 panel A and B).

Stimulation

One or two sets of four pairs of intracutaneous needle electrodes were inserted, with an interneedle distance of 2-3 mm, into predetermined sites of the skin on the volar side of a digit of the left forepaw of the animal (Fig. 6 panel B).

The needle electrodes constituted the electrical interfaces to the tactile afferents through which eight predefined spatiotemporal patterns and single pulse stimulation of skin afferents were delivered (see below for description of the spatiotemporal patterns). These stimulus patterns had variable duration but lasted less than 350 ms. Consecutive onsets of stimulus pattern delivery were separated by 1.8 s. Additionally, isolated single pulses to each of the four stimulation sites were delivered. These isolated single pulses were delivered in trains of five consecutive pulses at 3 Hz as 20 separate trains for each individual stimulation site. The eight spatiotemporal patterns and four single pulse stimulation trains were presented up to 100 times for each digit in a pseudo-random order.

For each skin site, the stimulation pulse was set to an intensity of 0.5 mA with a duration of 0.14 ms (DS3 Isolated Stimulator, Digitimer, UK), which is 2.5 times greater than the threshold for activating tactile afferents (Bengtsson et al. 2013; Rasmusson and Northgrave 1997), but well below the threshold intensity for A-delta (peak activation requires 6–10 times threshold intensity) and C-fibers (Ekerot et al. 1987).

Spatiotemporal tactile input patterns

As noted in the section *The complex relationship between the world and the brain* the nervous system needs to be able to handle an astronomical number of fundamental haptic dimensions. The degree of complexity inherent in the stimulation will naturally only illuminate neural mechanisms in relation to this

complexity, all in all relative to the underlying sensory space. Thus, the preferable stimulation when investigating the information processing of sensory input would be a true haptic event, i.e. exploring an object with touch. However, apart from the need of a complex stimulation is the requirement of repeatability. Currently there are no analytic methods that can gauge the decoding performance of individual neurons based on a single unique stimulation. Furthermore, there are several confounding factors when interacting with a real object. Contact with a real object has the potential of altering both the skin biomechanics and the object itself and a slight change in the relative positions of the object and the skin will produce a new set of field deformations in the skin and thus activate a different set of skin receptors, potentially abruptly changing the nature of the neural response.

This problem has a partial solution with a machine that produces repeatable spatiotemporal skin-strains. This machine however only exists for animals in the size of approximately cats (Jörntell et al. 2014) and not for smaller animals such as rats, the experimental animals used in papers I-III. However, psychophysical studies have shown that the activation of skin receptors using electrical pulses can evoke the illusion of touching a real object (Calogero Maria Oddo et al. 2016). An electrical interface has the added benefit that the activation of skin receptor primary afferents are highly accurate (Bengtsson et al. 2013) and reproducible, and thus mitigates the inherent stochasticity of receptor activation during a real haptic event (Jenmalm et al. 2003).

Nevertheless, in order to create a model that can generate spatiotemporal input patterns that mimics a real haptic event there is a need for an understanding of the various skin receptors and their dynamic responses relative to their biomechanical context. A context that will also need to approximate the deformable context of the skin. Oddo et al. (Calogero Maria Oddo et al. 2016; Calogero M. Oddo et al. 2017) have implemented such a model in an artificial fingertip equipped with a set of four neuromorphic sensors implanted in a polymeric compliant material (Dragon Skin, Smooth-On, USA) able to transduce tactile events.

This artificial fingertip was intended against a set of four predefined shapes using a cyclic motion (Fig. 7). The four neuromorphic sensors subsequently generated artificial receptor potentials that were converted to spike trains by the neuromorphic artificial touch system that used a customized implementation of Izhikevich spiking neuron model (Calogero M. Oddo et al. 2017). The neuron model mimicked two receptor types, fast and slow adapting skin receptors. Thus, for each of the four shapes two responses were generated to a grand total of eight different spatiotemporal patterns. In the previously described needle electrode interface (Fig. 6 panel B) the four needle electrode pairs were 1-to-1 connected to the four neuromorphic sensors of the artificial fingertip (Fig. 7).

The artificial fingertip allowed for synthesization of the spatiotemporal input patterns of skin sensor activation at quasi-natural rates that followed a natural overall temporal modulation (Middleton et al. 2006) similar to that the biological skin sensors display under dynamic indentation (Jenmalm et al. 2003). Hence, the eight different spatiotemporal input patterns should be regarded as a close approximation of a true haptic event. Providing a substrate for illumination of inherent processing mechanisms of the brain.

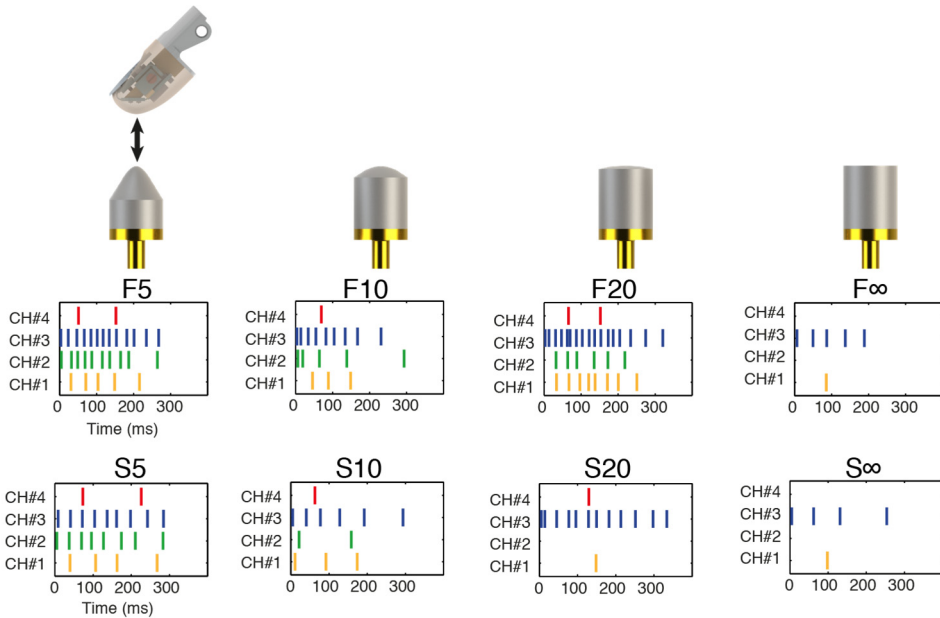


Figure 7. Adapted from paper I, *Somatosensory Cortical Neurons Decode Tactile Input Patterns and Location from Both Dominant and Non-dominant Digits*. In the top left the artificial fingertip used is shown, below are the four different probes that were touched in a dynamic motion. Below each probe two different spatiotemporal input patterns are shown. Each spatiotemporal input pattern consists of four channels corresponding to the four tactile sensors in the artificial fingertip. One channel per row and the color corresponds to the locations marked in Fig. 6. Each vertical dash indicates a stimulation pulse at that relative time.

Analysis methods

In all papers included in this thesis various standard statistical analytic methods were employed and does not need any further discussion or explanation than available in the particular papers. However, the method of estimating the decoding performance of the neuronal responses to the eight spatiotemporal input patterns used in papers I and III was extended as a part of this thesis and thus merits a deeper discussion.

The analysis method used in paper II will not be included in the explanation as it can be seen as an intermediary step of development.

Decoding of neuronal responses using Principal Component Analysis

After recording the activity of neocortical neurons (Fig. 8 panel A), concurrent to peripheral stimulation with aforementioned spatiotemporal input patterns, an analytic method needs to be employed that can answer the question whether the activity of the neurons could be used to identify the input pattern. A common practice in neuroscience is to create a peristimulus histogram (PSTH) for each group of unique stimulation (The process is described in Fig. 8). Then compare a number of characteristics of these PSTHs, like number of peaks, latencies of these peaks, rise-times etc., in order to determine whether the various groups are significantly different from each other. However, this species of method is burdened with the obvious researcher dependent choice of which characteristics to include in the analysis and often only results in a probability measurement (the p-value) on the likeliness of observation due to chance. Ergo, saying very little about the responses themselves.

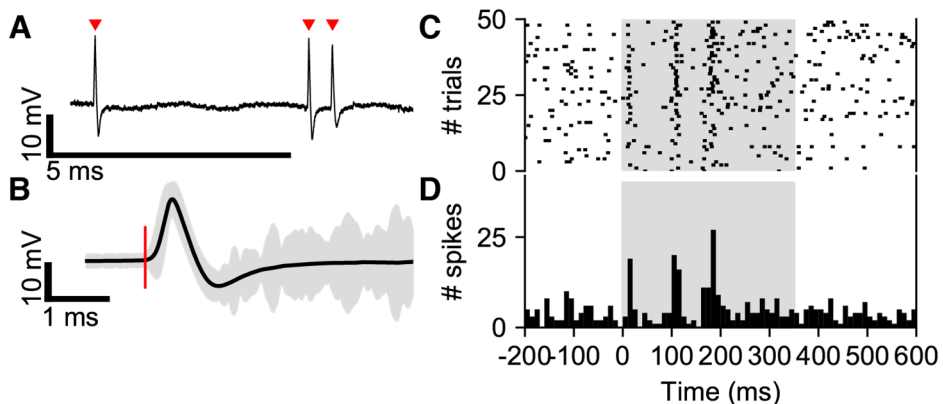


Figure 8. The process from an analogue neuronal recording to a PSTH. A) An example recording of a cortical neuron. Scale bar indicates voltage and time scales. Each individual spike is marked with a red downward caret. Those individual spikes are found by template matching and visual inspection using in-house software. The time point for the start of each spike is thus defined. B) Average spike profile from the previous example neuronal recording (average from N=10311 spikes) is drawn with a solid black line, gray background outlines ± 2 s.d.s. of voltage. Red vertical line indicates approximate start of spike. Scale bars indicates voltage and time scales. C) Raster plot of spike activity for 50 trials of spatiotemporal pattern presentation, S10. Each black dot represents a spike occurring. Gray background indicate max duration of stimulation. X-axis is shared with plot in panel D. D) PSTH of the neuronal activity concurrent to the stimulation. Total number of spikes along the y-axis and relative time in ms along the x-axis.

A better alternative would be a method that could give an indication of the performance of decoding of each individual response, researcher independence in selection of response characteristics to include, and the possibility of internal control

of chance. In light of these requirements a method using Principal Component Analysis (PCA) and k -nearest neighbors (kNN) classification was developed by Oddo et al. (2017). This method, however, had the problem of requiring relatively large amounts of data and no clear possibility of internal control. Thus, further development of that method was carried out as part of this thesis. However, during the process of publication of the papers included in this thesis it has been clear that PCA, kNN and similar methods of analysis has a weak presence in the neuroscientific field and thus merits a short introduction before the description of the developed decoding analysis.

Principal Component Analysis in general

PCA is a common statistical method used to decompose data into an arbitrary, but finite, number of dimensions (Pearson 1901; Hotelling 1933). A dimension here means some kind of characteristic that is representable as a decimal number and thus can be positioned along a number line. The data is said to have samples, where each sample has one or more variables that each can be seen as a dimension. Each sample is an independent data source while the variables are measurements from this source. For example, in the current case each neuronal recording is a sample and the degree of a response at each timepoint post a particular stimulation onset is a variable.

The decomposition of data is achieved by centering each variable around zero and then fitting a linear function to the data by maximizing the squared summed distance to origo. The coefficients of the fitted linear function is the principal component (PC). Each coefficient describes, in relative terms, the degree of variance for each variable.

Additional PCs can be calculated by fitting an additional linear functions perpendicular to the previous PCs. The variance of the data points around each PC decreases with the number of PCs already defined as each the coefficients for each PC accounts for some of the total variance. It follows, accordingly, that the coefficients of the first PC accounts for the highest degree of variance of the initial data. Furthermore, the theoretical maximum number of PCs that can be defined is the same as the number of variables for a sample. However, in practice the maximum number of PCs is either the number of variables or the number of samples, whichever is smaller.

But, PCA is superfluous if the number of dimensions before and after analysis are the same. Since it is possible to calculate the explained variance in the data for each PC, as noted above, it is common practice to only consider the number of PCs that explain enough of the variance of the data. This threshold of ‘enough’ is often set to 95%. Thus, apart from decomposing the data, a reduction of dimensionality is also performed. Finally, the number of PCs also indicate something about the data. For

example, if 2 PCs are enough to account for 95% of the variance of the data then it is feasible to assume that there are two distinct features present in the data.

Subsequent the calculation of the PCs from a dataset samples can be projected into this PC-space by calculating how much of each PC you need to restore your original sample. It can be seen as a cocktail recipe, that states “you need 1 part PC1, and 2 parts PC2 to recreate sample A”, thus positioning sample A at position (1, 2) in the PC-space.

Principal Component Analysis on neuronal responses

Prior to application of PCA unto the neuronal responses the responses themselves have to be prepared. This is because PCA require the data to have equal dimensionality. That is, each neuron has to have the same number of variables. Furthermore, action potential generation is inherently stochastic (Spanne et al. 2014), as well is the process of indicating where in the analog recording each action potential took place. Thus, a degree of uncertainty is always present in neurophysiological data. To account for this, a discrete set of spike times are convolved into a continuous signal with equal number of timepoints (ensuring equal dimensionality), and using an exponential kernel with a decay coefficient of 5 ms (representing the uncertainty outlined previously) (See Fig 9).

