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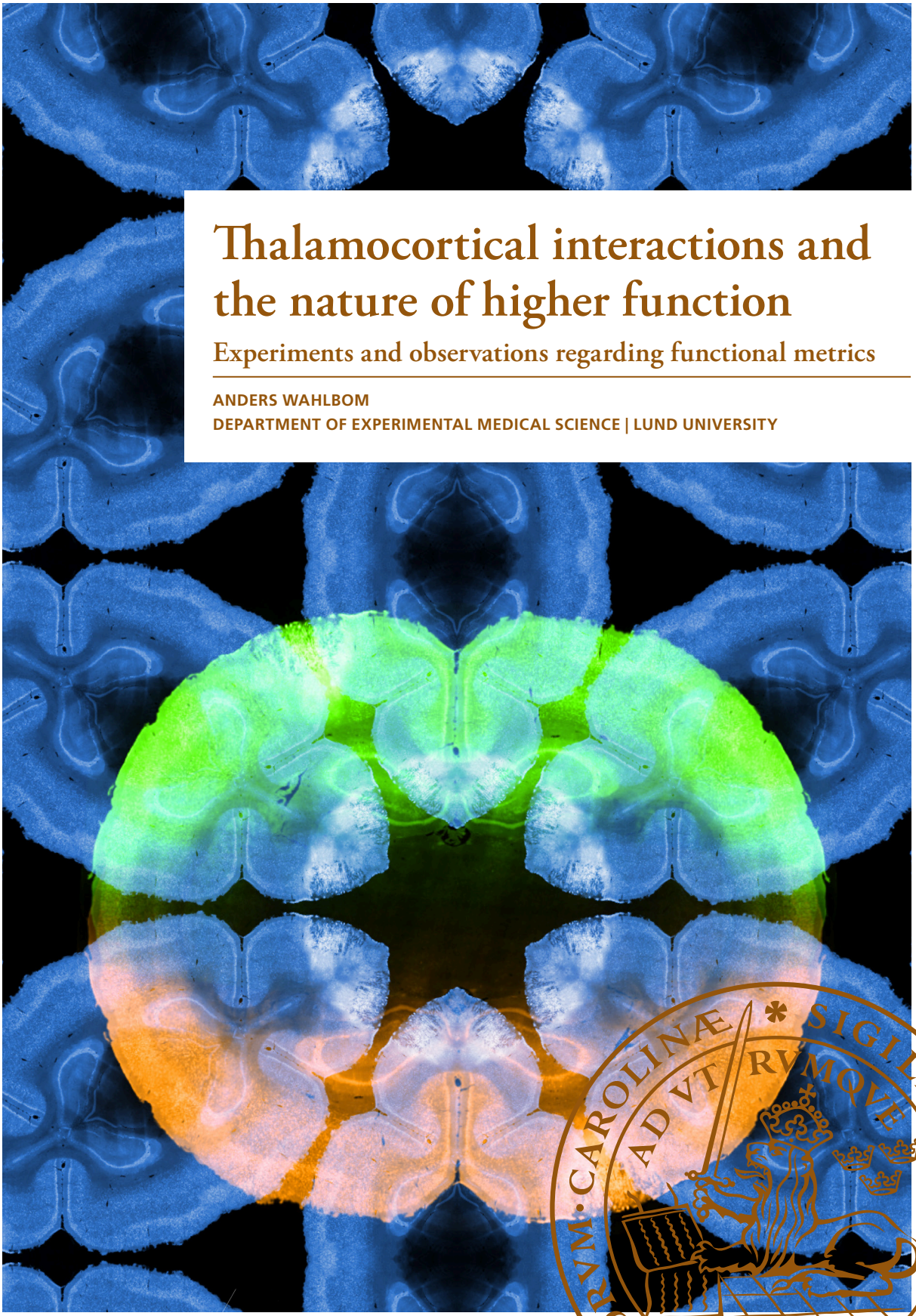

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Experiments and observations regarding functional metrics

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UNIVERSITY

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Thalamocortical interactions and the nature of higher function: Experiments and observations regarding functional metrics

Abstract

Thoughts about the operations of the mind have been occupying great thinkers over thousands of years and the past few centuries have been marked by discussion regarding two opposing ideas of functional principles for the brain. The most prominent theory is the one of functional localization, which states that certain areas of the brain are dedicated to specific functions. The opposing idea is that of global information processing, which states that each function is instead distributed over a large network.

This thesis has studied the flow of tactile information and how it is represented in the central nervous system, in order to help elucidate which of the opposing theories is more probable. This was done using animal experiments, where a set of electrotactile stimulation patterns were presented to the second forepaw digit of an anaesthetised rat, and the representation of the tactile information was studied in both the neocortex and the thalamus.

It was found that tactile information was represented in a large part of the thalamus, and in a bilateral manner in the neocortex. The neocortical representations were additionally found to be dependent on other distant cortical areas. An argument is then made that these findings, together with other functional and anatomical findings, support a distributed processing regime in the nervous system as more plausible.

The thesis concludes with a discussion regarding potential limitations and drawbacks of some common neurophysiological methods, and the importance of being aware of these when interpreting research data. An argument is made that these limitations might be one of the key reasons that a consensus about how the brain works has not yet been reached.

Key words

Somatosensory, Tactile, Distributed information processing, Neocortex, Thalamus, Function

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"The greatest enemy of knowledge is not ignorance; it is the illusion of knowledge."

- Stephen Hawking

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Preface

The purpose of this thesis is to discuss different functional principles of how the nervous system might processes tactile information. The thesis consists of four major parts.

The first part gives the reader an introduction to the tactile sensory system, both from the commonly accepted viewpoint of functional localisation while at the same time presenting findings supporting other functional principles. This is followed by a short presentation of common experimental and analytical tools employed by neuroscientists.

The second major part of the thesis is a general description of the methods used by the author in his research. The third part is a summary of the results of the research papers included in the thesis. The interested reader is referred to the four papers included in the thesis for a more in-depth description of the results and methods.

The fourth and final major part is a discussion about the presented results and how they might contribute to the discussion about different functional principles of information processing. This is followed by a general discussion about how the choice of experimental and analytical methods might influence the results from a study, and the conclusions drawn from them.

List of original papers

I. Clara Genna, Calogero M. Oddo, Alberto Mazzoni, **Anders Wahlbom**, Silvestro Micera and Henrik Jörntell. Bilateral Tactile Input Patterns Decoded at Comparable Levels But Different Time Scales in Neocortical Neurons. *The Journal of Neuroscience, 2018, 38 (15) 3669-3679*

II. **Anders Wahlbom***, Jonas M. D. Enander*, Fredrik Bengtsson and Henrik Jörntell. Focal neocortical lesions impair distant neuronal information processing. *The Journal of Physiology, 2019, 597 (16) 4357-4371*

III. **Anders Wahlbom**, Jonas M.D. Enander and Henrik Jörntell. Widespread Decoding of Tactile Input Patterns Among Thalamic Neurons. *Frontiers in Systems Neuroscience, 2021, 15:640085*

IV. **Anders Wahlbom**, Hannes Mogensen and Henrik Jörntell. Widely different correlation patterns between pairs of adjacent thalamic neurons *in vivo*. *Manuscript*

*Shared first authorship based on equal contributions

Important abbreviations

CNS	Central nervous system
PNS	Peripheral nervous system
VPL	Ventral posterolateral nucleus
VPM	Ventral posteromedial nucleus
SI	Primary somatosensory cortex
MRI	Magnetic resonance imaging
fMRI	Functional MRI
EEG	Electroencephalogram
ECoG	Electrocorticogram
AP	Action potential
LFP	Local field potential
ISI	Interspike interval
PSTH	Peristimulus time histogram
PSpTH	Peri-spike triggered time histogram
KDE	Kernel density estimation
SpT-KDE	Peri-spike triggered KDE
PCA	Principal component analysis
kNN	k-nearest neighbours
CL	Contralateral
IL	Ipsilateral

Abstract

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Introduction

How does the brain work?

The field of neuroscience is centred around the above question, and it has inspired thousands of neuroscientists over hundreds of years, myself included, but has still not been fully answered. The brain is the centre of our consciousness and the basis for our interactions with and understanding of the world that exists both outside and inside our bodies, yet we do not fully understand the brain itself. It is not difficult to imagine why many would find such a paradox alluring.

The nervous system of vertebrates is divided into the central nervous system (CNS) and the peripheral nervous system (PNS), with the CNS consisting primarily of the spinal cord and the brain, and the PNS branching out from the CNS to the rest of the body. Ramón y Cajal introduced the neuron doctrine theory in the 19th century further dividing the nervous system into discrete individual cells, known as neurons. Chemical or electrical signals containing information is transferred between different neurons through synapses connecting them, and several theories exist on exactly how the nervous system interprets these signals as useful information, in order to answer the question of how the brain works.

My thesis is focused on studying the flow of tactile information in the nervous system, in order to unravel some of its underlying principles, and with it I hope to contribute with at least a small part to the answer to this complicated question.

The tactile sensory pathway

The tactile system functions as our interface between the external world and our internal world, functioning both as a passive sensing system and an active explorative system.

The tactile system starts with the mechanoreceptors in the skin where a sensory signal is generated upon contact with the external world. From there the signal is transmitted

by first-order afferent neurons that then enter the spinal cord through its dorsal roots and proceed upwards along the dorsal columns until they reach a nucleus in the brainstem called nucleus cuneatus where they terminate on second-order neurons. These second-order neurons then cross over to the contralateral side and continue upwards to the subcortical structure known as the thalamus where they terminate. Third-order neurons project upwards from the thalamus and finally terminate in the neocortex.

According to the labelled line theory the nature and location of a stimulus is preserved through the entire pathway, meaning that input from the second digit of the left hand is delivered to a specific region of the primary somatosensory cortex, the input from the third digit is delivered to an adjacent region and so on. Each part of the body is then represented as a somatotopic map in the neocortex. Each sensory modality such as touch, vision and hearing is in a similar manner associated with a certain region of the neocortex.

A schematic of the pathway is shown in Fig. 1. We will now proceed with a more detailed, although not all-encompassing, description of each step of the pathway, starting at the skin of a fingertip.

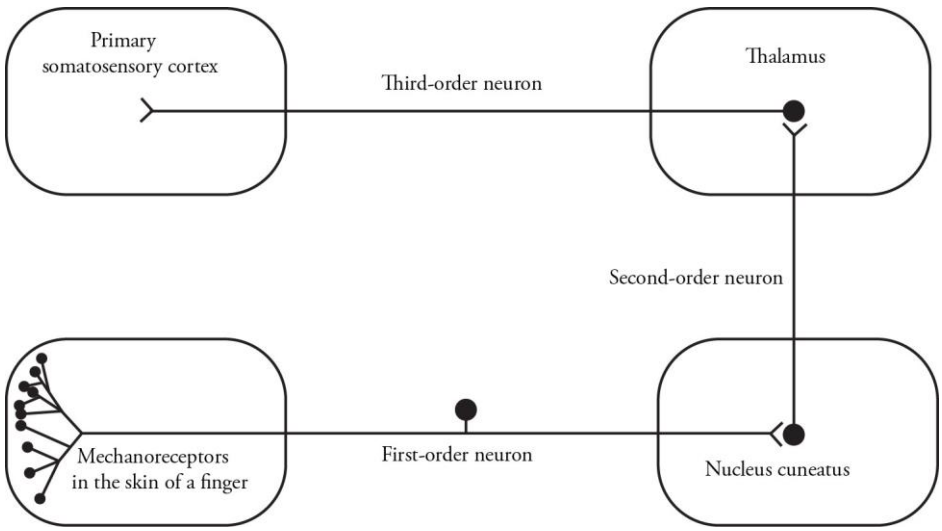

Figure 1. Schematic of the tactile sensory pathway
The tactile sensory pathway starting at the mechanoreceptor in the skin of a finger, followed by projections to the cuneate nucleus, the thalamus and the prmary somatosensory cortex. Filled circles indicate neuron cell bodies and open triangles indicate synapses.

Tactile sensors

The mechanoreceptors that respond to tactile stimuli are located in the skin and are present in astounding numbers. The density of receptors depend on their type and what part of the skin is studied, with denser receptor populations present in the skin of a fingertip compared to the skin on one's back. There are generally considered to exist four different types of mechanoreceptors, each with different sensing properties, and they cooperate in order to create an accurate representation of the skin-object interaction. These four types fall into two groups of two, with one group considered to be slow adapting and the other group fast adapting. Each mechanoreceptor has a receptive field, which is the skin area in which a stimulus can generate an action potential in the sensory neuron.