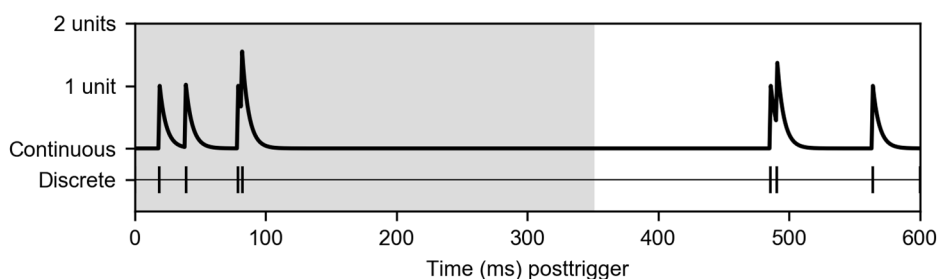


Figure 9. The discrete spike times (below) are convolved to the continuous signal (above) using an exponential kernel with decay coefficient of 5 ms. Stimulation onset is at time 0, and max duration of 350 ms is indicated using gray background. The process of acquiring the discrete spike times is outlined in the legend of Fig. 8.

Hence, a recording session with 100 responses for each of the eight spatiotemporal stimulation patterns is convolved into 800 continuous responses with a resolution of 1 ms. The duration of a response from the onset of the stimulation was typically 1000 ms.

The continuous responses is subsequently divided into a training and a test set stratified by the spatiotemporal stimulation pattern ratios, i.e. the fraction of responses were kept similar in both sets. Then, in order to make the method less dependent on large amounts of data, bootstrapping is introduced. Bootstrapping is a

statistical method of estimating properties of the underlying population as seen through the samples (i.e. neuronal recordings) (Efron 1992). By combining N responses (where N equals the number of available responses) through resampling with replacement (replacement means that the same response can be selected multiple times) a new, bootstrapped, response is generated. The bootstrapped response is not equal to the mean of all available responses due to the mechanics of replacement. However, any invariant signal in the data can be amplified while noise will cancel itself out due to the central limit theorem. Furthermore, the method becomes less dependent on large datasets since the number of unique combinations available even from quite small datasets is often astronomical.

PCA, as described above, is then applied to the bootstrapped training set, generating a number of PCs (Fig. 10). Next, the coefficients describing the linear combination between the generated PCs (from the training set) and the responses of both the training and the test set is calculated. In other words, for each response it is calculated how much of PC1 is needed to come as close as possible to that particular response, then how much of PC2 is needed to come even closer, etc. for all of the PCs. As coefficients can be placed on a number line, accordingly the responses could be positioned in a space, defined by each PC (shown for two PCs at the time in Fig. 11). This space, defined by the PCs from the training set, and the positioned responses, is used as the basis for the kNN classification analysis.

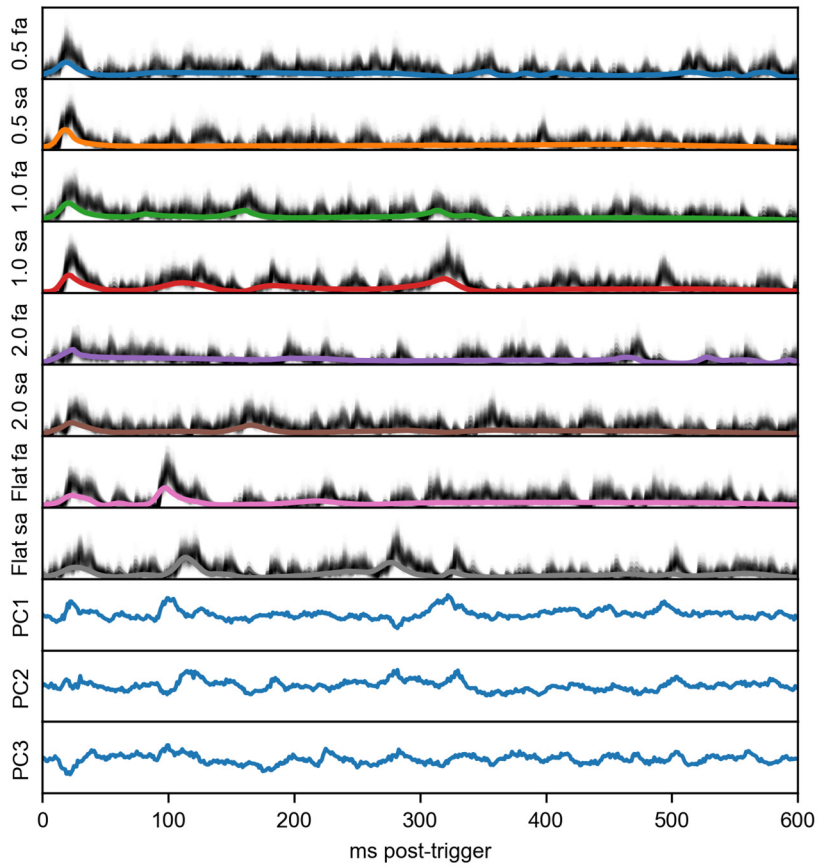


Figure 10. First eight rows, one per spatiotemporal input pattern, show continuous responses as black lines. Superimposed upon the continuous responses is the estimated mean signal by adaptive Kernel Density Estimation (Shimazaki and Shinomoto 2010). Last three rows show the first three PCs as calculated by PCA.

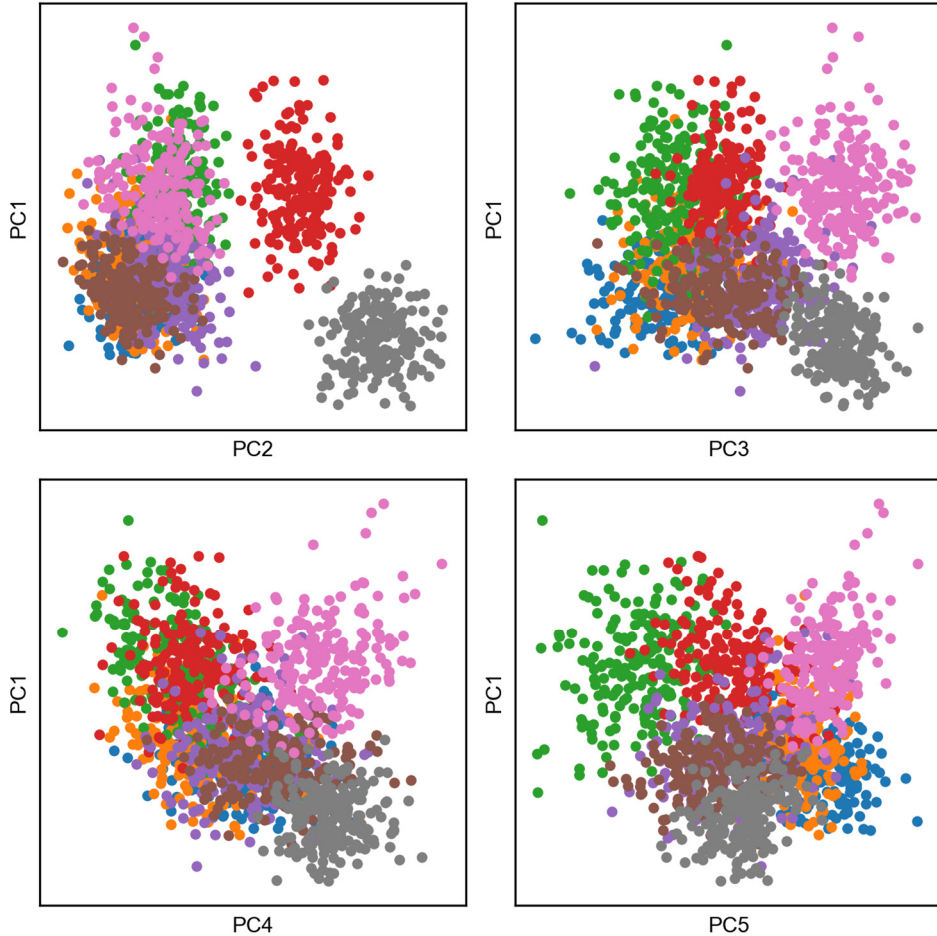


Figure 11. The test sets coefficients for PC1 versus the coefficients for PC2-5. Each data point is colored according to which spatiotemporal input pattern used concurrent to the registration.

The kNN classification algorithm

The kNN algorithm is an algorithm used for, among other tasks, classification. It operates on two sets of data points, a training set and a test set where the class (or group) for each data point is known. For each data point in the test set the k number of the closest data points in the training set are located. Each of the neighbors then “votes” on which class the test data point should belong to. For example, if the closest neighbors to a test data point has the classes “ice”, “fire” and “ice”, then the test data point receives two votes on the “ice” class and one vote on the “fire” class. In kNN the majority always wins, and would thus render the test data point to belong

to the “ice” class. This voted class is then compared to the known correct class, and the voted class can be marked as correct or incorrect.

In other words, the kNN classification algorithm explores how well the training data corresponds to, or describes, the test data. It is possible to evaluate to which degree this description is correct. The simplest metric is accuracy that is defined as the fraction of correctly classified items. However, a commonly regarded better metric than accuracy is F-score. F-score is the harmonic mean of Recall and Precision. Recall, also known as sensitivity, is the proportion of a specific class that was correctly classified as that class. Precision, on the other hand, is the proportion of a specific class that *actually* belongs to that class. F-score was used as the performance metric in papers I and III, and accuracy was used in paper II.

Internal control of chance level

When performing complex experiments that are trying to falsify quite esoteric hypothesis it is good practice to have a sanity check somewhere in the analytic method. The sanity check should answer the question if the results produced by the analytic method is due to error or chance. In the above outlined method it is possible to alter the process in such a way that it would gain this functional interpretation. In the normal case the method answers the question “to what degree does the responses identify the stimulation used concurrently”, but by prior to splitting the data into training and test set randomly shuffling the labels of each response (the label is equal to the spatiotemporal stimulation pattern used concurrent to the recorded response) the relationship between the stimulation and response is disrupted. The continued decoding analysis should then report a resulting performance metric close to chance level. If this is not the case then there is some kind of bias in the data that prevents further interpretation of the results.

Decoding algorithm

The algorithm described above and in figure 12 answers the question to what extent a certain response can be used to identify the stimuli concurrently applied. An important caveat is however that it is not implied, implicit or explicit, that the brain employs this method of analysing its activity. This method improves the commonly used PSTH based methods in several aspects, such as:

- No researcher dependent bias regarding inclusion and exclusion of parameters
- Less dependence on large amount of data
- Numerous graded metrics describing various aspects of the relationship between responses and stimulation
- Possibility of internal control of chance by randomly shuffling the labels of each response before splitting into training and test set

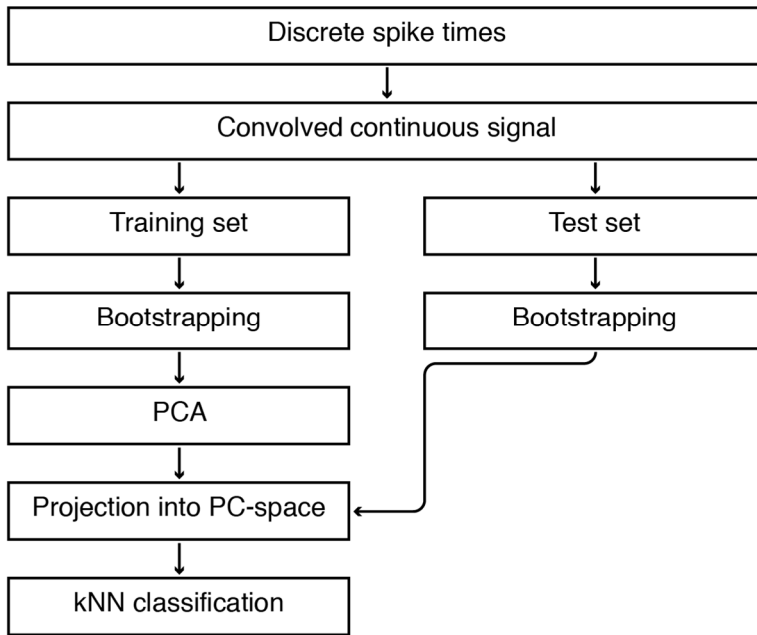


Figure 12. Flowchart describing the decoding algorithm.

Simulated neuron and associated network design

In paper IV, *A Model for Self-Organization of Sensorimotor Function: I. Spinal Monosynaptic Loop*, it is explored to what extent circuit formation in the nervous system can be based on synaptic learning rather than, for example, genetic preprogramming. In order to test this hypothesis an artificial organism is developed. The organism, called an Oropod (Fig. 16 panel A), has a basic musculoskeletal system with proprioceptive sensors (Fig. 16 panel B), connected to a neural network (Fig. 16 panel C). During simulations of the Oropod spontaneous muscle activations creates movements that are encoded by the proprioceptive sensors. The sensor activation projects into the neural network and continuously perturb the output that in turn affects the muscles, and so on and so forth.

The proper method of paper IV is the developed artificial neural network (ANN) implementation. What makes it important is the way it differs from most ANNs used today. Commonly used ANNs are based on backpropagation. Backpropagation, as the word suggests, propagates a learning signal backwards through the network in question in order to improve the output. Meaning, that when a learning event takes place and is projected upon the input layer of the ANN which subsequently produces

an output, this output is compared against the “correct” output. The difference between the produced output and the correct output is then propagated backwards through the network in order to improve the performance.

The ANN in paper IV does not employ neither backpropagation nor the need for a known “correct” answers. This is because the adjustment of the connections between nodes (artificial neurons) in the network is locally computed based on the seminal Hebbian plasticity rule (Hebb 1962). Hence, the ANN in paper IV is aimed to mimic a biological neural network.

For additional details, please refer to the appendix and paper IV, *A Model for Self-Organization of Sensorimotor Function: I. Spinal Monosynaptic Loop*.

Results

Somatosensory neurons decode tactile input patterns and location from both dominant and non-dominant digits

Specificity of neocortical functional areas is a cornerstone of the functional localist doctrine (cf. *Introduction*). Indeed, mapping of receptive fields down to the resolution of individual neurons has been an important part in many neurophysiological studies (Kaas et al. 1979; Vernon B. Mountcastle 1957; Penfield and Boldrey 1937; Woolsey, Marshall, and Bard 1942). In paper I we investigate the functional mapping of individual neurons using our highly resolvable and reproducible stimulation setup described in *Experimental methods*. The aim of the study was to perform a detailed exploration of the nature of interactions between representations of individual digits in the primary somatosensory cortex of the rat. As a consequence, apart from applying the stimulation only to the second digit of the left forepaw, we added an interface to the fifth digit of the same paw. The choice to use digits two and five was due to the fact that they have separate nerve innervation, thus minimizing the risk for stimulus spread. Digit two is innervated by median nerve, and digit five is innervated by the ulnar nerve.

Interactions between neocortical representations of digits is supported by neuroanatomical evidence primarily on the basis of extensive arborizational termination of single cortical neurons well outside their assigned functional area (Liao et al. 2013; Gerfen, Economo, and Chandrashekar 2016; Arnold, Li, and Waters 2001; Oberlaender et al. 2011). Reports of such for interactions is also available (Foffani, Chapin, and Moxon 2008; Lipton et al. 2010; Manns, Sakmann, and Brecht 2004; Christopher I. Moore and Nelson 1998; C. I. Moore, Nelson, and Sur 1999; Tutunculer et al. 2006). The nature of those interactions, however, has been sparsely characterized.

To find the area within which either digit two or five were represented we focused our search to stereotaxic coordinates previously reported to harbor these (Chapin and Lin 1984). The correct area was further established by the presence of local field potentials evoked by electrical stimulation to either digit two or digit five. The digitwise dominance of each neocortical neuron recorded was determined by the response to single pulses to each of the two sets of four electrode pairs. Digit

dominance was defined as a relative response intensity above 10% for that particular digit (Fig. 13 panel A).

When our spatiotemporal stimulation patterns were applied the resulting PSTHs indicated that the neurons had unique temporal responses (Fig. 13 panel B). This warranted a deeper investigation which was performed using our decoding analysis described in the section *Decoding of neuronal responses using Principal Component Analysis*. We found that, contrary to the ideas of functional localization, digit dominance did not predict decoding performance. A neuron that was dominated by digit five could often decode input from digit two with equal or higher precision than it decoded input from digit five, and vice versa. The analysis also revealed that the transition between digit dominances, and decoding performance, was gradual rather than binary (Fig. 13 panel A). We could not find any dependence between decoding performance and any parameter of the microscale functional parcellation suggested by the interaction between cortical layer and cortical column such as depth (not shown here, please refer to paper I and figure 7). However, the observed differences in the magnitude of the responses were in agreement with previous studies (de Kock et al. 2007; Oberlaender et al. 2011). Furthermore, individual neurons had unique responses to the same spatiotemporal pattern when applied to different digits and an extensive analysis consequently suggested that the cortical neurons decoded both input pattern and location of the applied stimuli, as a unique combination (Fig. 13 panel C, for further details please refer to paper I in the appendix).

In summary, we found that individual neurons could decode tactile input patterns and source location to a non-dominant and non-adjacent digit at a comparable or even a higher level than for inputs to the dominant digit. These findings illuminate primarily two aspects of information integration in the neocortex. First is that strict categorization of neurons into predefined categories by using simple stimuli might skew further hypothesis testing. Because, a strict categorization might not exist in the first place and the predefined categories might also be a construct by the experimenter and not an inherent feature of the neocortical network. Second is that simple stimulation can only elucidate integrative processes associated with that particular level of complexity and the results of paper I suggests that by using stimulation with a higher degree of complexity a larger part of the neuronal machinery is illuminated.

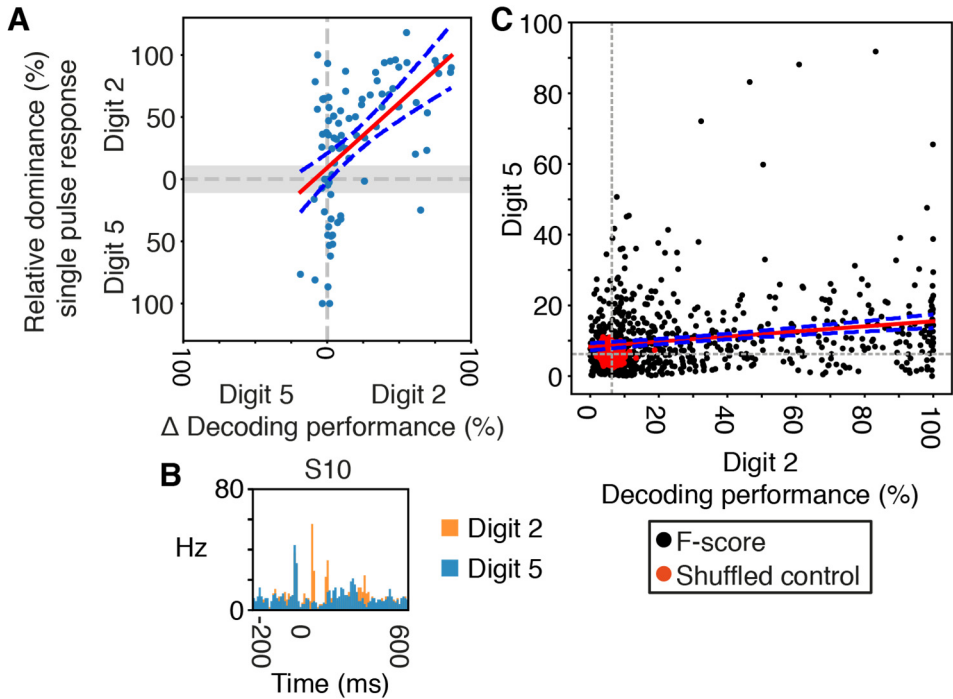


Figure 13. A) Scatterplot of the digit dominance versus digit decoding performance. The gray horizontal area indicates the $\pm 10\%$ limits within which the difference in response was considered to low to identify a dominant digit. B) Example neuronal responses to spatiotemporal pattern S10 applied to each digit as PSTH. A clear difference in the number and shape of peaks is visible. C) Scatterplot of the decoding performance for digit two versus digit five for each neuron is, thus, represented by eight data points. The corresponding results for the shuffled control analysis are indicated with red dots. The chance level is indicated with dashed gray lines at 6.25%. A linear regression model (red line) and its 95% CI (blue dashed lines) ($R^2 = 4.5\%$; slope, 0.07 [95% CI, 0.05–0.09]; intercept, 0.08; $p < 0.0001$) is also drawn.

Ubiquitous neocortical decoding of tactile input patterns

In paper II we continued the investigation into the functional specificity of neocortical areas, as well as paying homage to the intellectual heritage of Lashley (Lashley 1929) and all the way back to Flourens (Flourens 1824). This time increasing the area over which we searched for neurons with a receptive field encompassing our stimulation. The cortical area chosen for this exploration was as large extent of the dorsal surface of the right hemisphere that we could access (Fig. 14 panel A). Apart from the historical fundamentals already described, more recent evidence for a heavily interconnected neocortex exists (Bullmore and Sporns 2009). Hence, the hypothesis that information available to one area could also be available to others is still very relevant.

The method employed in paper II is in all relevant aspects equal to the general method described in *Experimental methods*. The recorded activity from our neocortical neurons were analyzed using a conceptually similar approach to the one outlined in *Decoding of neuronal responses using Principal Component Analysis*. PCA was, however, not employed since during the writing of paper II that method had not yet been developed¹³. Instead of PCA the activity during a number of time windows were used to position the responses into an arbitrary space. The segmentation of the responses into time windows was based on adaptive kernel density estimation (Shimazaki and Shinomoto 2010). The positioned responses in this space were then the basis for the already described kNN classification. Further details of the method can be found in paper II in the appendix. The important feature for the current discussion is that the output metric is comparable.

We recorded neurons both in the primary somatosensory cortex as defined by stereotaxic coordinates, and neurons outside the primary somatosensory cortex. The first group was named “S1” and the second group “Non-S1”. The decoding analysis of the responses to our spatiotemporal input patterns revealed that both groups included neurons with above chance level of decoding. We could not find any statistical difference between the decoding performance of the two groups of neurons (Fig. 14 panel B). Neither could we find any dependence between any grouping parameter and the decoding performance of the neurons when stratified by depth from the cortical surface or cortical area.

In a previous paper by our lab (Artificial spatiotemporal touch inputs reveal complementary decoding in neocortical neurons 2017) it was noted that different neurons exhibited differences in the responses to the same stimulation pattern. This heterogeneity allowed for a co-operative decoding analysis, i.e. where the responses from two or more neurons co-operated in decoding the concurrent stimulation. We adapted this co-operative decoding analysis method from that paper into paper II. With it we found that neurons from the S1-group could co-operate and the highest decoding performance increased from 46.8%, for an individual neuron to 56%, using 2 or 4 neurons with 400 ms of response time considered (Fig. 14 panel C top). We also performed this analysis for neurons located in the visual cortex (V1), a subgroup from the Non-S1 neurons. The analysis once again revealed an increase in decoding performance, with 4 neurons at 400 ms or 2 neurons at 200 ms with a decoding performance at 32% (Fig. 14 panel C bottom). The maximum decoding performance for an individual neuron in the visual cortex was 24.8%.

In summary, in paper II we found that regardless of location in the dorsal surface of the neocortex, we could find neurons whose activity concurrent with spatiotemporal

¹³ The included papers were written in a different chronological order than they were published. The chronological order of writing the papers is: II, I and III.

input patterns could be used to decode these patterns. We also found that the responses to these spatiotemporal input patterns were different in such a manner that they could be used in a co-operative fashion. This suggested that the responses of the neurons contained information regarding “what” the stimulation was. This can be contrasted to a mere binary reaction, meaning that the neurons could have been activated just because there was a stimulation, no matter the nature of that stimulation. However, if the neurons were activated by just the occurrence of the stimulation event and not the nature of the event, then the temporal evolution of the individual neuronal responses to the different spatiotemporal input patterns would be similar. This would in turn result in chance level decoding and no possibility of co-operative decoding.

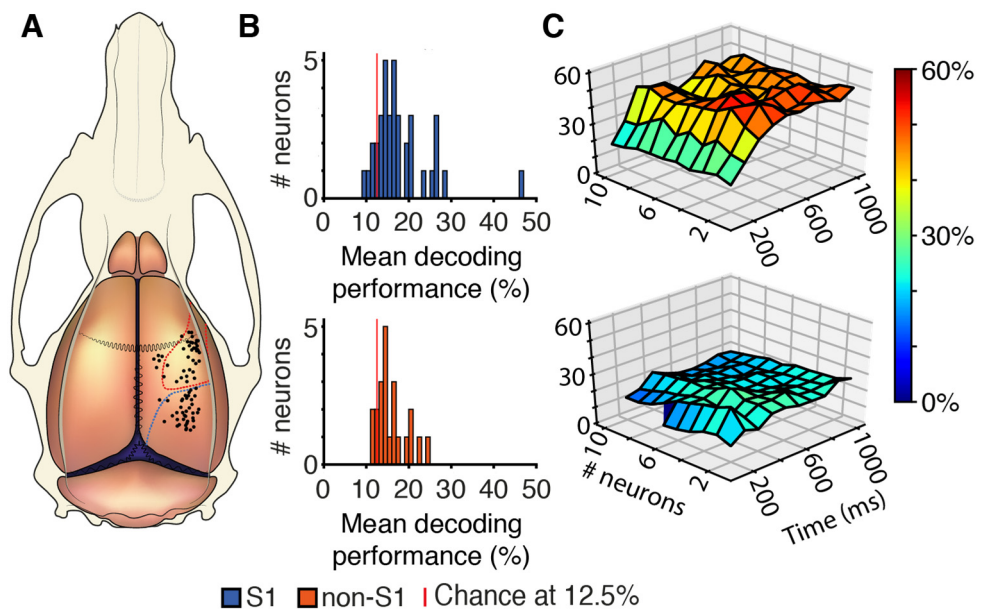


Figure 14. A) Illustration of a rat skull with brain. Each recording location is marked with a black dot. At each recording location several neurons could potentially be recorded. Red dashed lines demarcate the primary somatosensory (S1) cortex, it should be noted however that a large portion of recorded neurons within this area are outside the “paw” sub-area. Blue dashed line demarcate visual cortices. B) Histogram over decoding performance for individual neurons from S1 and non-S1 groups respectively. Red solid line demarks chance level (12.5%). C) Surface plots over co-operative decoding performance for S1-neurons (top) and V1-neurons (bottom). Number of neurons along x-axis, integration time along z-axis and decoding performance along y-axis. Color of surface according to colorbar (right) indicating decoding performance for that particular combination.