The slow adapting mechanoreceptors, meaning that they continue to respond to a long-lasting stimulus, are the Merkel cells with small receptive fields and said to respond to indention such as edges and points, and the Ruffini endings with large receptive fields and said to respond to stretching of the skin (Knibestol & Vallbo, 1970; Johansson & Flanagan, 2009; Abraira & Ginty, 2013). The fast-adapting mechanoreceptors, that is they respond to the onset of a stimulus, are called the Meissner corpuscles which respond to skin movement and have small receptive fields, and the Pacinian corpuscle with large receptive fields that respond to vibrations (Johansson & Flanagan, 2009; Abraira & Ginty, 2013). These four are used in combination to transmit information in a spatio-temporal fashion about the nature and location of the tactile stimulus.

At first glance this might seem like a straight forward coding system for tactile information however, Hayward (2011) suggests that the response of each receptor type is more complex than that, and that the response from each individual sensor is dependent on its biomechanical context. The specificity of the different mechanoreceptors have also been questioned, as their responses have been shown to overlap extensively under certain conditions (Johansson *et al.*, 1982). It has also been shown that seemingly simple skin-object interactions such as the tapping of a finger activates a large number of mechanoreceptors over a large area, including large portions of the hand and several fingers (Shao *et al.*, 2016, 2020). Findings such as these indicate the existence of highly complex representations of skin-object interactions even in seemingly simple interactions, which is then transferred further along the tactile sensory pathway.

Nucleus cuneatus

The tactile first-order afferent neurons from the upper limbs enter the spinal cord through its dorsal roots and then ascends along the dorsal column until it reaches a nucleus in the brainstem called the cuneate nucleus. In the cuneate nucleus the first-order neurons terminate on second-order neurons, which then cross over to the contralateral side and ascends, projecting to the thalamus, specifically to the ventroposterior lateral nucleus (VPL). The cuneate nucleus is considered by many to simply be a relay nucleus (Villanueva *et al.*, 1998; Zachariah *et al.*, 2001; Johansson & Flanagan, 2009; Purves, 2012; Kandel *et al.*, 2013).

However, Bengtsson *et al.* (2013) indicate that the cuneate nucleus might be more than a passive relay of information. Jones (2000) show that neurons in the cuneate nucleus receives input from hundreds of first-order neurons, and Bengtsson *et al.* (2013) show that these inputs are dominated by a small amount of high synaptic weight inputs, suggesting a learning mechanism that has shaped the output from the cuneate nucleus neurons. This was further expanded upon in Jorntell *et al.* (2014) where it was shown that single neurons in the cuneate nucleus with similar receptive fields were able to differentiate between different types of tactile input. Also, different neurons were indicated to respond to different features of the tactile inputs, suggesting further differentiation of the incoming tactile information.

As mentioned previously the cuneate nucleus is said to project to a region in the thalamus known as VPL however, the specificity of the cuneate projections to the VPL region can also be questioned, as some studies have indicated direct projections to other thalamic nuclei as well (Hand & Van Winkle, 1977; Berkley *et al.*, 1986).

Thalamus

The second-order neurons from the cuneate neurons then reach the thalamus, located at the dorsal part of the diencephalon. The thalamus is commonly divided into three parts, the epithalamus, the subthalamus and the dorsal thalamus. The dorsal is the largest of the three and is usually referred to as “the thalamus” and is also what is meant when “the thalamus” is referred to in this thesis beyond this specific paragraph (Purves, 2012; Sherman & Guillery, 2013).

The thalamus is commonly divided into a large number of distinct nuclei. The nucleus commonly associated with tactile input from the cuneate nucleus is the VPL, which

together with the ventroposterior medial nucleus (VPM) is said to constitute the somatosensory thalamus, located in the ventral nuclear group.

Classically, the thalamus has long been described as a simple relay when it comes to somatosensory information, where second-order neurons terminate on third-order neurons which then project the somatosensory information to the primary somatosensory cortex (SI), where it is then processed (Purves, 2012; Kandel *et al.*, 2013).

However, the thalamus receives not only ascending input from the cuneate nucleus, but also a large amount of descending input from the neocortex in addition to recurrent connections from the thalamus itself (Alitto & Usrey, 2003; Jones, 2012; Sherman & Guillery, 2013). These ascending and recurrent inputs have been shown to modulate the ascending somatosensory information, indicating that the thalamus is not a passive relay structure (Jones, 2002; Alitto & Usrey, 2003; Sherman, 2007, 2016).

The connectivity of the thalamus has also been shown to be more complex than previously thought. Thalamocortical projections mainly terminate in cortical layer IV, but Constantinople and Bruno (2013) showed the existence of thalamocortical projections not only to cortical layer IV but also layers V and VI. It has also been shown that primary sensory nuclei, such as VPL, project to multiple primary sensory cortical areas (Henschke *et al.*, 2015; Bieler *et al.*, 2018). Additionally, it has also been shown that cortical neurons project to thalamic nuclei not usually associated with sending input to that cortical area (Deschenes *et al.*, 1998; Halassa & Sherman, 2019).

Neocortex

The last part of the tactile sensory pathway is the cerebral cortex, more specifically the neocortex which constitutes the majority of the cortex (Purves, 2012; Kandel *et al.*, 2013). Other parts are the paleocortex and archicortex, but these will not be discussed further in this thesis.

The neocortex covers the topmost part of the brain and is separated by a longitudinal fissure into the left and right hemisphere, connected by the corpus callosum. The neocortex is classically further divided into six more or less distinct layers based on the density and types of neurons in combination with their inputs and outputs, with layer I being the most superficial layer and layer VI being the innermost layer (Brodmann, 1909).

How then does the neocortex process the tactile information it has received? Two of the more prominent theories will now be presented.

Hierarchical information processing based on functional localization

The most prominent theory of how information processing in the brain occurs is based on that each region of the neocortex is assigned a specific function, called functional localization.

The theory is old (Broca, 1861) but has continued to gather support into modern days (Penfield & Boldrey, 1937; Felleman & Van Essen, 1991; Maldjian *et al.*, 1999; Desmurget & Sirigu, 2015; Siegle *et al.*, 2021). In short, the theory states that the neocortex can be divided into different areas, each responsible for a specific function, and information is processed in a hierarchical manner, with information from a previous stage being combined into a more complex representation of the incoming information, becoming increasingly abstract as it travels from one region to another. Vernon Mountcastle further contributed to this view with his hypothesis about the cortical column, a small region of the neocortex spanning all six cortical layers where all neurons respond to stimuli originating from the same area and modality(Mountcastle *et al.*, 1955; Mountcastle, 1957).

Tactile information is said to arrive in the neocortex in the SI where each part of the body is represented in a different region. Different areas of SI processes different aspects of the sensory stimuli, such as location and stimulus type. This is later merged into a higher-level representation and then transferred to the secondary somatosensory cortex where the representations are further converged. Taken to its extreme, this theory ends up with the so-called grandmother neuron, with a single neuron representing a specific concept, such as the face of one's grandmother.

Global information processing

The opposite idea to that information processing occurs in specific locations would be that it is instead distributed over a larger area. This idea is known as global information processing, also called distributed or holistic information processing, and has existed in parallel to the theory of functional localization and has in a similar way gathered support over the centuries (Goltz, 1888; Lashley, 1929; Phillips *et al.*, 1984; Bassetti *et al.*, 1993; Connell *et al.*, 2008; Sporns, 2010; Corbetta *et al.*, 2015; Sathian & Crosson, 2015).

Taken to its extreme this theory would mean that every function would be represented in every neuron of the neocortex. This could be interpreted in two ways. It could either mean that we would only be able to represent one thing at a time, which would be very limiting although it would give incredibly rich representations of each thing. Another interpretation is that each unique combination of possible aspects of the external and internal world would be represented as a specific pattern of neural activity across the entire neocortex.

A less extreme version of the theory would be that each function is distributed over large areas but not represented in each neuron, either evenly distributed or with certain hubs, regions that are more important to the function but still being dependent on other regions (van den Heuvel *et al.*, 2012; van den Heuvel & Sporns, 2013).

The neocortex is of course not the end point of the information, as mentioned previously the neocortex sends information back to the thalamus and other subcortical structures. This is thought to modulate ascending information, and possibly spread the information to other parts of the nervous system, other than through corticocortical projections.

At first glance the tactile sensory pathway might seem simple and straightforward, but upon closer inspection each step of the pathway is seemingly more complex than what it appears

Sensory afferent information is often accompanied by efferent motor output, causing the body to move and in turn movement generates additional sensory information. In fact, this is probably the way that the sensorimotor system is tuned to the biomechanical limitations of our bodies already before we are born (Petersson *et al.*, 2003).

The debate on localized information processing versus global information processing has gone on for a very long time and is still very much alive. Although it is highly unlikely to bring an end to the discussion, I would like to make a contribution to it in *Discussion*.

Different ways to study the brain

Many different techniques exist which can be used to study the brain. Most methods are either used to gather structural of functional information. In many cases such techniques are used in combination. Here follows a description of some of the techniques we use as a window to view the brain, in order to understand how it in turn uses our body as a window to perceive and interact with the external world.

Techniques to study the brain's structure

Some common techniques used in clinical settings in order to gain information about the structure of the CNS is computerized tomography (CT) and magnetic resonance imaging (MRI) which are both non-invasive techniques and provide a two- or three-dimensional representation of the brain structure.

In addition to the non-invasive techniques, in research it is also common to use invasive techniques. The studied brain is then usually cut into thin slices, which are studied using various microscopic techniques. It is then common to highlight specific aspects of a neuron using different stains or genetic markers, providing information about things such as the structure of a neuron's cell membrane or the presence of specific proteins. It is also possible to use retrograde or anterograde tracers in order to mark neurons projecting to or away from the region injected with the tracer.

Techniques to study the brain's function

Some non-invasive techniques which are used to study brain function are positron emission tomography (PET), single-photon emission computerized tomography (SPECT and functional MRI (fMRI) which all use metabolic activity as an indirect measure of neural activity. A non-invasive technique which instead directly measure neural activity is electroencephalogram (EEG), closely related to the more indirect magnetoencephalography (MEG), measuring the electrical signals or the magnetic signals produced by the neural electric activity, respectively.

In the clinical setting these techniques are of course paired with a clinical examination.

Invasive techniques are used in order to get a higher spatial and temporal resolution. Common techniques involve different types of microelectrodes, usually used to record either action potentials (AP) from individual neurons or local field potentials (LFP) produced by synchronous activity from many neurons. In patch clamp techniques, glass micropipettes are used to record either extracellular signals such as APs or LFPs, or the intracellular signal of an individual neuron, showing detailed information about changes in the neuron's membrane potential or membrane currents.

Invasive techniques can be used in live animals (*in vivo*) or in extracted tissues, for example brain slices (*in vitro*). The results obtained from experimental studies are often expanded upon using simulations, where models are created in order to test different functional theories.

Stimulation

Most studies of the brain's function include some type of stimulation. Many times the stimulation is used to evoke a physiological response that activates a certain part of the nervous system or a direct stimulation of the nervous system that activates either afferents or particular areas of the brain. The number of available stimulation paradigms is vast, and many research groups create their own methods of stimulation depending on their research questions.

Modality based stimulation techniques evoke a response of a single or multiple modalities, such as touch or vision through the receptors of a particular modality. Such stimulations can be either natural, to actually touch a rubbery surface or view a photograph, or simple that directly activates specific mechanoreceptors or a limited specific set of photoreceptors. The nature of the stimulation can of course also be somewhere in between natural and simple.

An alternative is to stimulate the nervous system directly. One could then directly stimulate the afferent or efferent nerves of the PNS using microelectrodes or stimulate the CNS directly. Examples of direct CNS stimulation is to use microelectrodes to stimulate the cortex or deeper structures electrically, or using light in the case of optogenetics. A non-invasive option is to stimulate the brain using transcranial magnetic stimulation.

Metrics

The purpose of all techniques used to study the brain is to generate a basis of some kind of measurable metric used to describe what is studied, be it the structure of the brain as a whole, the electrophysiological properties of a neuron or how a specific receptor in a neuron's membrane responds to a neurotransmitter. As with stimulation the number of available metrics is vast, possibly due to the complexity of the extracted information, and new metrics are developed continuously. These metrics are then used to draw conclusions about the studied system, compare it with other studies and discuss with other researchers in order to elucidate the mechanisms of the brain.