Focal neocortical lesions impair distant neuronal decoding of tactile input patterns

In paper I the overlapping information processing of digit representations was investigated and further expanded in paper II where it was found that processing of information originating from the digits could be detected across the whole dorsal surface of the brain. Results from both of these papers suggests that information from the digits can spread across the neocortex well outside the boundaries of cortical functional maps. However, these findings only support that information from digits are available for other parts of the neocortex than what is defined by cortical functional maps. It does not elucidate whether the processing of tactile information depend on this unbounded spread. That is, the mere possibility of presence of information does not necessitate integration. It is, however, strongly implied since synaptic learning is based on correlation (Hebb 1962) and if the presence of information is not correlated with anything in the neuron then the correlated synapse ought be depressed.

In paper III we investigated this hypothetical dependence between the primary somatosensory cortex (S1) and distant areas. The dependence was argued to be non-imperative such that a lesion to the neocortical network would not completely abolish the processing but rather decrease the performance. This graded performance decline would be in line with both the findings of, for example, Lashley (Lashley 1929) but also with unnoticed cortical infarctions in humans (Wardlaw, Smith, and Dichgans 2013).

The scientific question of graded interdependence between neocortical areas has previously been hard to address since it requires a graded performance metric and not just an identification of the presence or absence of a response. This is, however, available to our lab, as outlined in the section *Decoding of neuronal responses using Principal Component Analysis*. We could therefore analyze the effects of distant localized cortical infarctions on the decoding performance of S1 neurons.

The method employed in paper III was, once again, in most important aspects equal to the one described in the section *Experimental methods* with the addition of the induction of cortical infarction. The cortical infarction was induced according to the description of Shanina et al. (2006), in which the bone of the skull was thinned out at the location of the intended lesion. Above the thinned out section a fiber-optic bundle was placed. The fiber-optic bundle in turn was connected to a light source. Induction of the lesion was initiated by injecting the dye Rose Bengal through the femoral vein, with the light source concurrently turned on. Rose Bengal exposed to the specific light wavelength (561 nm) initiates a cascade resulting in coagulation (Labat-gest and Tomasi 2013) and thus formation of the necessary localized clotting, i.e. the neocortical infarction, at the location illuminated in the neocortex.

Both morphological analysis and ECoG analysis was performed. The morphological analysis found a drastic decrease of intact cellular nuclei in the brain region targeted, as expected after a infarction (Hoff et al. 2005). The ECoG analysis found an abrupt but transitory decrease in the activity of, primarily, the gamma frequency band. This decrease in activity was often concurrent with a transitory decrease in neuronal spiking activity. Both findings are aspects of the phenomena of spreading depression, which is known to occur during stroke (Lauritzen et al. 2011; Strong et al. 2002). Thus, both aspects of analysis confirmed the cortical infarction in the animals.

Moreover, as an effect of the cortical infarctions we found a consistent decrease in the decoding performance for neurons recorded in S1 (Fig. 15 panel B). We could, however, not find any difference in the average activity of the individual neurons (Fig. 15 panel C) or find any relationship between the firing frequency and the decoding performance (Fig. 15 panel D). This indicates that the decrease in decoding performance was not due to a decrease in firing frequency but rather a less pronounced specificity of the responses. Finally, we analysed the ratio of time spent in synchronized:desynchronized brain state as defined by ECoG before and after induction of the cortical infarction, and could not find any difference in this parameter either.

The results in paper III were controlled with a separate set of experiments with sham surgeries. The only difference from the previously described method was that the light source was never turned on, preventing the cortical infarction from occurring. The data from these sham experiments are present in the figures referenced above (Fig. 15 panel B-D), and consolidate that the results seen were due to stroke effects and not by the surgery or injected substances since the observed effects of stroke was only present in the stroke material.

In summary, in paper III we found that focal cortical infarctions in the neocortex can affect the information processing at distant locations from the lesion site. Particularly, a focal cortical infarction in the parietal lobe decreases the decoding performance of S1 neurons without affecting conventional performance metrics such as firing frequency or brain state. This result, in conjunction with paper I and II, indicate a bilateral relationship between the areas of the neocortex.

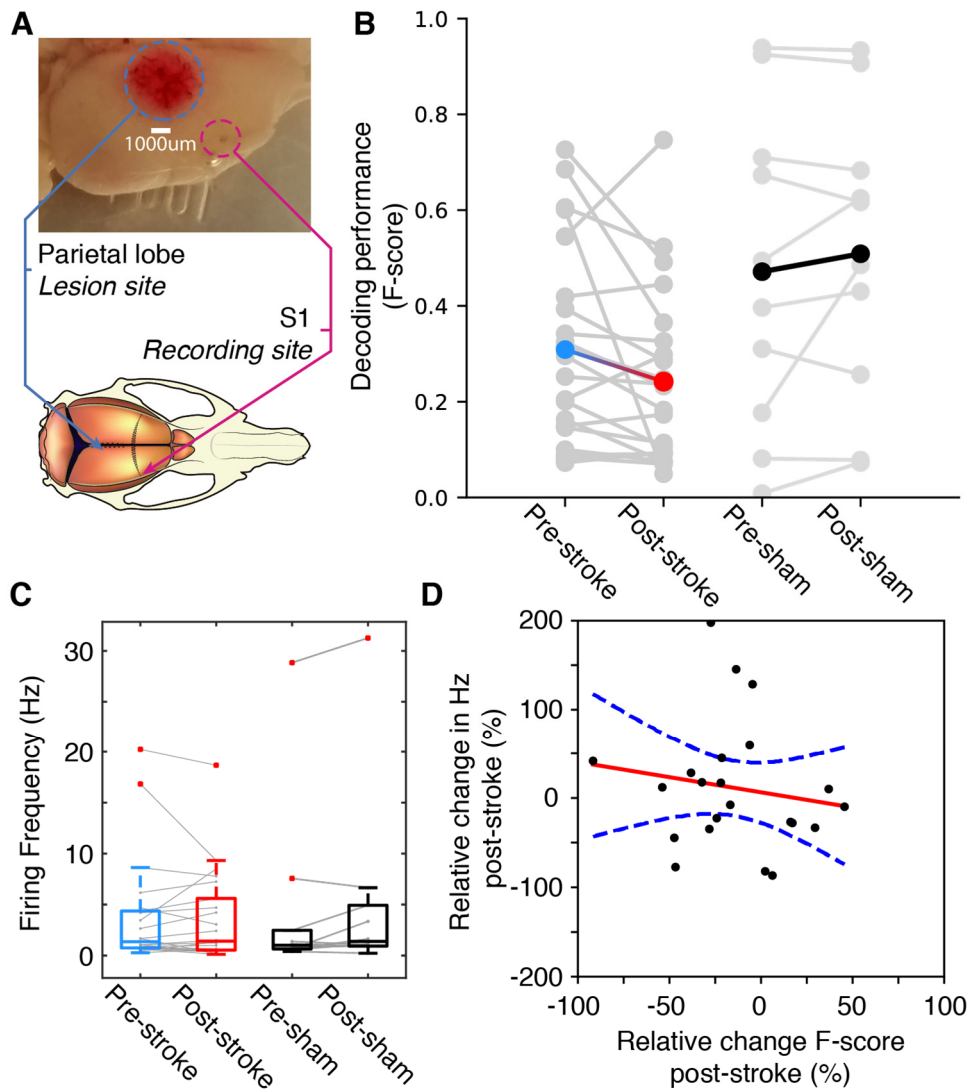


Figure 15. A) Illustration of rat skull and brain together with an example photo of an actual brain from the project. Recording site and site of induction of lesion marked with red and blue lines respectively. Note that the brain surface in the photo clearly shows the coagulated blood vessels. B) Decoding performance (as F-score and not accuracy as previously used. The reason is discussed in the methods section) before and after study protocol. Data are shown for lesion and sham groups separately. Mean values are indicated as non-gray markers. Individual neurons are indicated with gray color and connected lines. C) Boxplot over firing frequency before and after protocol. Individual neurons are shown as gray markers with connected lines. D) Firing frequency versus change in decoding performance for stroke group. A linear regression and its 95% confidence interval is also shown ($R^2 = 2.3\%$, $P = 0.499$, intercept = 0.63, slope = -0.339 ; CI 95% = -1.149 to 0.471).

Self-organization of spinal sensorimotor circuitry

Papers I-III were concerning the nature of somatosensory information processing in the neocortex. Each one considering a particular aspect relating to functional parcellation with results pointing towards a holistic paradigm of brain organization. However, prior to ever truly understand the information processing of the neocortex the subcortical systems has to be understood. This is because the subcortical systems provide the incoming information, and handles the outgoing information, therefore defining the formative context for any neocortical *modus operandi*. Hence, any argument regarding this *modus operandi* has to be seen as a speculation until the day the subcortical systems are fully characterized. As outlined in the section *Anatomical and connectionistic introduction* there is still much we do not understand about the functional properties of the subcortical structures and even regarding the spinal circuitry.

The final paper included in this thesis is paper IV, titled *A Model for Self-Organization of Sensorimotor Function: I. Spinal Monosynaptic Loop*. This paper is intended as the first paper in a series investigating if connection schemes and emergent function seen in biological nervous systems in general, and the spinal circuitry in particular, can be an effect of self-organization based on experience. Self-organization is contrasted against a genetic preprogramming hypothesis, which is a popular alternative and an active research field in itself (Delile et al. 2019; Hoang et al. 2018; Osseward and Pfaff 2019; Lai, Seal, and Johnson 2016).

In paper IV an artificial organism called an Oropod is developed. The Oropod and an overview of the development has already been described in the section *Artificial neuron and associated network design* and will not be repeated here.

The aim of the study was to simulate and investigate self-organization in the spinal circuitry. An auxiliary hypothesis was that the weaker muskuloskeletal state in the early fetal development had a developmental advantage in this aspect. This auxiliary hypothesis originated from the fact that the only primary afferent that forms monosynaptic connections with motor neurons (MNs) are Ia sensors. Ia sensors are activated by velocity changes in the muscle (G. E. Loeb and Hoffer 1985) where a lengthening of the muscle is denoted positive muscle velocity and shortening is denoted negative muscle velocity (Zajac 1989). Thus, in the most simple sense an activation of a muscle will cause contraction and as a result a negative muscle velocity which would silence the Ia sensor. Hence, the overt nature of the Ia sensors thus argues against the feasibility of Hebbian learning as a basis self-organization with strong homonymous synaptic connections. However, amphibian and fish muscles are generally innervated by β MNs that simultaneously activate extrafusal and intrafusal muscle fibers (Eyzaguirre 1957). Mammalian muscles also generally have a substantial but variable percentage of β MNs alongside their much more

evolved and independent α MN and γ MN subsystems that provide independent control of extrafusal and intrafusal muscle fibers respectively (Manuel and Zytnicki 2011). However, during early fetal development extrafusal muscle fibers are immature and weak (Gokhin et al. 2008), γ MN activity may be absent or uncoordinated (Shneider et al. 2009), and the body tends to be confined *in utero* or *in ovo*. In this situation the fusimotor effects of activating a β MN would likely produce a net increase in firing of the afferents in the muscle spindle that it innervates. Thus, the β MNs could potentially support a learning-based organization of the Ia-MN connectivity. (An in depth discussion can be found in paper IV in the appendix)

In order to assess the effect on the learning of the immaturity of the muscle fibers we made the simplification that a more immature muscle fiber outputs less muscle force proportionally to activation, i.e. a high MN output yields slower movement. For this reason the muscle force of the Oropod was decreased to 25% in the first set of simulations.

Simulations of the Oropod was carried out and for each new simulation the initial synaptic weights between the incoming Ia sensors and the MNs were randomized. Movement of the Oropods limbs were generated with a general Activity Pattern Generator (APG) that activated each MN with a random amplitude and duration. The MNs in turn activated the muscles of the Oropod in agreement. The activation of each MN was continuously perturbed by the composite signal of the APG and the incoming Ia sensor feedback. The MN output was also the basis for learning and the synaptic connections upon the MNs quickly converged such that Ia afferent feedback for the homonymous muscle were potentiated whereas those from non-homonymous muscles were depressed (Fig. 16 panel D), i.e. a similar synaptic weight matrix as observed for Ia-MN synapses in adult mammals (J. C. Eccles, Eccles, and Lundberg 1957).

An equal set of simulations was also performed but with an increased muscle force. As described above, increasing the muscle force would increase speed and amplitude of the muscle and limb dynamics. In agreement with the hypothesis the Ia-MN connection strengths decreased with increasing muscle force (Fig. 16 panel E).

Reduced APG and no fusimotor effect

A common idea relating to spinal development is the hypothesis of a Central Pattern Generator (CPG). CPG theory promotes the idea that there exists pre-wired neuronal circuitry that produces behaviorally relevant alternating activations of muscles that could support, for example, locomotion. Hence, by this definition a CPG would generate only a subset of the theoretically possible MN activation combinations in

contrast to our general APG which can generate the complete set of activation combinations.

Various reduced variants of the general APG were tested using our simulations and the Oropod. Each one converged with less pronounced homonymous Ia-MN connections compared to the general APG (not shown here, refer to paper IV in the appendix and figure 8).

It was also tested to see to what degree the fusimotor effect (i.e. tension of the muscle spindle, see Fig. 16 panel B) had on learning. A set of simulations were made with the fusimotor effect removed, effectively simulating an organism with only α MN. In this case, the synapse-specific potentiation of the Ia-MN projections seen in previous simulations disappeared.