A few common structural metrics are the volume of a certain brain region, the extent of damage caused by a stroke or traumatic brain injury, or the number of neurons present in or projecting away from a structure, and the target of those projections.

Many common metrics used in electrophysiology are based on the timing of action potentials compared to a stimulus onset. A neuron's firing behaviour can be described

by its interspike intervals (ISIs), either as an average value, as a variation coefficient or an ISI distribution. Spike times can also be used to measure the response latency or response amplitude of the neurons when a stimulus is presented. The metric could be the change in frequency content of an EEG signal or metabolic rate from an fMRI session over time.

Most metrics are then presented as a single number, based on the average value of a population of subjects, and the value of each subject is in turn often an average based on a number of repetitions. Alternatively a collection of metrics from one population can be compared to another population's metrics using the appropriate statistical test.

Some of the metrics used in the studies included in this thesis will be presented in *Methods*.

Stroke

A stroke is defined as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" (Aho *et al.*, 1980). During a stroke the blood flow providing neurons with their metabolic substrates is impaired, causing the neurons to be unable to maintain their ionic gradients at their membrane, which results in apoptotic and necrotic cell death (Murphy & Corbett, 2009). Three different types of strokes exist, classified by the cause of the blood flow disruption. A thrombotic stoke is caused by an obstruction of the blood vessel caused by an atherosclerotic build-up leading to the formation of a thrombus i.e., a blood clot. An embolic stroke is similarly to the thrombotic one caused by the obstruction of a blood vessel, but instead caused by an embolus i.e., an object loose in the blood stream originating from a different part of the body. The last type of stroke is a haemorrhagic stroke, caused by the rupture of a cerebral blood vessel, impairing its blood flow.

This concludes the introduction part of the thesis, where the tactile sensory pathway has been described in some detail, together with a short presentation of techniques used to study the brain in different setting. Now follows a description of some of the methods used in the papers included in the thesis.

Methods

Some of the more important methods used in the four papers included in this thesis are here described in some detail. If the reader desires further details or specific methods not mentioned here, please refer to the papers themselves, included in the appendix.

Experimental methods

Animal research

Adult male Sprague-Dawley rats were used in all papers included in the thesis. All use of experimental animals in all papers of this thesis was reviewed and approved by the Local Animal Ethics Committee of Lund, Sweden, and in all studies the principles of the Three Rs (Replacement, Reduction and Refinement) have been followed.

Anaesthesia

The animal was first sedated using isoflurane (2-3% mixed with air for 30-120s), followed by an intraperitoneal injection of a ketamine and xylazine mixture (40mg/kg of ketamine, 2mg/kg xylazine). Once an adequate level of anaesthesia had been achieved, characterised by an absence of withdrawal reflexes to noxious pinches to the hind paw, the right femoral vein was exposed, and a catheter was inserted. During the remainder of the experiment anaesthesia was maintained through a continuous infusion (approximately 5mg ketamine/hour, ratio ketamine:xylazine, 20:1). The level of anaesthesia was monitored using an electrocorticography (ECoG) signal, once the brain had been exposed, in combination with a continued absence of withdrawal reflexes to noxious pinches to the hind paw. The ECoG signal was characterized by irregular occurrences of sleep spindles, which is a sign of deep sleep (Niedermeyer & Da Silva, 2005).

Surgery

The head of the animal was first fixated using a stereotaxic frame, followed by the removal of the tissues covering the skull. A craniectomy was then performed in order to gain access to the brain surface, the location and extent of the craniectomy varied between the studies depending on whether the goal was to access the somatosensory cortex or the thalamus (Fig. 2A). The ECoG electrode was then placed on the cortical surface and a layer of agarose dissolved in saline was applied to both improve the stability of upcoming recording and provide a measure of protection for the exposed brain.

Inducing a photothrombotic lesion

In paper II photothrombotic lesion was used as a model for a cortical stroke. The bone of the skull was thinned at the chosen location and a fibre optic bundle connected to a light source was placed above the thinned-out region. The light source had a wavelength of 561 nm and a power of 400 mW, and the skull was illuminated as the dye Rose Bengal (1.3 mg/100g body weight) dissolved in saline was injected through the left femoral vein during the first 2 minutes of illumination, total time 20 minutes. This was in line with the protocol used in Shanina *et al.* (2006). Illumination of the dye causes it to activate and produce singlet oxygen which damages the endothelial cell membranes of the illuminated blood vessels, causing platelet aggregation and thrombus formation (Murphy & Corbett, 2009).

Electrotactile stimulation

Four (paper II, III and IV) or eight (paper I) pairs of intracutaneous needle electrodes (stainless steel insects pins, size 000, etched tips) were inserted into the skin of the volar side of the second forepaw digit of the contralateral paw (paper II, III and IV) or the contralateral and ipsilateral paw (paper I) with respect to the recording site, with an inter-needle distance of 2-3 mm (Fig 2B). The stimulation electrodes delivered pulses of 0.5 mA lasting 0.14 ms. The pulses were delivered in eight different predefined spatiotemporal patterns (named F5, S5, F10, S10, F20, S20, F∞ and S∞) in a pseudo-random order with up to 100 repetitions of each pattern. In addition to this single pulse simulation was delivered through the individual stimulation electrode pairs in sets of five pulses delivered at 3 Hz.

The patterns had a variable duration, but all lasted less than 350 ms, and the onset of each repetition was separated by 1.8 s. The eight patterns were designed to elicit a sensation of touching four different physical probes, representing either fast or slow

adapting skin receptors, thus eight patterns. The four probes and eight patterns are illustrated in Fig. 2C, for further details about these stimulation patterns, please see Oddo *et al.* (2017).

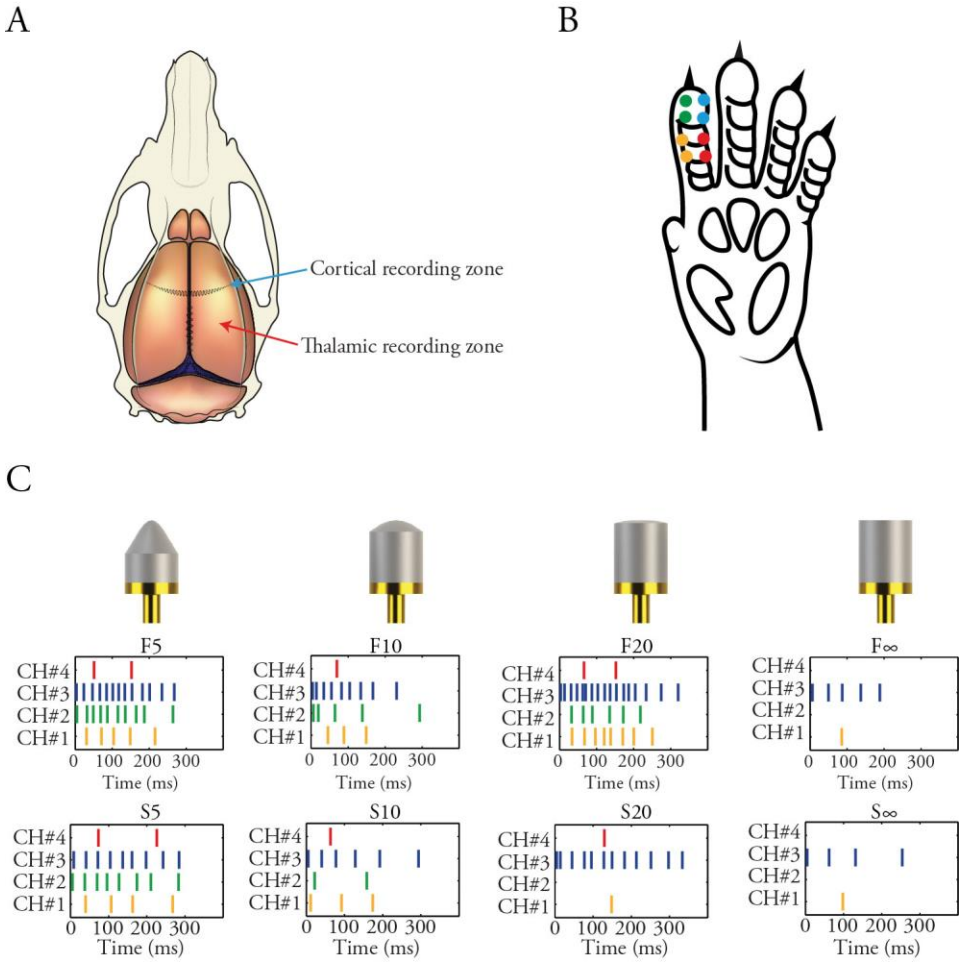

Figure 2. Experimental setup for recording and stimulation
A) Schematic showing the recording areas in primary somatosensory cortex and thalamus from a dorsal view. B) Schematic of the left rat forepaw with the placement of the four pairs of stimulation electrodes indicated, pairs shown in different colours. C) Top. The four different probes used o create the stimulation patterns. Bottom. The eight electrotactile stimulation patterns used, with stimulation in each channel colour coded as in B).

Recordings

Patch clamp

One (paper III and IV) or two (paper I and II) patch clamp electrodes were used to record individual neurons extracellularly in the loose-patch current clamp mode, using the EPC 800 Patch Clamp Amplifier (HEKA, Lambrecht, Germany). Patch clamp pipettes were pulled from borosilicate glass to 6-15 MΩ using a Sutter Instruments P-97 horizontal puller (Novato, CA, USA), and filled with an electrolyte solution. The composition of the electrolyte solution was (in mM) potassium-gluconate (135), HEPES (10), KCl (6), Mg-ATP (2) and EGTA (10). The solution was then titrated using 1 M KOH to 7.35-7.40 pH.

The patch electrodes were slowly (approximately 0.2-1 μm/s) advanced in a perpendicular direction to the brain surface using an electrical stepping motor and the electrode depth was recorded. During electrode advancement the cortical surface was monitored for any signs of deterioration, such as bleeding or oedema, using a microscope.

All data was digitized at 100 KHz using CED 1401 mk2 Spike2 software (Cambridge Electronic Design, CED, Cambridge, UK)

ECoG

The ECoG signal was recorded using a ball electrode placed on the cortical surface, in close proximity to the patch electrode.

Histology

In paper II, III and IV a histological analysis was made. The animals were in these cases, while under general anaesthesia, transcardially perfused using 100 ml phosphate buffered saline (PBS), followed by 75 ml 4% paraformaldehyde (PFA) solution. The brain was extracted and then post-fixed in 4% PFA for 48-72 h and then stored in PBS. Before sectioning the brain was placed in 25% sucrose in PBS solution for 48 h. The brain was then sectioned using a cryostat-microtome.

In paper II the sections were stained using a primary antibody against the neuron-specific nuclear protein NeuN followed by a secondary antibody conjugated with Alexa Fluor 488. The staining was studied using a confocal microscope in order to determine the location and extent of the induced photothrombotic lesion.

In paper III and IV Neurobiotin Tracer (Vector Laboratories, Oxfordshire, UK) was in some experiments added to the electrolyte solution used in the patch pipette

electrodes, in order to stain the recorded neurons and the electrode tract. The brain sections were stained using Streptavidin (Molecular Probes Inc) conjugated to Alexa Fluor 488. This was used to determine the location of the recorded neuron.

Analytical methods

Spike detection

The recorded signal was imported from Spike2 to MATLAB (The MathWorks Inc, MA, USA) and low pass filtered using a moving average over 50 μs. Neural spikes, i.e. action potentials, were identified using in house software utilizing tailored template matching routines with manually constructed templates. The performance of the spike identification templates was verified through visual inspection of the identified spikes, throughout the recordings. A raw trace sample with identified spikes can be seen in Fig. 3A, and a sample response to a specific pattern is shown as a peristimulus time histogram (PSTH) with an overlaid kernel density estimation (KDE) in Fig. 3B.