Support for functional self-organization

In summary, paper IV presents a basis for functional self-organization of the Ia-MN connectivity in the spinal cord based on sensorimotor experience resulting from random activations of the MNs during early development. No *a priori* knowledge had to be injected into the neural network for natural looking synaptic weight matrices to emerge. Rather, when the commonly accepted CPG theory was incorporated a reduction of clarity in these matrices resulted.

Paper IV takes a first step towards an exploration into deeper functional self-organization, based on experience rather than predetermined wiring. An exploration that will try to elucidate the spinal circuitry and then reach upwards towards the neocortex, trying to examine if it is possible to simulate a neocortex based on the holistic viewpoint indicated by the results of papers I-III.

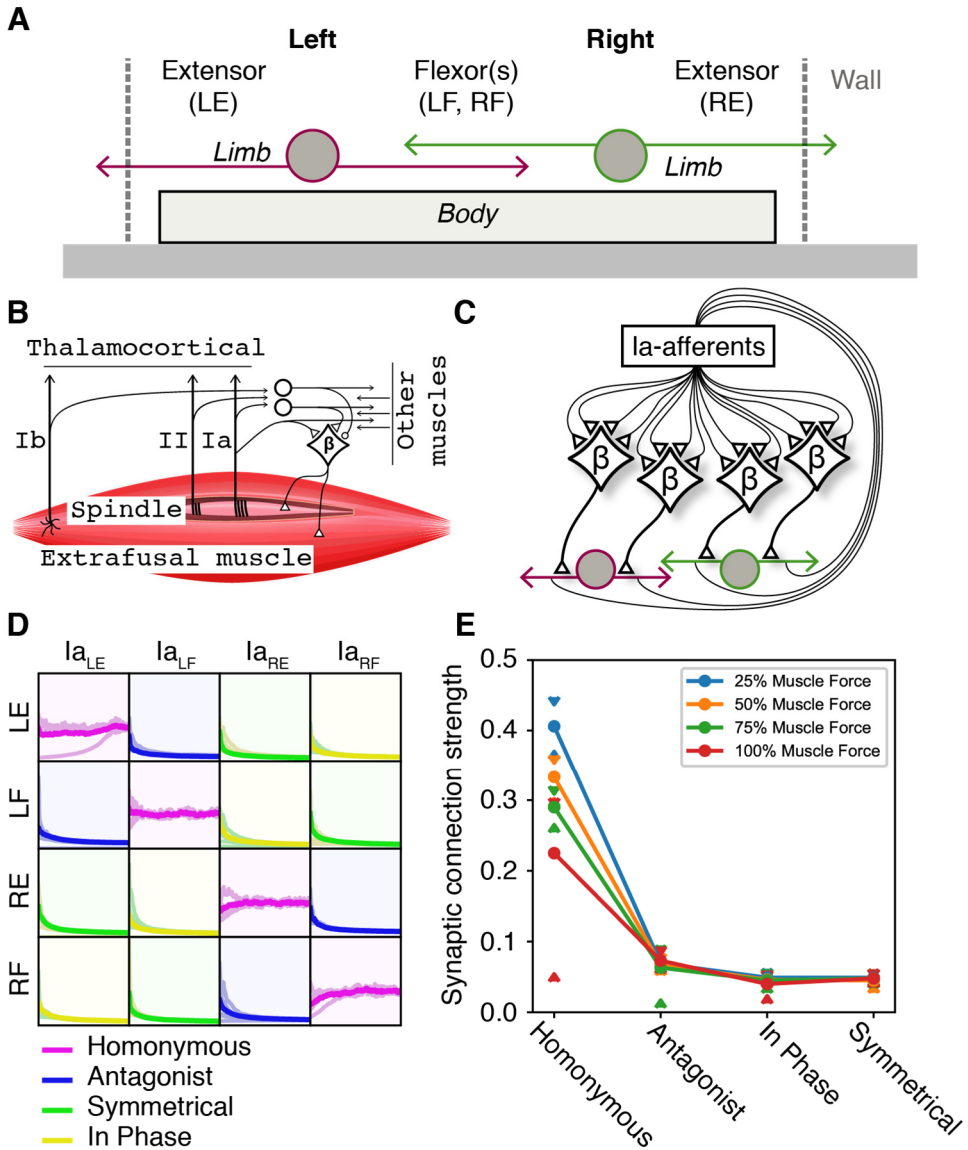


Figure 16. A) Macroscopic anatomy of the Oropod organism with Body, limbs and corresponding muscles named according to location and function: Left Extensor (LE), Left Flexor (LF), Right Flexor (RF) and Right Extensor (RE). Left and right walls of the Oropods world are indicated with gray dashed lines. B) Illustration of muscle with proprioceptive sensors and their connectivity. C) Illustration of neural network design with a fully connected spinal circuitry. From each muscle Ia afferents synapse onto β MNs that project back unto their respective muscle (both extra- and intrafusal muscle fibers). D) 4-by-4 synaptic weight matrix for N=5 simulations using the general APG and muscle force at 25%. One β MN per row and their respective Ia synapses per column. The colors indicate the functional relationship between the β MN and that particular Ia afferent according to the legend. The temporal evolution of the synaptic weight for each individual seed weight is displayed with a less saturated color. E) Mean synaptic weight per MN category during the last 1/25th of simulation duration. Each data set is from N=5 simulations with muscle forces set at 25%, 50%, 75% and 100% respectively. Caret up/down indicates minimum and maximum values in each set and category.

Discussion

This thesis is based upon the four included papers listed in the beginning. In paper I a high-level interaction between the neocortical representations of individual digits is shown, questioning the discrete nature of historically popular cortical maps. In paper II this is further expanded when complex responses to tactile stimuli is found across the whole dorsal surface of the neocortex. The interdependence between these findings are implicated in paper III, thus serving as support for the holistic theory of an indivisible neocortical *modus operandi*. Finally, in paper IV an initial argument is made for self-organization rather than detailed preprogramming as the formative rule for circuit formation.

Indeed, throughout this thesis, and the included papers, a specific hypothesis has been held forward. That the function of the nervous system is unitary, as contrasted against the more common view to see it as a conglomerate of discrete centers. The debate between these viewpoints has been going on for centuries and over the years it has become more apparent that the definition of function and what the function is comprised of is of utmost importance to be able to continue this debate. This was noted already by Golgi in his speech when receiving the Nobel Prize in 1906.

“We find the same situation regarding the so-called physiological independence of the neuron. Just as we have said regarding the functional mechanism, far from being able to accept the idea of the individuality and independence of each nerve element, I have never had reason, up to now, to give up the concept which I have always stressed, that nerve cells, instead of working individually, act together, so that we must think that several groups of elements exercise a cumulative effect on the peripheral organs through whole bundles of fibres. It is understood that this concept implies another regarding the opposite action of sensory functions. However opposed it may seem to the popular tendency to individualize the elements, I cannot abandon the idea of a unitary action of the nervous system, without bothering if, by that, I approach old conceptions.” (Golgi Nobel Lecture 1906, 216)

Moreover, as briefly touched upon in the section *The complex relationship between the world and the brain*, any particular definition of function as seen by an external observer is, at least, dependent upon the the sensory origin or motor endpoint (Fig. 17). Hence, any discussion of results regarding the machinery of the nervous system has to define some stance on the topic of function relative all the possible interpretations of opinions and scientific observations. This is true no matter if the

currently accepted theory of functional organization of functional localization continues to dominate, or if the holistic theory can become the preferred mode of interpretation. Therefore, before the in depth discussion of the particular results of the included papers of this thesis an attempt to make at least a rudimentary definition of function in the nervous system will be presented.

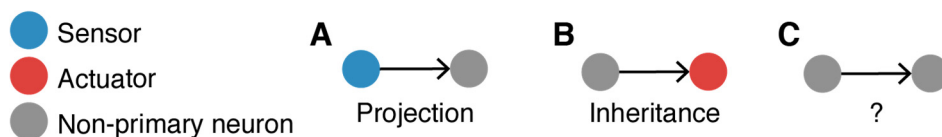


Figure 17. Function as seen by an external observer can only be inferred by projection (A) or inheritance (B) from a node with an already externally defined function, such as a sensor or an actuator. The dynamics between “naïve” nodes (C) however is harder to define.

A definition of function

With the establishment of the neural doctrine by Ramon y Cajal during the end of the 19th century (Finger 1994) an important bifurcation within the neuroscientific field occurred that set the study of the brain apart from other studies of biological organs. Other organs are reducible in a somewhat orderly fashion. The understanding of enzymes in single cells in the liver directly explains one aspect of the organ’s *raison d’être*. With the establishment of the neural doctrine this was no longer the case within neuroscience. On one hand there was the biological part of the machinery within the cells that explained the production, excretion and uptake of neurotransmitters. On the other hand was the functional part; the communication between cells and the consequential creation of vast neural networks affecting the environment. Understanding the cellular machinery, theoretically isolated by the neural doctrine, did not directly explain the functional aspect. Indeed, throughout this thesis descriptions and arguments concerning the functional aspects of the nervous system has been presented, similar to other publications concerning the nervous system. After all, the purpose of most scientific inquiries into the nervous system are aimed at understanding the function of it. Yet, one might stop and ask if there exists a common appreciation of what a definition of a function within the network of the nervous system would require. Also, if there exists a risk, without a definition of function *a priori*, that the external observer (often the researcher) projects a predefined notion upon the object that is observed.

Mathematics has already been the source of explanations for peculiar mechanics present in the nervous system, such as the definition of small-world networks (Watts and Strogatz 1998) explaining the observation of impressively short chains of neurons needed to “travel” from one end of the brain to the other (Arbib et al. 1998).

Hence, it is not surprising to find additional assistance in mathematics when trying to define the function of these networks.

Functional decomposition

Within mathematics there is a concept of ‘functional decomposition’ which aims to resolve the constituent parts of a system and their relationship in such a way that the original function can be restored. There are two reasons why the concept of functional decomposition is important. First, there is the intrinsic reason in functional parcellation of decreasing the number of dimensions in a system which is important when trying to find underlying relationships between inputs (Spanne and Jörntell 2015). Second, there is the extrinsic reason of understanding each part which enables manipulation. The ability to manipulate, in turn, is often the reason to perform scientific inquiries in the first place.

In order to try to define a function within the nervous system some notation from mathematics and functional decomposition is borrowed. A general function can be defined such that $f: X \rightarrow Y$, meaning that the function f maps elements from the set X to specific elements in set Y (also often written as $y = f(x)$, where x and y are elements of X and Y respectively). The input source (X) into the function is called the domain of the function, and the output source (Y) is called the codomain. Thus, as so described, the process of functional decomposition includes defining the input (X), the output (Y) and the function (f). If it would be the case that a system is composed by a number of functions ordered in a hierarchical fashion then each part has to be defined through the process of reduction. Reduction has the aim of isolating a function in its ultimate basic condition, i.e. find an atomic function which is captured and intrinsic within the particular part studied (Fig. 18 panel A). Furthermore, the input and the output should be disjoint sets and non-interacting apart from the mapping from input to output. Finally, the process of defining each component is often carried out in light of externally observed properties, or behaviours of the system, as guides. A final note is that the defined functions should be distinct from their variables.

However, a decomposable system has to be contrasted against a dynamic system. In a dynamic system the properties of the system emerges as a product of the interaction within the system. Consider the example in Fig 18 panel B. Assume that within an observable unit (U) there is an agent (A) that can act within an environment (E) through the function f . The agents actions influence the environment and the agent can sense this environment through the function g . The sensing of the environment in turn influences the agent such that it is mediated through f . This can also be written as the initial state of A_0 affects the initial state of E_0 by $f(A_0)$, which is sensed by $g(f(A_0), E_0)$ which defines the next state of A that affects the next state of E by $f(g(f(A_0), E_0))$, and so on and so forth.

The properties of U as seen by an external observer are a product of the cumulative interaction between A and E through the functions f and g . If any of the constituent parts changes the produced properties will change. The state of the system U (Fig. 18 panel B) will be dependent upon the previous interaction between the constituent parts up to that moment while the state of the system in Fig. 18 panel A will only be dependent upon the current input of A and B . This also implies that if the agent with its functions was placed in another environment X the externally observed properties of U might be completely different from when the environment was E . Thus, even though $A, f, g,$ and E are definable the externally observed properties are dependent on their particular interaction, hence emergent. Furthermore, the externally observed properties does not necessarily inform the external observer about the underlying constituents (Haken 1983). Therefore, categorizing observed properties is not necessarily equal to defining underlying functions.