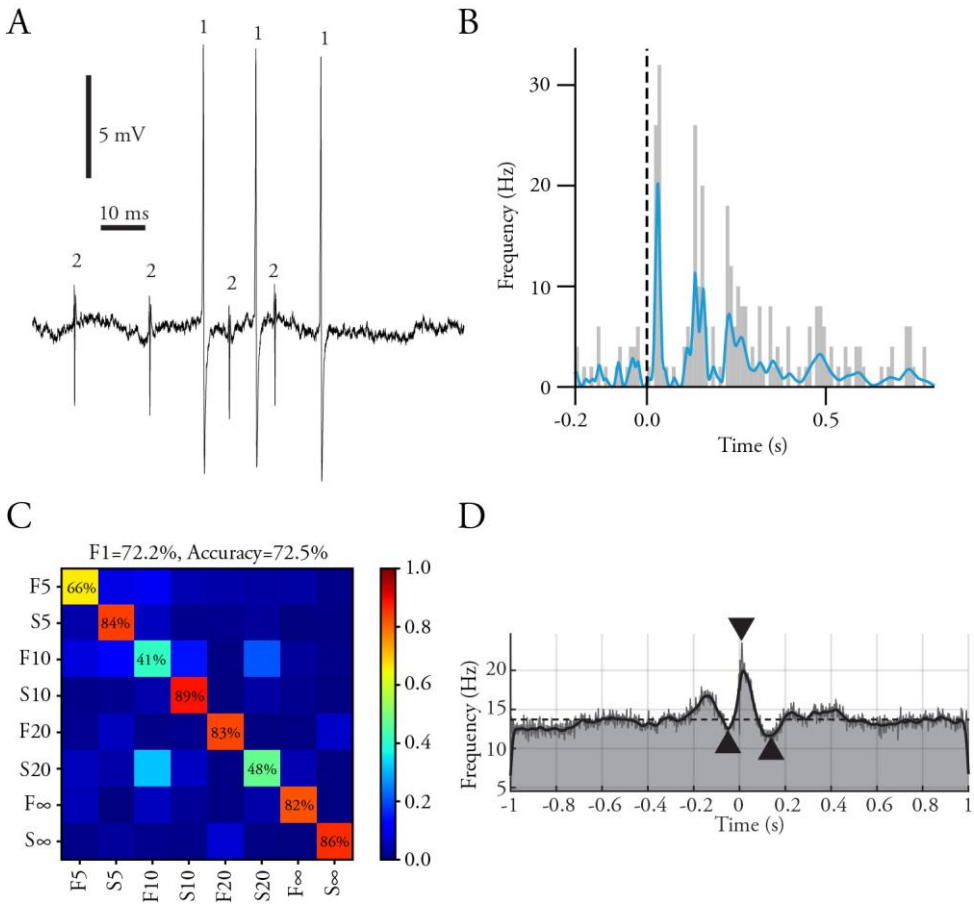

Figure 3. Showcase of analytical methods
A) A sample raw trace of a signal recorded by a patch clamp electrode. Action potentials from two different neurons can be seen, indicated by numerals 1 and 2, respectively. B) A peristimulus time histogram (grey bars)overlaid with a kernel density estimation (KDE) (blue line), showing the response of a sample cell to one of the eight stimulation patterns. C) A confusion matrix showing the decoding performance (F1-score) for all eight stimulation patterns of a sample cell. D) Peri-spike triggered histograms (grey bars) overlaid with two KDEs with different characteristic times (grey and black line) showing the correlation pattern of the two adjacent neurons shown in A).

Neural decoding performance

In order to evaluate the response to the electrotactile stimulation, an analysis method combining bootstrapping, principal component analysis (PCA) and k-nearest neighbour (kNN) classification was used in order to estimate how well the spike output of a neuron can be used to identify which electrotactile stimulation pattern was presented to the contralateral forepaw digit two. The original method was published in Oddo *et al.* (2017), but a slightly modified version has been used in paper II, III and IV. The method is described in six steps below.

i. An exponential kernel with a characteristic time of 5 ms is used to convolve the spike trains recorded after each representation of the eight electrotactile stimulation patterns into continuous functions, including the first 1000 ms after each stimulation onset.

ii. The continuous responses were randomly assigned to either a training data set or a test data set, half in each.

iii. The training data set was bootstrapped 200 times without any stimulation pattern labels: a new sample of M responses was taken from the training set using sampling with replacement, where M was the number of available responses. The sum of the M responses was then considered one bootstrapped response. PCA was then used to determine the N principal components required to explain 95% of the variance in the bootstrapped data. The test and training data sets were then grouped by stimulation pattern label and bootstrapped separately in a similar manner, creating a bootstrapped test and training data set.

iv. The scalar product between each bootstrapped response in the test and training data set and the N principal components was then calculated using the least squares method. This positioned each bootstrapped response in an N-dimensional space defined by the principal component vectors.

v. The nine closest bootstrapped training set responses to each bootstrapped test set response was determined using a Euclidian distance calculation in the N-dimensional space. The kNN-classification procedure was then used to classify the test response as belonging to the stimulation pattern that elicited the relative majority of the nine nearest neighbours. The result of the classification procedure was then stored in a confusion matrix.

vi. The above five steps were then repeated 50 times, and from these 50 repetitions an average confusion matrix was obtained.

From the average confusion matrix, the metrics precision and recall could be calculated as

$$Precision = \frac{True\ positives}{True\ positives + False\ positives} \quad (1)$$

$$Recall = \frac{True\ positives}{True\ positives + False\ \text{negatives}} \quad (2)$$

The neurons decoding performance was then determined to be the F1-score of the confusion matrix, that is the harmonic mean of the matrix precision and recall. A sample confusion matrix showing the F1-score can be seen in Fig 3C.

$$F1 = 2 \times \frac{Precision \times Recall}{\text{Precision} + \text{Recall}} \quad (3)$$

A chance level decoding performance was estimated by performing the above analysis a second time, but with the spike train responses and stimulation pattern labels being shuffled. The chance level decoding was then defined as the mean decoding performance of the neuron population plus two standard deviations.

Response latency

Two different methods were used in order to determine a neuron's response latency, both based on a PSTH. In paper I a KDE was calculated based on the PSTH, and the response latency was defined as the time of the maximum value of the KDE after stimulus onset, up to 1 second later.

In paper III the mean and standard deviation of spontaneous neural activity was calculated based on a time window preceding stimulation onset in a PSTH with 2 ms bins. The response latency was then defined as the first time point after stimulus onset that two consecutive bins in the PSTH exceeded the mean plus two standard deviations of the PSTH before stimulus onset, up to 1 second after stimulus onset.

Firing behaviour metrics

Various metrics which can be used to describe a neuron's firing behaviour exists and a few different ones has been used in the papers included in this thesis. The simplest and most straight forward one is the average firing frequency, which is calculated by dividing the observed number of recorded spikes with the recording duration and has the unit Hz.

The three remaining metrics are all dimensionless and based on the neuron's interspike interval (ISI). The coefficient of variation (CV) is calculated as

$$CV = \frac{\sigma_{ISI}}{\mu_{ISI}} \quad (4)$$

where σ_{ISI} is the standard deviation of the ISIs and μ_{ISI} is the mean ISI. The metric CV2 compares two adjacent ISIs as

$$CV2 = \frac{2|ISI_{i+1} - ISI_i|}{ISI_{i+1} + ISI_1} \quad (5)$$

where ISI_i is the ith ISI and ISI_{i+1} is the following ISI. This results in a CV2 value for each pair of ISIs but was instead presented as an average ISI for each neuron. This metric was developed by Holt *et al.* (1996). The last firing metring used was called the firing regularity, as shown in Mochizuki *et al.* (2016). A gamma distribution was fitted to the neurons ISI distribution and a maximum likelihood estimate for the gamma distributions shape factor was calculated. The firing regularity was then presented as the logarithm of the shape factor.

Neural correlation patterns

Paper IV was centred around the analysis of the correlation patterns in the spike firing activity of pairs of adjacent neurons. The correlation patterns were based on peri-spike triggered time histograms (PSpTH). One neuron in a pair of adjacent neurons was designated as the triggering neuron and the other the responding neuron. The PSpTH was then created based on the relative timing of the spikes of the responding neuron to each of the spikes in the triggering neuron, one second before and after the triggering spike. The PSpTH then represented the correlation pattern for this specific constellation of neurons. For further analysis two KDEs were calculated using the PSpTH (SpT-KDEs), one with a characteristic time of 1 ms and one of 10 ms. From the two SpT-KDEs several parameters describing the correlation patterns could be extracted for further analysis. Fig 3D shows an example of a spike triggered correlation pattern, showing both the PSpTH and SpT-KDEs. The entire procedure was then repeated, but with the identity of the triggering and responding neuron reversed.

Results

Paper I: Bilateral tactile input patterns decoded at comparable levels but different time scales in neocortical neurons

The processing of sensory information from the peripheral nervous system is largely considered to occur in the contralateral hemisphere (Kandel *et al.*, 2013), however several reports have been made showing bilateral cortical activation in response to unilateral stimulation (Pidoux & Verley, 1979; Iwamura *et al.*, 1994; Shuler *et al.*, 2001; Tutunculer *et al.*, 2006), which indicates that both cortical hemispheres may be involved in the processing of unilateral input. This notion is supported by studies such as Brasil-Neto and de Lima (2008), which shows that a unilateral stroke affects the perception of tactile stimulations to both hands.

In paper I we wanted to study the quality of this bilateral processing of information, in order to see to what extent neurons receive information about what kind of tactile input they receive from bilateral inputs. We used the electrotactile stimulation outlined in *Methods* to stimulate the second digit of both forepaws of the experimental animal while performing extracellular neural recordings in the right primary somatosensory cortex (Fig. 4A).

A PSTH was generated for each neuron and input type, and from this the maximum amplitude deflection (denoted as standard deviations from mean activity, Z-score) and timing was extracted (Fig. 4B). We found consistent responses to both contralateral (CL) and ipsilateral (IL) stimulation, however the IL response had overall a lower response amplitude and a longer response latency (Figs. 4C and 4D).

We next calculated the "Neural decoding performance" as described in *Methods* in order to estimate to what extent a single neuron could differentiate between the eight presented stimulation patterns, both CL and IL. We found that the decoding performance of the neural population was similar for CL and IL input, with a tendency that CL decoding performance was slightly better. We also observed that a neuron's Cl decoding performance had some predictive value regarding the IL decoding

performance, with a high CL performance tended to be coupled with a high IL performance.

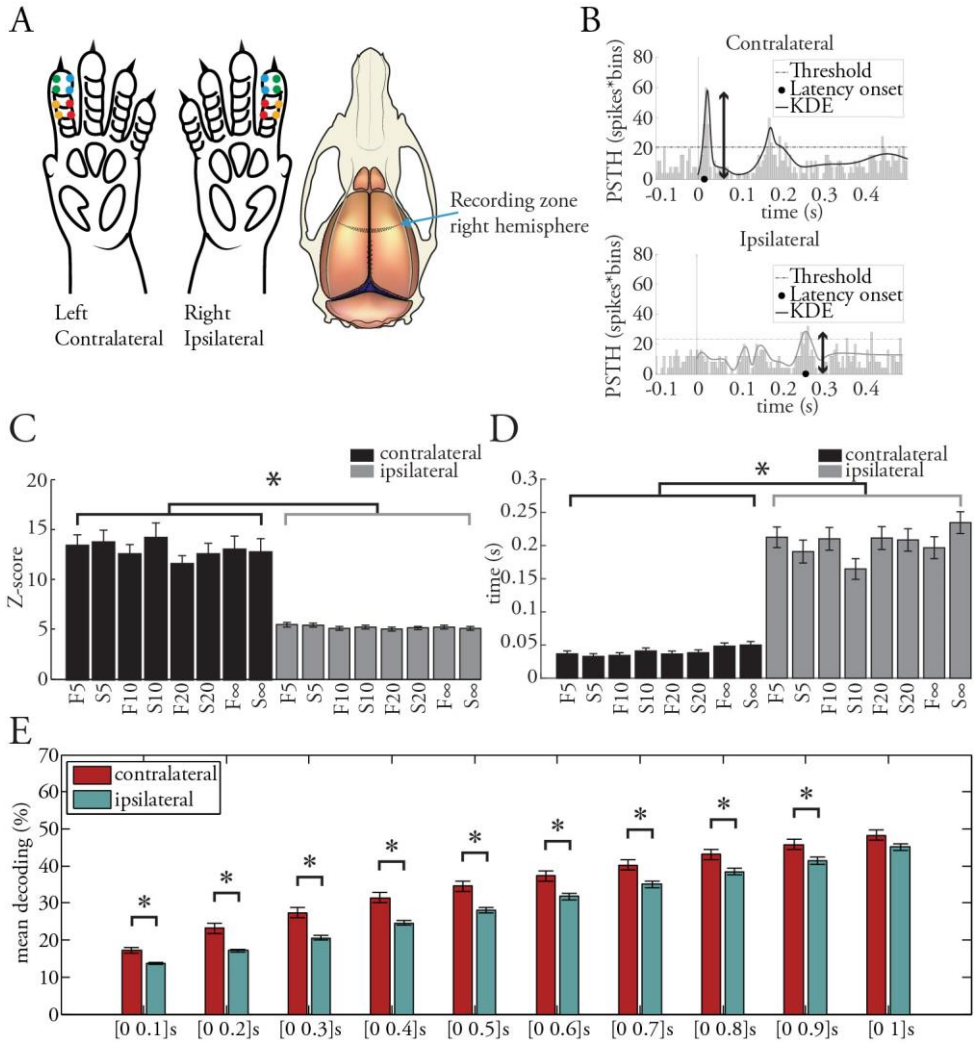

Figure 4. Summary of results from paper I.
A) A schematic showing the placement of stimulation electrodes on the right and left forepaw together with a schematic showing the recording location in the right hemisphere. B) Example PSTH overlaid with a KDE showing the response of one neuron to one stimulation pattern delivered to the contralateral (CL) (top) and ipsilateral (IL) (bottom) paw. The maximum response amplitude is indicated by the black arrows and the black dots indicate the response latency time. C) Population average response amplitude Z-score for each stimulation pattern presented to either the CL (black) or IL paw (grey). D) Population average response time latency for each pattern, presented to either the contralateral (black) or ipsilateral paw (grey). E) Population mean decoding performance of CL (red) and IL (blue) stimulation, presented for different analysis time windows.

In order to look further into detail about the decoding performance and the fact that the IL response latency tended to be higher we also looked into the decoding performance over different time windows (0.1 s to 1 s, increased in steps of 0.1 s). We found that while the CL performance was similar but significantly better than IL performance at shorter time windows after stimulation onset, but this difference disappeared when looking at long time windows (Fig 4E). This suggests that the SI cortex receives detailed information about both CL and IL inputs.

Lastly, we also compared the decoding performance of simultaneous bilateral stimulation (SYN) to the CL and IL performance, but found that there seemed to be no difference in performance compared to CL performance, which suggested no additional benefit to performance during bilateral input.

Paper II: Focal neocortical lesions impair distant neuronal information processing

As discussed in *Introduction* there is a longstanding debate about functional localization and global processing within the research society however, in clinical neurology there seem to be tendency to support the idea of functional localization: "A cornerstone of clinical neurology is that focal brain injury causes specific behavioural symptoms or syndromes that reflect the functional specialization of different brain modules" (Corbetta *et al.*, 2015). There is however, an accumulation of clinical observations that questions the correlation between the location of brain injuries and the observed functional deficits (Connell *et al.*, 2008; Corbetta *et al.*, 2015), which is also supported by the previously mentioned bilateral effects of tactile function caused by unilateral stroke (Kim & Choi-Kwon, 1996; Brasil-Neto & de Lima, 2008).

Enander *et al.* (2019) showed that information about tactile input was seemingly present over a large extent of the contralateral cortex. But the presence of information in a region does not necessarily mean that it is used in the processing of said information. Hence in paper II we wanted to study the effects of a distant disturbance to the cortical network would affect the processing of tactile information in SI. This was done by inducing a photothrombotic stroke-like lesion in the parietal cortex, as described in *Methods,* and observe how it affected the decoding performance of SI neurons, (Fig. 5A) when the second contralateral digit was stimulated with the same electrotactile stimulation patterns as described previously, recorded before, during and after lesion induction.

A morphological analysis was made in order to determine the location and extent of the lesion (Figs. 5A and 5B). The targeted area showed a drastic decrease of intact nuclei compared to surrounding areas, and this difference was used to define the lesion borders. The lesion area was characterized by areas of tissues affected to different degrees, with different densities of intact nuclei, likely corresponding to the core infarct and penumbra zone (Hoff *et al.*, 2005). An interesting observation was that the lesion was not characterized by a dark area such as in Ding *et al.* (2009), but rather a bright area (Fig. 5B). This was likely due to the short time between lesion induction and fixation of the tissue.

An analysis of the ECoG signal and the firing frequency of the recorded neurons showed the occurrence of an abrupt decrease in the ECoG spectral power shortly after the initiation of lesion induction, often accompanied by a decrease in firing frequency. This decrease was however temporary, as both ECoG spectral power density and neural firing frequency returned to their previous levels shortly thereafter. These findings suggest the occurrence of the phenomenon spreading depression, which is know to occur during stroke (Strong *et al.*, 2002; Lauritzen *et al.*, 2011).

We then looked at the neural response to the electrotactile stimulation before and after lesion induction, denoted pre-stroke and post-stroke. The response of a sample neuron pre- and post-stroke is shown in Fig. 5C. We used these responses in order to calculate the neurons decoding performance, as previously described, but this time with sixteen classes, eight patterns pre-stroke and eight patterns post-stroke (Fig. 5D). We found that the decoding performance consistently performed worse post-stroke compared to pre-stroke (Fig. 5E). As mentioned previously no statistically relevant change in firing frequency was observed for the neural population (Fig. 5F), and the individual changes that were observed did not seem to correlate with any changes in decoding performance.

A series of sham experiments was performed, where Rose Bengal was injected as described in *Methods* but the light source was never turned on This was done in order to ascertain that the observed effects was not caused by the injection, or could simply be attributed to the long recording duration. These sham experiments showed no changes in either firing frequency (Fig 5F) or decoding performance (Fig. 5E).

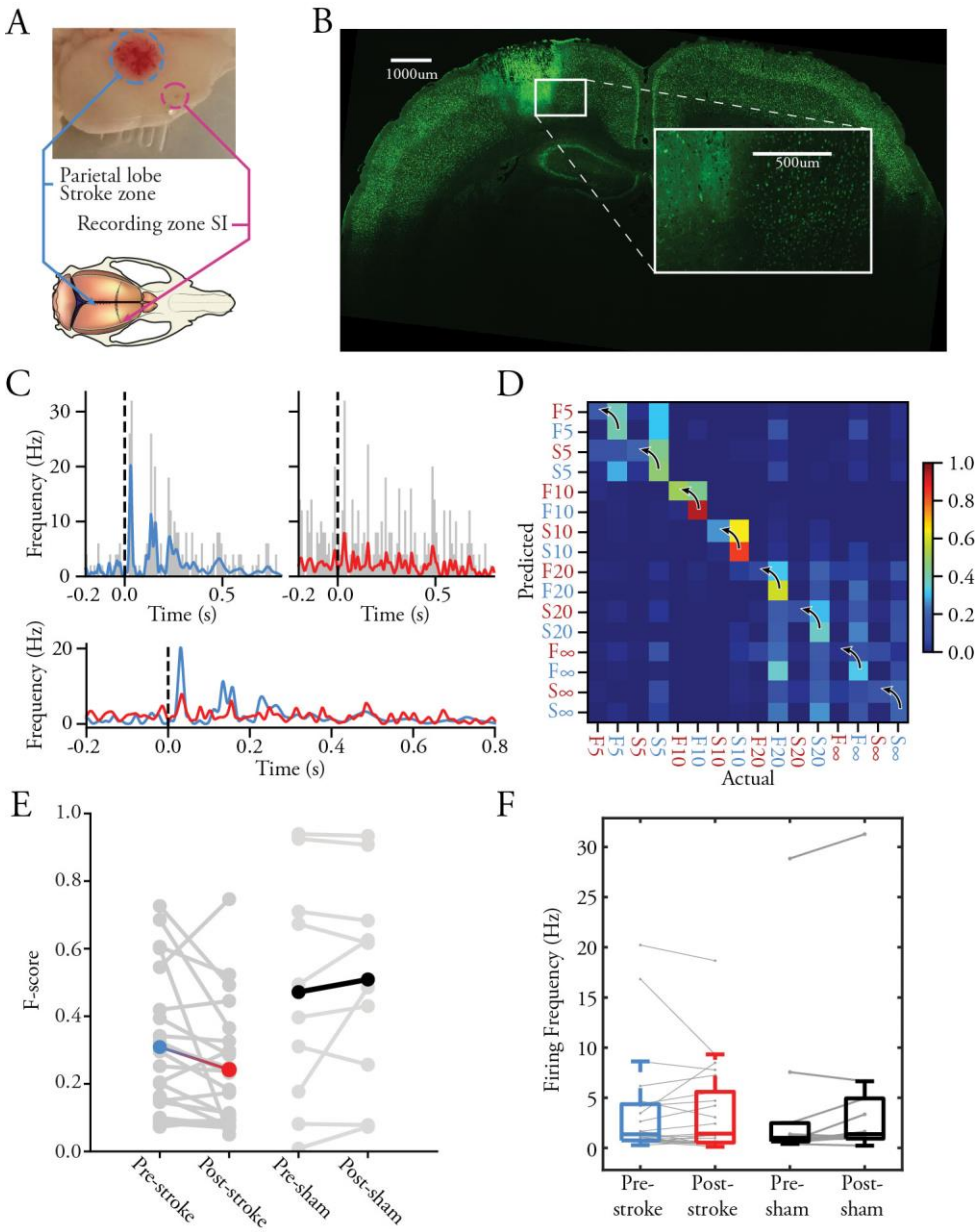

Figure 5. Summary of results from paper II.
A) A photograph (top) and schematic (bottom) of the rat brain with the lesion and recording location indicated in blue and red, respectively. B) A transversal section of the brain stained using NeuN staining, showing a lesioned area. C) A PSTH and KDE showing a neuron's response to a stimulation pattern, presented before (top left, blue) and after stroke-like lesion (top right, red). Both KDEs are shown overlaid each other at the bottom. D) Confusion matrix of the decoding performance of the sample neuron before (blue labels) and after stroke-like lesion (red labels). Arrows indicate the same pattern before and after lesion. E) Mean decoding performance for all recorded neurons, before and after stroke-like lesion (left) and before and after a sham lesion (right) shown as grey bars. Average for all neurons are presented by a red and blue bar for lesion experiments and a black bar for sham experiment. F) Average firing frequency of all neurons

presented as grey bars with an overlaid box plot, before (blue) and after (red) stroke-like lesion to the left, to the right average firing frequency before and after sham lesion, both in black.

Paper III: Widespread decoding of tactile input patterns among thalamic neurons

The results from paper I, paper II and Enander *et al.* (2019) suggests that the processing of tactile information is distributed over a large area of the cortex. This notion is supported by the findings in Henschke *et al.* (2015) which shows that several primary sensory thalamic nuclei project to multiple primary sensory cortical areas. Only limited regions of the thalamus receive direct tactile afferent cuneate nucleus input (Alloway *et al.*, 1994; Bermejo *et al.*, 2003), but the presence of diverse corticothalamic projections (Deschenes *et al.*, 1998; Halassa & Sherman, 2019) enables a distributed presence of tactile information also in the thalamus. Indeed, in Bieler *et al.* (2018) it was shown that tactile inputs evoke field potential responses in the lateral geniculate nucleus (LGN) which is commonly associated with visual information (Alitto & Usrey, 2003). Reversely Allen *et al.* (2017) showed that visual stimuli affected the response of the ventral posteromedial nucleus (VPM) to tactile whisker stimuli.

In paper III we thus set out to explore to what extent tactile information was distributed in the thalamus. We did this by performing extracellular recordings from a number of different thalamic nuclei while presenting the same electrotactile stimulation of the second contralateral digit as previously described.

Recording location was estimated using stereotaxic coordinates in relation to bregma, in combination with the atlas created by Paxinos and Watson (2006). According to this we recorded from neurons in the ventroposterior lateral nucleus (VPL), ventroposterior medial nucleus (VPM), ventrolateral nucleus (VL) and posterior complex (PO). A histological analysis was performed in order to estimate the accuracy of the stereotaxic coordinates (Fig. 6A), which was deemed to have a reasonably low deviation from actual recording location.