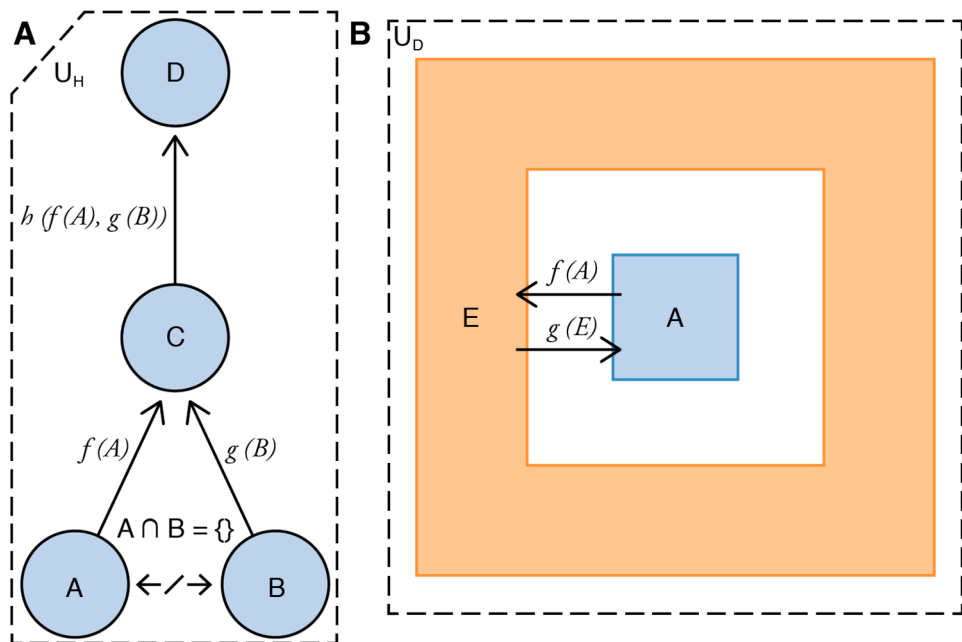


Figure 18. A) Requirements for hierarchical functional decomposition are that the input into a function needs to be disjoint sets of non-interacting components ($A \cap B = \{\}$). The relative configuration in a functional space should also follow the geodesic description of the figure. If the input cannot be defined in geodesic terms in accordance with the notion of this figure, then further reduction is not possible. B) Example of a dynamic system, adapted from Mind as motion (van Gelder and Port 1995).

Neuronal parameterization

Returning to the tentative function of the nervous system given the context above will focus the discussion. Obvious is that there are a number of variables that are needed to be defined in order to determine the function of U (the observed unit). In the following paragraphs U will be contrasted as either being a single neuron or a cluster of neurons in a network.

If f is part of a hierarchical functional construct U_H (as in Fig. 18) and the definition of U_H is sought after then the exact nature of the input is most definitely needed and also the exact nature of the mapped output. Using these two variables the parameters of U_H and the constituent functions should be possible to define.

An example for a single neuron could be the input of a current across the membrane that by a function is mapped to a particular sequence of action potentials (such as the Hodgkin–Huxley model (1952)). Another example, but concerning a network of neurons (or any nodes), could be a subcortical nucleus as long as the exact nature of the input is a disjoint and non-interacting set to the output. The nucleus cuneatus is perhaps a prime example, with a reasonable defined input set of sensory information from the upper trunk (Zaqout and Al-Hussain 2013) and a reasonable defined set of output axons terminating in the thalamus. Experimental and computational evidence support an overall function of the network of cuneate neurons to be creation of a feature space and relaying of that composite information (Rongala et al. 2018; Jörntell et al. 2014). The composite information would in the particular case of the nucleus cuneatus would be haptic dimensions. Noteworthy is that the relation to haptic dimensionality is not implied by the responses themselves, but rather due to an external hypothesis grounded in the theoretical analysis of haptic interactions (cf. *The dimensions of experience*). Or in other words, the observed responses did not inform the external observer about the, tentative, underlying function.

If U , however, is in itself part of a larger dynamic system then the question of function quickly become more elusive. This is easiest to illustrate with a direct example. Imagine that we want to investigate the assumed function of neurons in a certain area of the neocortex. We have decided to do this by applying a weak electrical current unto the neocortical surface directly above the cluster of neuron we are focusing on. Concurrent to when we apply this stimulation we observe or measure the response (neuronal output or maybe an arbitrary externally observed property) somewhere else, e.g. stimulation applied to a specific part of the primary motor cortex while measuring the contraction of muscles in the contralateral arm. When we find an area of the neocortex that reliably results in the contraction of the muscles of the contralateral arm we assign that area the function of controlling the contralateral arm, i.e. “arm area”. Now, let’s consider the assumed context when defining a function to the neurons we are investigating in this way. First, we implicitly say that the neurons within the specific area is the complete set of neurons

controlling the arm. That is, when controlling the arm we by our own definition have to use these neurons and no other. If this would not be the case then the logic in defining a “arm area” would be lost. Second, we assume that the output from the neurons within the specified area does not affect the functional state from which it normally receives its input. If this would be the case then the functional isolation we need to study the cells are lost. Thus, no neuron within the set of neurons of the specified area can be connected to a neocortical neuron outside this set that in turn connects to a network that feeds back into the initial set, i.e. the input has to be disjoint from the output. If the two sets are not disjoint then we have two alternatives:

1. Expand the set of neurons that we suppose are controlling the arm with the connected network, while asserting that each neuron included into the set adheres to the rules specified,
- or,
2. accept that the observed function of U is not exclusively carried within the investigated cluster of neocortical neurons.

Third, we assume that the input, or activation, we used in obtaining the results (i.e. contraction of arm muscles) is capable of generating a natural response. Meaning that a concurrent activation of all neurons of the set should not generate an aberrant behaviour of the organism as contrasted to the more probable temporal diverse activation commonly coursing through the cluster of neurons. If concurrent activation of the set of neurons does indeed generate an aberrant behaviour then our methodology is at fault and any results are hard to interpret.

Continuing the example with the neocortex, the above suggested limitations are hard to fulfill. Particularly concerning motor control over specific limbs it is hard to imagine how such fine-grained level of control would be possible. Just by assuming that the previous description regarding the spinal circuitry is true (cf. *The spinal circuitry*) with the broad termination territories of corticospinal axons (Jankowska 1992). Secondly, no evidence exists to support isolated connectivity within the defined motor areas (Winnubst et al. 2019). On the contrary, pyramidal neurons have been shown to extend to very large parts of the neocortex (Gerfen, Economo, and Chandrashekar 2016). Furthermore, the columnar organization as suggested by Mountcastle (Vernon B. Mountcastle 1957) had been disproven based on both failure to provide the necessary isolation in connectivity as well as based on theoretical considerations of too tight restrictions in processing capability (Horton and Adams 2005; Towe 1975). Likewise, the layer specific differentiation of information processing has failed to emerge in previous papers (Calogero M. Oddo et al. 2017) and also in the included papers of this thesis (Enander and Jörntell 2019; Enander et al. 2019). Moreover, the opposing argument as a potential dynamically distributed activation has been shown to realise itself, further suggesting that a

functional decomposition of the neocortex is deceptive (Nicoletis et al. 1993). However, to what extent concurrent activation of all neurons within a subsection of the neocortex generates aberrant behavior relative to a more natural spatiotemporal activation is not known. Finally, extending the above argumentation to characterize the input into a hypothetical set of investigated neurons follows the same line. Thus, the possibility of a strict definition of input is infinitesimal.

Hence, the suggestion of requirements in order to define a specific function in the nervous system are:

1. Defined input sets that are disjoint and non-interacting.
2. Application of general functional decomposition methods aiming at separating the mapping (the abstract function) from the variables, thus defining the function as a distinct abstract entity.
3. Defined output as mapped from the input.

Furthermore, it is explicitly implied that the description of the function is separate from the nature of the input, an aspect that has already been described in neuroscience for the proposed function of the cerebellum, for example by Dean et al. (2010) (cf. *Cerebellum as some kind of neuronal machine*). It is also implied that a definition of function is not dependent upon the external classification by the nature of the input, as long as the input can be clearly defined in terms of the domain, i.e. it is possible to define the cerebellum as an adaptive filter without the knowledge that the input is motor and sensory in nature.

However, the previously suggested requirements for a definition of function does imply that it is impossible to define a function for a set of (in a geodesic sense) local neurons in the neocortex since it is arguable impossible to define, in a strict sense, the input into the neurons of consideration (Winnubst et al. 2019; Gerfen, Economo, and Chandrashekar 2016). The remaining question thus become if it is possible to define the functions of the nervous system at all.

Bounded representations

Paper I performed an investigation into the uniqueness of neuronal populations with regard to processing focus. The results, as already presented, indicated that categorization of neurons made with simple stimuli such as single pulse trains created no obvious binary classification. The responsiveness to this kind of stimuli instead seemed graded (Fig. 13 panel A). Furthermore, the relative degree of responsiveness gave no good prediction to what extent the uniqueness of the neuronal response was to more complex spatiotemporal input patterns. Our analysis indicated that the neuronal responses contained features that included both “where”

the stimulation had taken place and also “what” happened. This suggests, all in all, that the externally observed somatotopy has low impact on the organization of information processing and that previously suggested discrete and strictly hierarchically organized processing is unlikely. Furthermore, the uncovered principle of unbounded representation is unlikely to only be applicable to the two digits we explored. This implicate that processing of sensory information is highly integrated even in what is seen as primary areas. Thus, if entertaining the thought of a sequential stream of neocortical information processing (famously first suggested for the visual system (Goodale and Milner 1992)) it would imply that the initial data into that stream would be one with high-level constituents, questioning the need of a “stream” in the first place.

Furthermore, the graded aspect of the decoding performance is another aspect of importance apart from the indication of presence of high-level information in primary areas. This diffuse selectivity of neurons prevents a strict classification into discrete centers as prescribed by cortical functional localization theory. This is not only problematic for that theory in the sense of creating a map but more relevant is the diffuse nature of the integrated “receptive fields” of neurons which is consequently projected inwards into the vast neocortical network. The *modus operandi* suggested is hence the combination of the unlabeled functional rule in Fig. 17 panel C and the dynamic context in Fig. 18 panel B which would be the perfect foundation for a dense representation of high-dimensional states. This is further supported by the unbounded availability of digit processing suggested by the results of paper II.

This is very bad news if there would exist an inherent benefit in parcelating nervous processing into discrete centers since parcellation rather suggests a sparsification of representation. While sparse representations are often faster to learn a dense representation in a network generalizes better and thus can handle novel, but related, situations to a higher degree (Spanne and Jörntell 2015). Indeed, the results of paper I-III supports a more dense and diffuse representation and together with the proposed definition of function it is further suggested that the neocortex is an indivisible unit of processing.

Abolishing and restituting observed properties

The now suggested view of the neocortical processing is as an indivisible unit of a dynamic system suggests that the observed properties of the unit would change by changing the “environment” (cf. Fig. 18 panel B). Paper III investigated this with the results in line with that prediction, with the effect of reducing the distinctiveness of information that was possible to extract from neurons in the primary

somatosensory cortex. Since the neocortex operates on the incoming information, which should be a true statement no matter which theoretical foundation one has *a priori* as a researcher, it would be a plausible interpretation that if the quality of that information is decreased any operation that depend on that information also decreases in quality. Similar interpretations have been made previously by other researchers, but on different kinds of results (Goltz 1888; Lashley 1929; Phillips, Zeki, and Barlow 1984; Kim and Choi-Kwon 1996; Brasil-Neto and de Lima 2008).

Moreover, if the decrease in quality of the decoding performance is equated to an observed property then the decrease in quality should be possible to be to such an extent that the observed property is abolished relative to the observers examination method. Yet, if the dynamics of the system is the source of the observed property, and the damaged part of the network is non-essential for the generation of the property, then it would also support the restitution of the same property. Which is a complicated way of saying that an indivisible dynamic system would support the observations regarding restitution made by Goltz (1888) and Flourens (1824), while also supporting the observation that some damages are small enough to not be noticed at all (Wardlaw, Smith, and Dichgans 2013).

Analysis of the neocortex from the perspective as a dynamic system has been made (Tognoli and Kelso 2014; Sporns et al. 2004; Bullmore and Sporns 2009; Bassett and Bullmore 2006) and suggests that there are areas that are more important for the operations of the network than others, often called “hub zones” or “hub nodes” (Bullmore and Sporns 2009). This is also implied by the small-world theory alone (Watts and Strogatz 1998). However, it should be noted that the particular **locations** of these areas are probably of secondary interest from a functional perspective (as hinted by the properties of small-world networks and the estimations of Arbib et al. (1998)). This kind of analysis also suggests that the degree of effect a lesion has relates to which particular “nodes” are removed (Váša et al. 2015). Thus, if the damage to the network is either to the input of a specific kind, large enough, or happens to destroy “hub nodes” then the restitution might be prevented. Worth pointing out is that even though an observed property of a system is abolished by destroying a particular node that does not place that particular property at that node (as already explained, cf. Fig. 18 panel B).

Holistic and dynamic

All in all, the neocortex is suggested not to be a conglomerate of discrete centers organized in a hierarchical decomposable manner but a unitary undivisible dynamic system. This is referred to in some historical accounts as a “holistic” view (Finger 1994). However, there is still the case of the somatotopy found in most places of the

nervous system, the somatotopy which serves as a foundation for large parts of the localist theory. An attempt to close in on this topic of somatotopy will be made.

First, there is the prelude of embryologic and later development that results in the initial wiring of the spinal cord. This has to some extent already been described (cf. *The spinal circuitry*) but in essence there is interneurons upon which the majority of corticospinal axons terminate and overlapping neuronal motorpools exerting control over muscles. The topology of these motorpools are such that proximal muscles are controlled by medial pools and distal muscles are controlled by more lateral pools. However, an in depth description of the complex developmental queues and stages leading up to the initial spinal topology won't be written here. It would require an amount of text that would be disproportionate against the fact that this thesis is regarding neurophysiology and not developmental genetics/biology. Furthermore, the specifics regarding this is accepted as is and does not necessarily affect the remainder of the arguments. The interested reader is directed to a textbook on the subject like Eric Kandel's *Principles of Neural Science* (2012). However, please note that it will only be the cohesive topology of connections from motor neurons onto muscles that is accepted without further ado.