Several different metrics describing a neuron's firing behaviour, see *Methods*, was used to study the recorded neurons, however no distinct clusters could be observed for any metric, which were rather characterized by continuums. Thus no clear division into different types of neurons was made, and all recorded neurons was assumed to be putative thalamic projection neurons, which match the observations of Arcelli *et al.* (1997) and Spreafico *et al.* (1994) estimating that to be the overwhelming majority of neurons in the thalamic sensory relay nuclei.

The decoding performance of the recorded neurons was calculated, again as described in *Methods*, and a majority of the recorded neurons were found to have an above chance level decoding (Fig. 6B). The response latency was of the neurons varied greatly, with some having a response latency of only a few milliseconds, likely due to monosynaptic input from the cuneate nucleus, while others had much longer response latencies, probably receiving their tactile input through less direct pathways. When comparing decoding performance and response latency a short latency was often coupled with a high decoding performance however, high decoding performance could also be observed for longer latencies.

We then looked at the relationship between the location of the recorded neurons and their decoding performance and response latency (Figs. 6C). We found no clear relationship between the location and decoding performance or response latency, indicating that tactile information was distributed over a large area of the thalamus, corresponding to several different thalamic nuclei.

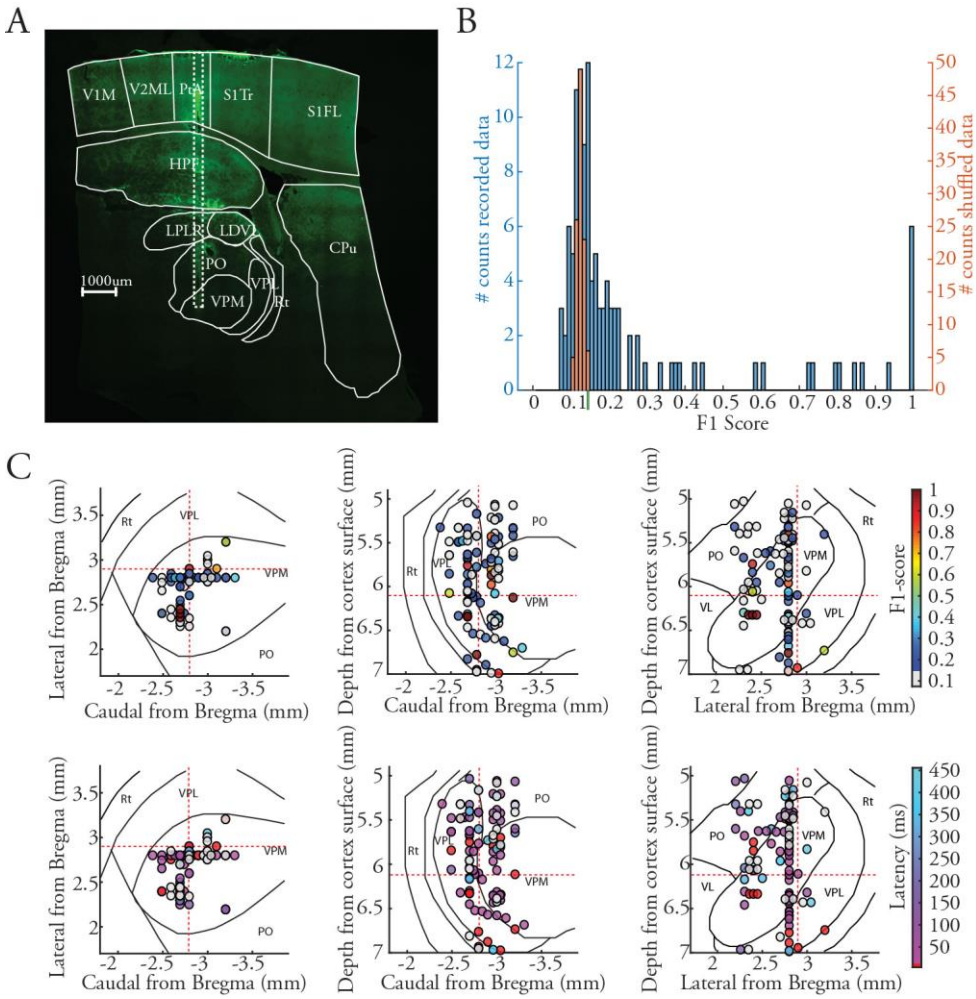

Figure 6. Summary of results from paper III

A) Sagittal section of the brain with different structures outlined. An electrode track is outlined by white dotted lines. B) Decoding performance of all recorded neurons (blue) and decoding performance but with shuffled stimulation pattern labels (orange). Estimated chance decoding level, estimated as two standard deviations above the mean shuffled decoding performance, indicated as a green bar below the x-axis. C) Estimated recording locaion for all neurons, shown from three different viewing directions mapped onto different planes (horizontal 6.3 mm, sagittal 2.9 mm and coronal -2.8 mm). Decoding performance and response time latency indicated by colour, above and below, respectively. Note that representing the recording locations with only one plane in each direction does not give an accurate representation of the recording location, for a more detailed representation please refer to paper III. (V1 primary visual cortex; V2 secondary visual cortex,, PtA parietal area; S1 primary somatosensory cortex; HPF hippocampal formation; CPu caudate putamen; LPLR lateropostero laterorostral nucleus; LDVL laterodorsal ventrolateral nucleus; PO posterior complex; VPL ventroposterior lateral nucleus; VPM ventroposterior medial nucleus; Rt reticular thalamic nucleus)

Paper IV: Widely different correlation patterns between pairs of adjacent thalamic neurons *in vivo*

In paper III we showed that information about tactile afferent input was present in a large part of the thalamus, possibly enabled by diverse corticothalamic projections (Turner & Salt, 1998). We next asked to what extent adjacent thalamic neurons correlate in their firing activity. The dendritic fields of adjacent neurons can be expected to overlap to a large extent, thus giving the two neurons access to a similar set of available afferent inputs. If the two neurons receive the same synaptic input, they could be expected to have a very strong co-activation and firing behaviour. An alternative hypothesis is that the overlapping dendritic trees merely provides an initial set of similar inputs, but that learning processes then affects the available synaptic weights, thus differentiating the firing behaviour of the two neurons.

In paper IV we examined the probability of these two alternative hypotheses using a method similar to that of Mogensen *et al.* (2019), briefly described in *Methods*, to compare the spike firing correlation patterns of the recorded neurons (Fig. 3D). Extracellular recordings of adjacent thalamic neurons were made in the VPL, VPM, VL and PO of both spontaneous activity and activity evoked by the previously mentioned electrotactile stimulation patterns, accompanied by an ECoG recording.

We found a great variety in the observed correlation patterns, both quantitatively and qualitatively (Fig. 7A), which indicated that the behavioural relationship within pairs of recorded neurons varied between different pairs.

Ketamine and xylazine which was used to induce anaesthesia in the study is known to affect the ECoG state (Soltesz & Deschenes, 1993). The ECoG state has also been shown to be affected by thalamic activity, especially through a synchronization of the oscillatory behaviour often observed in thalamic neurons (Steriade *et al.*, 1991; Hirata & Castro-Alamancos, 2010). We thus asked ourselves if the difference observed in the pairwise correlation patterns could be attributed to persistent differences in the ECoG state.

We split the recording sessions based on the ECoG state being classified as synchronized or desynchronized (Fig 7B) and compared the correlation patterns generated by spikes occurring during the different states (Fig. 7C), and found remarkable little difference. We further checked if the ratio of desynchronized activity impacted the quantitative measures extracted from the correlation patterns but could see no clear relation. These findings indicated that the difference in correlation patterns was seemingly not caused by differences in ECoG sates.

Next we checked if the intrinsic firing properties, described in *Methods*, of the recorded neurons could explain the observed differences in correlation patterns. But no predictive value could e found between any of the four firing metrics and the six extracted metrics describing the correlation patterns.

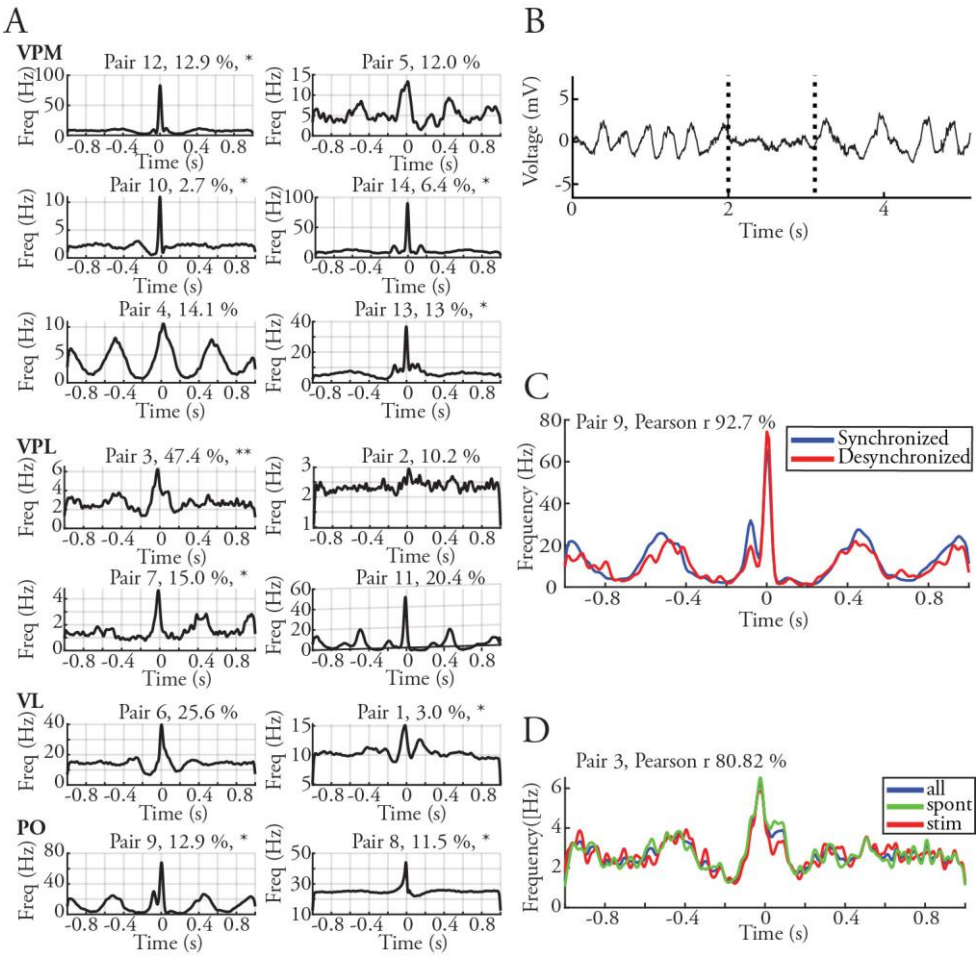

Figure 7. Summary of results from paper IV

A) The correlation pattern for all 14 recorded neuron pairs. The ratio of time spent in a desynchronized ECoG state is indicated by a percentage, and asterisks are used to indicate the pairs with one (*) or two (**) neurons with a decoding performance above the chance decoding level (indicated in Fig. 6B). B) A sample raw trace of ECoG signal showing segments of synchronized and desynchronized (between the dashed lines) activity. C) A comparison of the correlation pattern of a sample pair of neurons, where the triggering spikes occur during either synchronized (blue) or desynchronized (red) activity. D) A comparison of the correlation patterns of a sample neuron pair, comparing trigger spikes occurring during the entire recording (blue, only during spontaneous activity (green) or during stimulated activity (red). (VPM ventroposterior medial nucleus; VPL ventroposterior lateral nucleus; VL ventrolateral nucleus; PO posterior complex)

Lastly, we studied the impact of the electrotactile stimulation patterns on the correlation patterns by dividing the recorded spikes into periods of stimulated or spontaneous activity (Fig. 7D), but no major impact could be observed. This was however not surprising, as the overall decoding ability of the recorded neurons was low.

Discussion

This part of the thesis will start off with a short summary of the results of each individual paper, coupled with possible interpretations and explanations of the results. First off will be the papers where recordings were performed in the thalamus, paper III and IV, followed by the papers where recordings were performed in the neocortex, paper I and II. The results of all papers will then be discussed in a more general manner. This is followed by discussions regarding different experimental methods. Lastly some limitations regarding common analytical methods will be discussed.

Local, global or something in between?

Tactile information in the thalamus

In paper III we showed that neurons in several different thalamic nuclei received tactile input from the contralateral forepaws second digit. The neurons not only had a response to the stimulation, as indicated by a response latency estimation, but were seemingly also able to decode what kind of stimulation was presented.

Neurons with a high decoding performance also tended to have a short response latency, which indicates that they received direct tactile input from the cuneate nucleus. These neurons were not confined to the VPL, which receives a majority of the direct cuneate nucleus projections but were also found in other thalamic nuclei, such as the VPM and VL. This could possibly be made possible by cuneate nucleus projections to thalamic nuclei other than VPL (Hand & Van Winkle, 1977; Berkley *et al.*, 1986).

Other neurons with an above chance decoding performance but longer response latency likely did not receive direct tactile input from the cuneate neurons, but rather from other longer indirect pathways. Possible such pathways from the cuneate nucleus to the thalamus includes the superior colliculus (Bezdudnaya & Castro-Alamancos, 2011; Gharaei *et al.*, 2020) and other potential brainstem pathways (Loutit *et al.*, 2021). Another possible pathway for the tactile information is via spinal interneurons and the lateral reticular nucleus to the cerebellar nuclei (Bengtsson & Jörntell, 2014; Jorntell,

2017), which then projects to the thalamic nuclei VL(Jorntell & Ekerot, 1999). Tactile input to the nuclei other than VPL could also come from the neocortex, which has been shown to provide input to non-homonymous thalamic nuclei (Deschenes *et al.*, 1998; Halassa & Sherman, 2019). Additionally the neocortex has been shown to have a ubiquitous representation of tactile input (Enander *et al.*, 2019), meaning that many potential corticothalamic pathways exist.

In paper IV we recorded the spike firing activity of pairs of adjacent neurons in the lateral thalamus and studied the spike firing correlation patterns of the pairs. We found that the correlation patterns varied greatly between different pairs and found no apparent correlation between the identity of the thalamic nuclei a pair were located in and the shape of the correlation pattern.

Adjacent neurons can be expected to have a large overlap of their dendritic trees and thus the available synaptic inputs can be assumed to be as similar as possible. This was seemingly indeed the case, as the observed correlation patterns were characterized by a sharp central peak, indicating that the neurons of a pair tended to fire at the same time. However, when looking at the entire correlation patterns they were often asymmetrical and varied greatly between the pairs.

Assuming that the neurons of a pair had access to similar synaptic inputs but that their correlation patterns varied to such an extent as observed, we suggested two possible explanations. The first hypothesis was that the intrinsic firing properties of the neurons were different, which would result in different behaviour when presented with the same input. However, no correlation was found between the six quantitative parameters describing the correlation patterns and four different metrics used to describe the firing behaviour of the neurons, indicating that this was probably not the only cause of the different correlation patterns.

The second hypothesis was that although the neurons of a pair would have access to similar synaptic inputs, a learning mechanism might change the synaptic weights of the available inputs, thus differentiating the behaviour of the neurons which would enable a richer representation of the synaptic inputs.

Many correlation patterns had a similar periodicity, indicating a similar oscillatory behaviour of the recorded neurons. Thalamic neurons are known to have a tendency to produce rhythmic oscillatory behaviour (Llinas & Jahnsen, 1982; McCormick & Pape, 1990), and a synchronization of such oscillatory behaviour to some extent induces cortical synchronized behaviour, which can be observed using EEG (Steriade *et al.*, 1991; Hirata & Castro-Alamancos, 2010). Such oscillatory EEG activity can be observed during sleep and a relaxed state (Sachdev *et al.*, 2015), thus we decided to examine whether different levels of anaesthesia could explain the observed differences

in correlation patterns. This was done both by comparing the correlation patterns created when the triggering spike occurred during desynchronized or synchronized cortical activity, and examining the relation of the ratio of desynchronized activity and the quantitative parameters describing the correlation patterns. However, both these examinations indicated that different levels of anaesthesia were likely not the cause of the observed differences in correlation patterns.

Neocortical representations of tactile information

Moving on to the cortex, in paper I we found that neurons in the somatosensory cortex had access to detailed information about both contralateral and ipsilateral tactile stimulation.

Several previous studies have shown the presence of bilateral somatosensory information in the neocortex (Pidoux & Verley, 1979; Iwamura *et al.*, 1994; Shuler *et al.*, 2001; Tutunculer *et al.*, 2006), and the effects on the tactile perception of both hands following a unilateral stroke reported in Brasil-Neto and de Lima (2008) suggests not only a presence of bilateral tactile information but also a functional purpose of the ipsilateral information.

Our results indicated that the neurons in SI not only had detailed enough information to differentiate between the eight presented ipsilateral stimulation patterns but could do so at a performance level similar to the contralateral stimulation. The ipsilateral stimulation resulted in a lower response amplitude and longer response latency, indicating. This is in line with previous studies (Armstrong-James & George, 1988; Tutunculer *et al.*, 2006; Moxon *et al.*, 2008), and indicates that longer indirect routes, such as corticocortical, is primarily used for ipsilateral information transfer between the two hemispheres.

We hypothesised that simultaneous stimulation ipsi- and contralateral could lead to a higher decoding performance, since the delayed ipsilateral response could be added to the initial contralateral response. However, this was not observed, and the decoding performance of the simultaneous stimulation closely resembled the contralateral stimulation, indicating that tactile information processing might be dominated by the stronger and faster contralateral response. However, the studies showing bilateral effects after unilateral strokes indicate that the ipsilateral hemisphere to some degree contributes to the processing of contralateral information (Kim & Choi-Kwon, 1996; Brasil-Neto & de Lima, 2008).

In paper II we showed that a distant focal photothrombotic lesion in the parietal cortex impaired the decoding performance of neurons in SI. Enander *et al.* (2019) showed

that tactile information was present in a large part of the neocortex, and the results of paper II indicate that this presence of information also has a functional meaning. The results indicate that the information processing in SI is dependent on the integrity of a cortical network that expands beyond SI.

Several possible explanations of the observed results exist. The area damaged by the lesion could be a direct part of the tactile information processing network, connected to SI either through corticocortical or corticothalamocortical connection. Another possibility is that the lesioned area through some possible pathway provides permissive excitation to SI enabling it to properly process incoming information. A third possibility is that the lesioned area could be modulating the ascending primary afferent input from the cuneate nucleus or the thalamus.

The probability of the lesioned area being the only region outside of the somatosensory cortex that contributes to tactile information processing could be argued to be low due to the accumulation of clinical observations that no obvious connection can be made between the location of a stroke and the functional deficits that can be observed (Brasil-Neto & de Lima, 2008; Connell *et al.*, 2008; Corbetta *et al.*, 2015). This indicates that somatosensory processing is dependent on widely distributed networks in the brain.

Observations regarding a functional principle

This section is an attempt to summarize my own and other findings and use that as a basis to present my opinion regarding a functional principle of the nervous system.

Several studies have been made that support the notion that individual neurons are able to differentiate between different tactile inputs in the cuneate nucleus (Jorntell *et al.*, 2014), the thalamus (paper III) and the neocortex (Oddo *et al.*, 2017; Enander & Jorntell, 2019; Enander *et al.*, 2019)(paper I and II), indicating that each recorded neuron receives a complex representation of tactile information input. It has also been suggested that different neurons pick up different features of the incoming tactile information, suggesting complementary or population coding of information (Doetsch, 2000; Bale *et al.*, 2015; Oddo *et al.*, 2017; Enander *et al.*, 2019).

The ability of individual neurons to differentiate between different tactile input patterns was not limited to a specific area, rather neurons over a wide area of both the thalamus (paper III) and the neocortex (Enander *et al.*, 2019)(paper I) showed this ability. This widespread presence of information is further supported by paper I and previous observations (Pidoux & Verley, 1979; Armstrong-James & George, 1988; Iwamura *et al.*, 1994; Shuler *et al.*, 2001; Tutunculer *et al.*, 2006) showing bilateral activity of neurons to unilateral stimulation. In the neocortex, this ability was seemingly

not related to the cortical depth of the recording, suggesting that neurons in several cortical layers display the ability to differentiate between different tactile input (Oddo *et al.*, 2017; Enander *et al.*, 2019).

Paper IV and Mogensen *et al.* (2019) suggests that adjacent neurons in the thalamus and cortex to some extent receives similar synaptic input, but that differences in their intrinsic firing properties or a learning mechanism changing the synaptic weights of available input has differentiated their responses. Differences in responses to similar input enables a richer representation of said inputs.

Paper II together with clinical observations (Bassetti *et al.*, 1993; Kim & Choi-Kwon, 1996; Brasil-Neto & de Lima, 2008; Connell *et al.*, 2008; Corbetta *et al.*, 2015; Sathian & Crosson, 2015) suggests not only a distributed presence of tactile information, but also a distributed functionality regarding the processing of said tactile information by showing that there is no clear correlation between the location of a stroke and the observed functional deficits.

Let us now take a look at possible anatomical support for such distributed information processing.

Hand and Van Winkle (1977) and Berkley *et al.* (1986) showed projections from the cuneate nucleus to areas in the thalamus other than the VPL, and several other possible indirect pathways for tactile information from the cuneate nucleus to the thalamus exists (Bezdudnaya & Castro-Alamancos, 2011; Gharaei *et al.*, 2020; Loutit *et al.*, 2021), in addition to pathways via the cerebellar nuclei (Jorntell & Ekerot, 1999; Bengtsson & Jörntell, 2014; Jorntell, 2017).

Henschke *et al.* (2015) showed the existence of projections from the VPL not only to SI but to multiple sensory regions in the neocortex, enabling a wide distribution of tactile information. Henschke *et al.* (2015) and Bieler *et al.* (2018) further showed that this was not observed only in the VPL but also several other thalamic nuclei, which if they also receive tactile sensory input would further enable a wide distribution of tactile information.

The presence of wide corticocortical and corticothalamocortical projections (Frostig *et al.*, 2008; Negyessy *et al.*, 2013; Ashaber *et al.*, 2014; Henschke *et al.*, 2015; Sherman, 2016; Wall *et al.*, 2016; Gerfen *et al.*, 2018; Lin *et al.*, 2018; Economo *et al.*, 2019) and the presence of non-homonymous corticothalamic projections (Deschenes *et al.*, 1998; Halassa & Sherman, 2019) would further facilitate a wide distribution of tactile information. This high interconnectivity was predicted already by (Arbib *et al.*, 1998) who estimated that any neocortical neuron could reach any other neocortical neuron with synaptic linkages involving no more than five neurons on average.

However, it is important to note that the observations showing diverse projections from the cuneate nucleus (Hand & Van Winkle, 1977; Berkley *et al.*, 1986) and the thalamus (Henschke *et al.*, 2015) also showed that a relative majority of the observed projections followed along the pathway from the cuneate nucleus to VPL and then to SI.

Let us now assume that this anatomical substrate with a main sensory pathway expanded by diverse projections, and corticocortical and corticothalamocortical projections is similar between both individuals of the same species but also between different species. Let us next also assume that the projections are not exactly the same between each individual and/or that learning mechanisms has shaped the functional properties of the nervous system of each individual. These assumptions would give rise to a nervous system with certain main points of entry of sensory information, which may or may not also be central in a functional perspective, but also that both information and function are to some extent distributed over large parts of the nervous system. This would give rise to a nervous system with functional hubs of higher importance to the systems functionality such as suggested by Bullmore and Sporns (2009), (van den Heuvel *et al.*, 2012) and (van den Heuvel & Sporns, 2013), similar to the idea of "small-world networks" introduced by Watts and Strogatz (1998).

When an external observer looks at such a system and tries to find areas of higher neural activity after the presentation of a certain stimulus, such as studies looking at LFPs or fMRI images, what would stand out from the rest would be the points of major inflow of information and other potential hubs, thus supporting the theory of functional localization. But focusing only on the points could result in a "tip of the iceberg" effect, where the activity of the rest of the nervous system is assumed to be irrelevant to the processing of the presented stimulation. In a similar manner, if one studies the effects of a disruption to the nervous system, such as a stroke at a particular region, and looks at a population of subjects, the commonly shared functional deficit could be attributed to any commonly shared hubs in that region, such as major inflows of a specific sensory modality. However, this does not necessarily mean that the specific function in located solely at that region.

If one instead observes the individual cases the deficits observed after a stroke in a specific region often vary between the cases, and often affect multiple modalities. This could be explained by a distributed processing regime and the assumed individual variance in the distribution of function. It is, however, hard to determine to what extent a certain function is distributed, as that would certainly also vary between individuals.