Remaining to be explained are the connectivity between primary sensory afferents and motor neurons sharing the same homonymous muscle, the connectivity between primary sensory afferents and interneurons and motor neurons, and the apparent somatotopy within these connections.

An experience based explanation for the connectivity between primary sensory afferents and motor neurons sharing the same homonymous muscle has been proposed in paper IV (cf. *Self-organization of spinal sensorimotor circuitry*). Thus, suggesting the principle of self-organization (Granmo, Petersson, and Schouenborg 2008) which is also the hypothesis to be the explanation to the remaining parts to be explained. If that hypothesis would find support it would imply that the somatotopy seen in the spinal cord is a remnant from the developmental staging of motor neuronal connectivity and that further functional somatotopy is seeded by this. Indeed, no further rule might be necessary for the observed basic somatotopic connectivity patterns to emerge. This kind of arguments where maps emerge through haphazard wiring on a substrate that exhibit a disjoint organizational principle has previously been made for the visual cortex (Ringach 2004), hence implying a formative connectivity from peripheral sensor structure unto more central networks.

Extrapolation of this theory would in principle say that a functional somatotopy based on a cohesive topology of motor neuronal connectivity unto muscles could emerge in later stages of a network without any locally intrinsic demand. An additional consequence of this is that as some movement patterns of some clusters of muscles are more important than others (e.g. the hand for a primate) the correlated

activity in the network will share this higher degree of importance but still not represent the evolutionary value as an intrinsic and local phenomena. In simpler words: the “hub” neurons controlling the hand **are** not important, they **become** important.

Turning the above argument on its head, one can see the biomechanic plant (i.e. the body) as imposing imperative restrictions upon the nervous circuitry which might be seen as **enabling** restrictions. The biomechanic plant is thus formative for somatotopic patterns which is further enabled by the growth rules during development (proximal muscles controlled by medial pools and distal muscles controlled by more lateral pools and so on). Thus, the interaction between the initial developmental growth rules together with the formative biomechanic restrictions upon activity dependent learning forms a natural basis for somatotopic maps in the spinal cord.

Finally, a small digression is needed on the topic of maps. As it happens, maps exists in a philosophical dilemma. A map is without meaning if there is no one there to read it. A map in itself does not contain more information by virtue of being a map. For two neurons that are close to each other as defined by a map the existence of the map does not affect their actual relationship. Hence, finding and drawing maps does not validate the existence of the map. The question that has to be asked is “do the creation of maps contribute to the understanding of the function of the nervous system?”, and the suggested answer to this is in most cases: no.

Internal models and dynamic maintenance

A general assumption is that the neocortex maintain internal models regarding the progression of internal and external states (Berkes et al. 2011; Kawato, Hayakawa, and Inui 1993). Apart from the experimental evidence this can also be argued on theoretical grounds based on the previous considerations. Beginning with the sensorimotor loop that is present in the spine.

As shown in paper IV, the action-feedback-relationship between the activity from motor neurons and the subsequent sensory feedback is enough to shape the synaptic weights to a natural connection scheme. Still left to show is if the sensory feedback projected into the interneurons who in turn perturb the activity of the motor neurons is enough to shape the connectivity of the interneurons. However, entertaining the thought that this will be possible a descriptive analysis is then expected. The relationships that are expected to be formative for the interneuronal synapses are the correlation between their output and the subsequent sensory feedback. The feedback depends on the dynamics of the musculoskeletal plant, that in turn is inescapably restricted by the physical laws of the world. Thus, the transformation of muscle

activity into sensory feedback will be determined by the properties of the muscle (length, strength, etc), the physical laws of the world and the properties of the particular sensor. In a mathematical sense one can say that the function that transforms muscle activation into sensor feedback is parametrized by the muscle properties, physical laws and sensor properties. The interneurons then extract, by definition, the invariant signal in the feedback relative to the output thus forming a model of this relationship. This continuous loop with motor neuron activity into the musculoskeletal plant dynamics and returned as sensory feedback will assert that the functional relationship between output and input in the most peripheral layer stays relevant and up to date (Fig. 19). The imperative implication here is that the function emerges and is not predefined.

Climbing upwards in the nervous system (or inwards, depending on your personal taste) from the spinal cord towards the neocortex sensory information is relayed to nucleus cuneatus (or nucleus gracilis if considering sensory information from the lower trunk) where more high-level haptic features are extracted (Jörntell et al. 2014). An interesting point to think about at this point is the differences between the cuneate and spinal networks. As described above, the neurons in the spinal network has a continuous potential control over the externally generated synaptic feedback, i.e. the output from a neuron in the spinal network can potentially control the external state such that it shapes the synaptic feedback. This is not true to the same degree for cuneate neurons since they to a higher degree passively receive sensory information, processes this and then transmit the extracted features onwards (Fig. 19). One might suggest that the spinal neurons should be more prone to extract the invariant relationships between input and output, while cuneate neurons should extract invariant features in the input alone.

The integrated information from the nucleus cuneatus is transmitted to the particular subnuclei of the thalamus (exact name depends upon the specific organism). The information is now inside the neocortical network and subject to that particular dynamic. The exact nature of the thalamic contribution in the neocortical network is uncertain and outside the scope of this thesis. It will however provide neocortical neurons in at least layers 4, 5 and 6 with whatever information it generates. Therefore it is reasonable to argue that the integrative process of any neocortical neuron receiving information from the thalamus will be upon that particular information. This might sound like a quite nonsensical thing to propose, but it is not without its merit. Because a more exact clarification of the nature of the input into a neocortical neuron is hard to make and the functional maps seem to be less than helpful in this matter (Enander et al. 2019). The implication however from the suggestion is that the neocortex operates on whatever information it receives from the thalamus and that the incoming information is of an abstract type (Jörntell et al. 2014). Hence, the models generated by any neocortical neuron ought to depend on primary abstract dimensions and not primarily represent concrete things (suggested

and argued for on a theoretical basis by Friedrich August von Hayek (Koestler and Smythies 1972, 309). These primarily abstract dimensions furthermore would initially be crude but with experience and training increase in resolution and utility (Gerald E. Loeb 1983; Spanne 2015). For example, the abstract ‘redness’ of a rose is initially captured by cones in the retina and the ‘sharpness’ of its thorns is captured by deformation fields of the skin but are not integrated to form the concrete representation of a rose until later when several abstract notions converge in the suggested abstract space of the neocortex. This concrete notion that depend upon all these abstract dimensions will probably be richer to an expert botanist than to a naïve amateur because the abstract dimensions of the botanist is of higher resolution due to experience and not because he or she is in possession of better eyes and skin.

Hence, any control that the neocortex subsequently exerts on the spinal cord is by consequence based on, for example and in part, abstract haptic features and their relation to at least the physical laws of the world. Furthermore, due to the inherent delay in any transient command that the neocortex projects unto the spinal network and the consequential feedback the only option for the neocortex if it should be useful is to predict the *future* consequential feedback from its command. Necessarily, the nature of this feedback changes with the context, but with some imperative invariance. This implies that the models maintained by the neocortical neurons with regards to motor control ought to be the relationship between the internal particular abstract features and the expected feedback of the consequences as filtered through the spinal network, the musculoskeletal plant and physical laws of the world, and subcortical nuclei such as nucleus cuneatus (Fig. 19).

Hence, any attempt to define a function of, for example, the neocortex the researcher has to accept that the responses themselves will not inform him of any inherent underlying abstract dimension. Thus, prior to the studies a hypothesis should be defined based on formal analysis of the world (cf. *The complex relationship between the world and the brain*) which then acts as the generator of interpretations of the abstract dimensions of the neocortex. The location for finding a possible correlation to this hypothesised dimension however cannot be defined *a priori*. Furthermore, the probability of finding a specific localized neocortical circuit for an externally concrete thing, as contrasted to a distributed representation based on several abstract dimensions, is highly improbable. This finally implies a true understanding of the neocortex is improbable until there is a true understanding of the subcortical structures.

Thus, if the maintained neocortical models emerge from the interaction between the environment, the musculoskeletal plant and the nervous system, then that would ensure that the models would be able to handle changes to either. Gradual changes would be adapted to (e.g. climate change (environmental), evolutionary changes or

changes due to age (musculoskeletal), hormonal changes due to puberty and the like (nervous system)), while sudden changes would decrease the performance of the organism (e.g. cataclysmic events, traumatic orthopedic injuries or nervous infarctions), but maybe only temporary until the system had time to readjust. However, an hard-wired system with imperative connections in any of these dependencies would cease functioning as soon as anything changed.

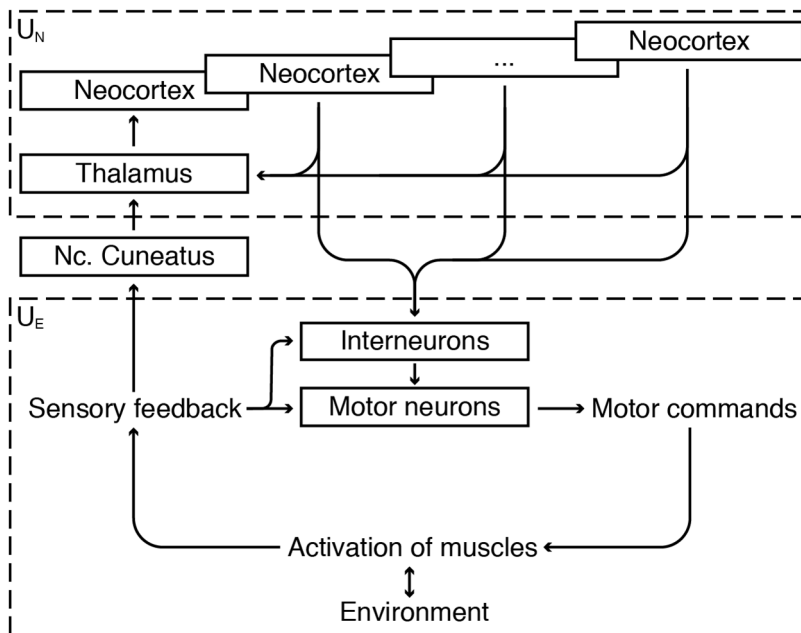


Figure 19. A simplified illustration of the nervous system relative tactile processing.

Conclusions

The generally accepted theory of functional localization intended to explain the functional organization of the nervous system has been examined in this thesis. It has been contrasted with the holistic theory and the experiments and simulations performed in the included papers have been aimed towards illuminating potential cruxes when differentiating the two theories.

The support for a higher degree of interconnectedness in the nervous system has been accumulating in recent years (Winnubst et al. 2019; Gerfen, Economo, and Chandrashekar 2016) and a theoretical foundation in mathematics has risen to explain and explore the characteristics of these vast networks (Watts and Strogatz 1998; Bullmore and Sporns 2009; Bassett and Bullmore 2006). Increasingly, the *modus operandi* of the nervous system seems to be one of emergent functions dependent upon the whole network, rather than a conglomerate of discrete functional centers as dictated by the maps of functional localization. This is further established by papers I-III where each one illuminates a particular aspect of this proposed holistic integrative process.

Paper I finds a non-binary and integrative processing of tactile inputs from different digits. Paper II extends this finding by showing that tactile features can be found in the activity of cells in any of the studied cortical areas. Paper III establish the active relationship between these processes by showing that there exists a co-operative dependence between geographically remote brain areas. Paper IV suggests that the organizational principle that shapes these co-operative and unitary networks can be self-organization rather than preprogrammed, which is argued in this thesis to be a necessity. However, paper IV is particularly concerned with the spinal circuitry and the validity of the organizational principle for the rest of the nervous system, e.g. neocortex, thus remains to be shown.

A holistic functional brain organization must thus be seen as plausible and with it follows consequences for how information processing can occur in the network of the nervous system and also how a functional decomposition might be possible, or impossible, to perform. One such consequence is that the neocortex should be seen as an indivisible unit of a dynamic system.

A holistic view on brain organization might also be suggested to be superior to functional localization on the basis of the philosophical principle known as Occam's

razor. A common misinterpretation of Occam's razor is that a simpler explanation is preferable to a more complex one. This is, however, not the meaning of the principle that is Occam's razor. Occam wrote in latin "*pluralitas non est ponenda sine necessitate*", which translates to "*plurality should not be posited without necessity*" (Duignan 2018). Thus, Occam's razor states that a theory is less preferable if it depends upon auxiliary theories compared to one that does not. This does not, however, indicate anything on the nature how hard the theories are to understand for the particular human. The holistic view on brain organization needs hardly any auxiliary theories in order to provide an explanation for many observed phenomena, while functional localization seems to need a new one for every new synaptic fork in the road.

Populärvetenskaplig sammanfattning

Hjärnan och nervsystemet är källan till vårt medvetande och vår kontroll över våra kroppar. Trots att vi vetat detta i över 2000 år har vi fortfarande inte en förklaring till hur det går till. Exempelvis vet vi inte exakt hur ryggmärgen kontrollerar våra armar och ben. En orsak till detta är att nervsystemet är otroligt komplext, bestående av cirka 89 miljarder nervceller som kopplas ihop till varandra med hundratals biljoner kontakter till ett enormt nätverk.

Genom historien har många försökt förstå nervsystemets komplexitet genom att förenkla och reducera det till färre och mer hanterliga delar. Ett illustrativt exempel är skapandet av kartor över nervsystemet. Dessa kartor har innehållit etiketter till avgränsade områden som har beskrivit funktionen som just de nervcellerna inom det avgränsade området ansetts inneha. Avgränsningen har gjorts antingen på anatomisk grund, att man tyckt sig se en strukturell skillnad mellan ett område med celler jämfört med ett annat närliggande område; eller på funktionell grund.

Just att avgöra funktionen hos en samling nervceller har krävt stora vetenskapliga insatser och många olika tekniker. Generellt kan man dock säga att det finns två typer av experiment som genomförts med målet att avgöra funktionen hos specifika nervceller.

Den ena typen av experiment innebär att man aktiverar nervcellerna man ämnar att studera med hjälp av en, till exempel, svag elektrisk ström. Den elektriska strömmen påverkar nervcellerna så att de skickar iväg så kallade aktionspotentialer som är kemoelektriska impulser med vilka nervcellerna kommunicerar med varandra. Detta sker genom att aktionspotentialen aktiverar kontakterna som den aktuella nervcellen har med andra nervceller och på så vis skickas aktivitet vidare i nervsystemet. Om man observerar en repeterbar effekt av aktiveringen av nervcellerna man studerar, som exempelvis att ena armen rör på sig, anser man att man har funnit funktionen för de studerade nervcellerna, d.v.s. att röra armen.

Den andra typen av experiment är liknande, men istället för att aktivera nervcellerna så tystar man dem. Detta uppnås oftast genom att skada cellerna så de inte kan fungera normalt. Om skadan genererar ett bortfall av en observerbar effekt, så som att armen nu blir slapp, anser man ånyo att man funnit funktionen för nervcellerna (att röra på armen). Dessa två metoder har med fördel använts i kombination.

Med hjälp av bland annat dessa två typer av experiment har alltså kartor skapats över nervsystemets olika delar där ingående beskrivningar har föreslagits för olika indelningar av nervcellerna. Den övergripande teorin bakom detta kallas för funktionell lokalisation och går ut på att observerade funktioner är lokaliserade till specifika lokalt samlade nervceller, det vill säga nervcellssamlingar eller områden.

Det föreligger dock en alternativ teori om hur nervsystemet är funktionellt organiserat. Det är *den holistiska teorin*. Den holistiska teorin anser att man inte förbehållslöst kan avgöra funktionen hos nervceller enligt paradigmet beskrivet ovan. Teorin utvecklades historiskt sett parallellt med funktionell lokalisation och fram till 1900-talets början förekom det en debatt om vilken av de två teorierna som egentligen stämde. Frekvent framförda argument av anhängarna till den holistiska synen var att många inte helt ovanligt förekommande neurologiska fenomen inte kunde förklaras på ett tillfredsställande sätt med hjälp av teorin funktionell lokalisation. Ett exempel var svårigheten att förutspå vilka symptom som en stroke borde ge upphov till. Om de kartor som ritats av anhängarna till teorin om funktionell lokalisation var korrekta borde effekterna av en skada som uppstår i nervsystemet med lätthet kunna förutspås, något som visade sig vara svårt att bevisa.

Den holistiska synen på nervsystemets funktionella organisation utgick ifrån faktumet om nervcellernas mycket komplexa sammankoppling. Man menade att detta faktum i princip omöjliggjorde en strikt uppdelning av nervceller på ett sådant lokalt plan som var en förutsättning för att kunna rita de kartor som den funktionella lokalisationen utgick ifrån. Vidare framlades bevis i form av observationer att funktioner som föll bort vid skada av storhjärnan kunde återkomma efter en tid. Detta menade man talade emot inneboende funktion hos specifika lokala nervcellssamlingar.

Debatten om vilken av teorierna som egentligen stämde rann ut i sanden under början av 1900-talet när förespråkarna av den holistiska teorin inte kunde frambringa en sammanhållen elegant teori med tillhörande gripande resultat. Förespråkarna av funktionell lokalisation däremot uppvisade allt mer detaljerade kartor vilka blev populära inom neurovetenskapen. Således är teorin om funktionell lokalisation den teori som lärts ut både när man läser biologi i grundskolan och likaledes när man läser neurofysiologi vid läkarprogrammet. Funktionell lokalisation är alltså den allmänt förhärskande teorin om hur nervsystemet är funktionellt organiserat.

Sedan slutet av 1990-talet har det dock framkommit teoretiska underlag som givit nytt liv till den holistiska teorin. Underlagen kom främst från matematiken och dess teoretiska analys av nätverk och beskrivningen av det som kallas för dynamiska system. Upptäckterna beskrev hur nätverk av noder med i sig själv enkla funktioner kunde samverka och ur samverkan mellan tillräckligt många noder kunde nya

komplexa funktioner uppstå. Vidare visades det att enstaka genvägar i ett nätverk var tillräckligt för att föra samtliga noder närmare varandra.

Mot bakgrund av dessa nya teorier har denna avhandling sin början. Första delarbetet handlar om de kartor som ligger till grund för teorin om funktionell lokalisation. Vi utforskade de områden i råttans storhjärna som enligt vedertagna kartor skall vara specifika för bearbetande av beröringsinformation från andra respektive femte fingret. Detta utfördes genom att stimulera huden på fyra förutbestämda platser på andra respektive femte fingret med svaga elektriska strömmar. Först stimulerade vi med enstaka pulser samtidigt som vi långsamt förflyttade en registreringselektrod genom råttans storhjärna och hittade på så vis nervceller som aktiverades mer av stimulering vars ursprung var från andra respektive femte fingret. Sedan stimulerade vi de fyra förutbestämda platserna på fingret med mönster som ändrades både över tid och rum på ett strukturerat vis. Dessa mönster hade skapats tidigare med hjälp av ett artificiellt finger som berört fyra olika geometriska former. Aktiveringsmönstren kunde erhållas från fingret för att det var utrustat med syntetisk hud och beröringsensorer från vilka artificiella aktionspotentialer skapades när fingret berörde något. Slutligen beräknade vi hur bra varje enskild nervcell var på att avgöra vilken av de geometriska formerna som det artificiella fingret hade berört, och på så vis kunde vi fastslå cellens *avkodningsförmåga*.

Det visade sig att nervceller i råttans storhjärna som aktiverades av enstaka pulser med ursprung i ett av fingrarna lika gärna kunde besitta en högre avkodningsförmåga för aktiveringsmönster som applicerades mot andra fingret. Resultaten från det första delarbetet pekar alltså mot att tillgängligheten av beröringsinformation är större än vad som är beskrivet av de funktionella kartorna. Dessa kartor skapades oftast med hjälp av enkla stimuli, vilket sannolikt underskattar den möjliga utbredningen av information samt nervcellernas förmåga till högre analys i form av avkodningsförmåga.

Det andra delarbetet utvecklade detta resultat ytterligare. Även i detta arbete användes de sammansatta aktiveringsmönstren, dock endast mot det andra fingret. En skillnad var dock att nu utfördes jakten på nervceller som svarade på aktiveringen över hela storhjärnan (bortsett från hjärnans undersida vilken vilar mot skallbasen och är komplicerad att komma åt för studium). Överraskande nog hittades nervceller som uppvisade en god avkodningsförmåga över hela det genomsökta området. Det visade sig också att nervcellerna hade unika svar på de olika aktiveringsmönstren. Dessa unika svar kunde kombineras på sådant vis att avkodningen blev ännu högre. Vi kunde alltså med ännu högre säkerhet säga vilken geometrisk form som det artificiella fingret hade berört om vi använde aktivitet från flera nervceller samtidigt. Resultaten från det andra delarbetet följde således fynden från det första och gav ytterligare stöd till teorin att utbredningen av förmåga till

högre analys av beröring inte följer de kartor som framläggs av teorin om funktionell lokalisation.

Det första och andra delarbetet pekar alltså mot att beröringsinformation finns tillgängligt över större delen av storchjärnan hos en råtta. Det har inte framkommit några motbevis till varför detta inte skulle stämma för hela storchjärnan. Om det föreligger ett beroendeförhållande mellan dessa olika delar med avseende på hantering av information kan dock inte avgöras utifrån dessa resultat. Därför utfördes det tredje delarbetet för att försöka sprida ljus över detta.

Det tredje delarbetet liknade även det de två föregående. Aktiveringsmönster applicerades mot en rattas andra finger och aktiveringen registrerades från nervceller i det område som anses hantera sådan enligt funktionell lokalisation, ofta benämnt det primära känselområdet. Förändringen i detta arbete var att efter en tid anlades en blodpropp i en avlägsen del av hjärnan på rattan. Sedan undersöktes det hur avkodningsförmågan hos nervceller i primära känselområdet var före och efter anläggningen av blodproppen. Vi kunde påvisa att avkodningsförmågan generellt sett gick ner efter en blodpropp i ett avlägset område.

Således har vi påvisat att förmågan till högre analys sprider sig över hela hjärnan, men också att den högre analysen är beroende av nätverket som helhet. Det vill säga att de "slutsatser" som uppkommer i det primära känselområdet inte enbart beror på aktivitet i just det området, utan på den simultana hanteringen av beröringsinformation i resten av nätverket. Det är osannolikt att detta endast gäller beröringsinformation. Studier av andra forskare har visat, ofta som bifynd, att andra modaliteter såsom hörsel, syn och rörelse kan förekomma utanför sitt primära område. Hanteringen av dessa andra modaliteter har alltså också förutsättningarna för att bero av nätverket som helhet, i likhet med beröringsinformation.

Fynden från samtliga av de tre första delarbetena ligger alltså i linje med en holistisk syn på funktionell organisation i nervsystemet, snarare än den förhärskande uppfattningen om funktionell lokalisation. Acceptans av den holistiska synen skulle påverka neurovetenskapen i grunden då många stora vetenskapliga projekt har sin startpunkt i just den funktionella organisationen av nervsystemet, vilket styr både var man letar efter resultat men också hur man tolkar de resultat man finner.

Det fjärde delarbetet i denna avhandling är av en annan typ än de tre första, men har sitt ursprung i samma diskussion. En holistisk syn på nervsystemet förutsätter nämligen att de dynamiska tillstånd som hanterar olika upplevelser uppkommer ur interaktionen med omvärlden. Nervsystemet måste alltså kunna organisera sig själv, automatiskt, i relation till sin omvärld. Detta är i viss kontrast till funktionell lokalisation där man ofta sökt förklaringar till den observerade organisationen inom genetiken, det vill säga att man har tänkt sig att hjärnans organisation är förprogrammerad.

Det fjärde delarbetet utforskar således om ett "tomt" nervsystem kan självorganisera sig. Det genomfördes genom att en simulerad organism, kallad en Oropod, med ett artificiellt nervsystem fick interagera med sin omvärld slumpmässigt. Sättet som nervcellerna i det artificiella nervsystemet lärde sig nya saker efterliknade den biologiska motsvarigheten. Det visade sig att det artificiella nervsystemet kunde självorganisera sig på ett sådant vis att det liknade nätverkskonfigurationer som ses i biologiska organismer. Nervsystemet i Oropoden var dock endast den enklaste formen av en ryggmärg. Resultaten från det fjärde delarbetet pekar dock mot att självorganisation av nervsystemet är en rimlig hypotes som bör fortsätta utforskas.

Således täcker samtliga fyra delarbeten i denna avhandling in varsin aspekt som stödjer en holistisk syn på nervsystemet. Den holistiska synen på nervsystemet är fundamentalt skild från den förhärskande synen på nervsystemets funktionella organisation. Acceptans av den holistiska teorin för nervsystemets funktionella organisation skulle ha genomträngande effekt inom samtliga nivåer av neurovetenskapen, ända från förståelse av grundläggande processer till hantering av stroke på sjukhuset.

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I met a traveller from an antique land
Who said: Two vast and trunkless legs of stone
Stand in the desert. Near them, on the sand,
Half sunk, a shattered visage lies, whose frown,
And wrinkled lip, and sneer of cold command,
Tell that its sculptor well those passions read
Which yet survive, stamped on these lifeless things,
The hand that mocked them and the heart that fed:
And on the pedestal these words appear:
'My name is Ozymandias, king of kings:
Look on my works, ye Mighty, and despair!'
Nothing beside remains. Round the decay
Of that colossal wreck, boundless and bare
The lone and level sands stretch far away

— Ozymandias by Percy B. Shelley
from *Miscellaneous and Posthumous Poems of Percy Bysshe Shelley*
page 100 (1826)

Information Processing in the Nervous System



Jonas Enander graduated from Lund University and the medical programme in 2015 and received his Swedish licence 2017. In parallel to the studies of medicine he began his PhD studies 2015 in the lab Neural Basis of Sensorimotor Control. There he investigated the information processing in the nervous system with experiments using simulated touch and virtual simulations of developmental stages of the nervous system. The result from those studies forms the basis for this thesis.

Within this thesis a discussion is held comparing two opposing theories of brain organization. On one hand the accepted theory of functional localization and on the other a holistic theory viewing the nervous system as a unitary system. The holistic theory is not a new idea, but this thesis tries to modernize it and argue why it is superior to the accepted dogma.

“In one sense, no organ of the body, however simple in its organisation, is single. The eye, that delicately constructed and admirable adapted organ of the reception of the rays of light, is not single as regards to various parts which to constitute its unity and individuality of function. Nor is the stomach single, only in the oneness of the purpose for which its parts were constructed.”

- J.P. Harrison, 1825, The Philadelphia journal of the medical and physical sciences. volume 11, page 237