A distributed processing regime would also give the nervous system a certain level of redundancy, supporting the observations regarding full or partial recovery of function after a stroke (Cramer, 2008; Murphy & Corbett, 2009). This is also in line with the

observations made by Goltz (1888) regarding reinstitution of function, and the observations by Wardlaw *et al.* (2013) indicating that many localized cortical infarcts are small enough to not be noticed at all.

A distributed processing regime would thus be able to support observations indicating both functional localization and widespread information processing, in addition to observations regarding redundancy in the nervous system, depending on the viewpoint of the observer. I would thus argue that the nervous system functions according to a distributed processing regime, rather than functional localization.

Now follows a methodological discussion about a number of experimental and analytical methods, some employed in the papers included in the thesis, and some of the limitations that has to be considered when using said methods.

Perceiving the world through sleeping eyes

Experiments involving animals are generally performed with the animal in either an awake or anaesthetised state, which both have their advantages and drawbacks that needs to be considered when designing a study or interpreting results.

The awake state has the advantage of being the default state the nervous system is in when processing somatosensory information, such as visual or auditory input, or tactile information generated during exploration of one's surroundings. It can then be assumed to generate neural activity which most accurately represents the processing of such information. However, the awake state comes with the disadvantages that it makes it harder to deliver the exact same sensory input stimulation in some cases, such as tactile stimulation. It is also difficult to know how attention modulates the incoming sensory information (Wiesman & Wilson, 2020) or how it might be affected by internal brain activity, such as predictions or expectations (Eskandar & Assad, 1999).

The anaesthetised state has the advantage that there are minimal such systematic variations in brain states preceding the presentation of a stimuli (Wallach *et al.*, 2016). However, the anaesthetised state cannot be considered the natural state for processing somatosensory information, and thus it is not certain that the observed neural activity would give an accurate representation of the processing of such information. Further anaesthesia has been shown to affect the efficacy of synaptic transmission (Bengtsson & Jorntell, 2007), which might also impact the accuracy of the representation of neural activity. However, response latency times in the somatosensory cortex has been shown to be similar in awake and anaesthetised rats (Shuler *et al.*, 2001; Wiest *et al.*, 2005). Further more, it has been indicated that the recruitment order of a population of

neurons after presentation of a stimulus remains the same in an awake and anaesthetised state (Luczak *et al.*, 2009; Luczak & Bartho, 2012).

Active processing in an awake animal is characterised by desynchronized EEG waves (Petersen & Crochet, 2013), but deep sleep is instead characterised by synchronised slow waves with irregular occurrences of desynchronized activity (Niedermeyer & Da Silva, 2005). Enander *et al.* (2019) showed that the measured decoding performance of neocortical neurons was higher during a desynchronized state compared to the synchronized state. This could indicate that the decoding performance measured in the papers included in this thesis is in fact an underestimation, since all recordings were performed in the anaesthetised state. However, the decrease of internal brain activity (Eskandar & Assad, 1999) and lack of attentional modulation (Wiesman & Wilson, 2020) might instead result in an increased decoding performance in the anaesthetised state, if the incoming tactile information takes precedence due to the decreased internal activity.

The question of whether our measured decoding performance is over or underestimated is highly relevant. However, since all experiments using the same electrotactile stimulation patterns and decoding performance analysis as used in paper I-IV have been performed in the anaesthetised state, this is not a question that can currently be answered.

Creating a sensation

When choosing a stimulation paradigm to use for a study one must ponder over whether to use a stimulation that closely resembles a natural sensation or to use a stimulation that elicits a simplified sensory afferent activation, as they both have their own set of advantages and disadvantages.

Tactile interactions have been shown to activate mechanoreceptors in the skin at a large distance away from the actual contact between the skin and an object (Shao *et al.*, 2016, 2020), giving rise to a complex representation of the interaction in sensory afferent activation, even with simple tactile interactions. From a mechanical point view this is not surprising, as vibrational waves would spread out from the point of contact to a certain degree limited by the dampening effects of the skin.

A tactile stimulation involving touching a physical object would generate the sensory afferent activation and activity in the CNS which most accurately represents natural tactile interactions. However, such stimulation inherently has a lot of variation (Jenmalm *et al.*, 2003; Hayward *et al.*, 2014). Each mechanical tactile interaction would

to some degree deform the skin, thus changing the response properties of the skin's mechanoreceptors due to a change in their biomechanical context after each stimulus presentation, and the interaction might also deform the object interacted with. Depending on how the stimulus is presented there could also be variations between the force and angle of contact with the object interacted with.

A simplified tactile stimulation could be an electrical stimulation activating only a small number of tactile sensory afferents. These kinds of stimulations have the advantage of producing highly reproducible activation of sensory afferents. But a major drawback is that such simple stimulation would not evoke the same complex sensory activity as natural stimulation, and would thus create a simplified activity in sensory afferents and simplified activity in the CNS, not necessarily showing an accurate representation of sensory information processing (Felsen *et al.*, 2005; Berkes *et al.*, 2011).

The electrotactile stimulation used in papers I-IV is an attempt to achieve a maximum value in the trade-off between the complexity of natural stimulation and the reproducibility of simple stimulation.

The electrotactile stimulation patterns used was created by Oddo *et al.* (2017). An artificial fingertip was equipped with a 2x2 piezo-resistive sensor array encompassed in a polymeric compliant material used in order to mimic the biomechanical properties of skin. Four mechanical probes of different shapes were then pressed against the fingertip, causing the four sensors to generate artificial receptor potentials, which could then be transformed into spike trains using a Izhikevich spiking neuron model. For each probe, two spatiotemporal patterns were generated, one representing fast adapting skin receptors and one representing slow adapting skin receptors, resulting in a total of eight spatiotemporal patterns. These patterns were then delivered to the experimental animal using four pairs of stimulation electrodes inserted into the second digit of the front paw., each pair representing one neuromorphic sensor in the artificial fingertip. This was done in order to create a stimulation method with a very high reproducibility, that at the same time created an as close as possible representation of natural sensory afferent activation.

The stimulation paradigm is of course not a perfect representation of a natural tactile interaction, as it does not give rise to the same biomechanical skin deformation and widespread activation of mechanoreceptors as reported in (Shao *et al.*, 2016).

The curse of averaging

How does an observation lead to a hypothesis about function? Some of the limitations of methods commonly employed by neuroscientists to answer the question "how does the brain work", will be discussed here. Far from all possible methods and their limitations will be covered, but the presented reasoning can be employed also in a more generalized sense.

One common method to try to determine the function of a certain region of the brain is to study what happens when said region is damaged. The observed functional deficits are then usually attributed to the damaged region. However, as already mentioned in "*Observations regarding a functional principle*" it is hard to verify whether the function is limited to only that particular region, as argued by Prince (1910). The theory of diaschisis elaborates on this reasoning, saying that the damaged region in itself might not be involved directly with the function, but might instead influence other areas, resulting in the observed deficit (von Monakow, 1914; Carrera & Tononi, 2014).

Another common method to elucidate how the brain works is to record from a large region of the brain at the same time, either imaging methods such as fMRI or electrophysiological methods such as EEG. As mentioned in "*Observations regarding a functional principle*" fMRI suffers from a "tip of the iceberg" effect, where only activity above a baseline level is considered important. Additionally how this baseline is defined has be argued to be rather ambiguous (Stark & Squire, 2001). An additional drawback of fMRI is that it does not measure neural activity directly, but rather the oxygen dependent magnetic properties of blood, resulting in poor spatial and temporal resolution (Logothetis, 2008). EEG has the advantage of directly measuring the electrical activities of neurons with a high temporal resolution, but with a poor spatial resolution. However, some arguments have been put forth that the temporal resolution of EEG might often be overestimated (Burle *et al.*, 2015).

In order to improve the spatial and temporal resolution one might instead use invasive techniques in order to record the spike activity of single or multiple neurons, up to thousands at the same time. From these recordings a large number of metrics can be derived, some of briefly described in *Metrics*, which are then commonly used to describe the behaviour of a neuron. One common metric is the response latency time, used to measure the time between a stimulus presentation and an average increased spiking activity of the recorded neuron. But that in itself does not necessarily say anything about whether the neuron is related to the processing of the presented stimulus. Further, a myriad of different methods to define the response latency exists (Levakova *et al.*, 2015), making it hard to compare response latency times between different studies as

they might have been calculated differently. The same limitations as for response latency also applies to measures of response amplitude.

Other metrics describe the behaviour of a neuron, such as the coefficient of variation of a neuron's interspike intervals, or a neuron's average firing frequency. However, one might question the relevance of such a metric, if what is important regarding a neuron's spiking activity is the temporal evolution of said activity, then the informative ability of a single metric is certainly limited.

A common denominator for many the methods presented so far is that they are based on some kind of averaging. But any kind of averaging comes with an assumption that some parts of the observed data is less important than others. Averaging instead highlights the common features of multiple observations, but at a cost of the less common features, which are assumed to be noise.

Indeed, electrophysiological signals are often described as noisy due to the fact that the nervous system is constantly active through spontaneous activity. In order to find meaningful information about a response to a stimulus many repetitions of said stimuli is performed, and an averaged representation of the response is created in order to separate the stimuli response from the spontaneous activity. But how do we determine what activity is important and what activity is unimportant, is the noise really noise?

Spontaneous activity reflects the internal state of the brain, and can be argued to affect how any incoming information about a presented stimulus will be interpreted (Hartmann *et al.*, 2015). With the human brain having an estimated 86 billion neurons (Azevedo *et al.*, 2009) it is not unreasonable to assume that the exact same internal brain state will not occur more than once during an average human lifetime. This means that the neural activity in the brain elicited by repeated presentations of a stimulus will always to some degree be unique.

It is not hard to imagine the difficulties in trying to study such an incredibly complex system and draw accurate conclusion using methods that are limited spatially and/or temporally. The methods available to neuroscientists are limited, with methods providing both a high spatial and temporal resolution only able to record from a relatively small number of neurons at the same time. It can also be noted that the extracellular signal can be considered to contain much less information than the intracellular signal, which is in turn limited to being recordable from a very limited number of neurons at the same time.

An alternative to directly studying the brain would be to instead create a simulation of the brain. This is a great way to observe how different behavioural properties could arise in a network of neurons. However, in order to create a simulation that completely

accurately represents the brain one would first need to fully understand the brain, which makes this idea somewhat less appealing.

The limitations of methods based on averaging does of course not mean that neuroscientists should give up and do nothing. But it is important to be aware of the limitations of one's methods, to be honest when presenting any results and be humble when drawing conclusions and discussing the results with others.

Methods based on averaging often obscure the fine details and trying to draw conclusions regarding the function of a system as complex as the nervous system based upon limited information would often lead to different conclusions being drawn by every observer. This could possibly be one of the reasons why a consensus about how the brain works has not yet been reached, even after hundreds of years.

Concluding remarks

This thesis has looked at the flow of tactile information, how disruptions to the neocortical network might affect that flow and how different functional principles can be used to interpret the observed results.

The findings of paper I and III indicate that tactile information is distributed over a wide area of the neocortex and thalamus. Paper II indicate that the representation of tactile information in SI is dependent on distant parts of the neocortex. The findings in paper IV indicate that either a learning mechanisms or intrinsic properties of adjacent thalamic neurons have diversified their response to tactile information in order to create a richer representation of said information.

A discussion about these and other results was then held, which concluded that a distributed processing regime with hubs of functional importance would be able to explain all mentioned observations, while also having an anatomical support, while the functional localization theory would not be able to fully explain the observations. It can thus be argued that a distributed processing regime would better describe the actual functional properties of the brain, rather than the theory of functional localization.

In future studies it would be interesting to see a similar approach to measure the representation of information in different areas, but instead of tactile information study other modalities. It would also be interesting to further explore to what extent single neurons receive detailed information regarding multiple modalities.

All methods and metrics have their own set of flaws and limitations, and it is important to acknowledge that in order to facilitate discussion and the growth of our collective knowledge. It is important to continuously question previous observations and assumptions, after all according to the scientific theory it is impossible to prove a theory correct by agreement with observations, as it can always be proven incorrect by future observations (Popper, 2005). Then again, the observation claiming to disprove a theory might itself suffer from poor methodological execution or interpretations. It is thus of utter importance that a research must always be both humble and vigilant.

This line of thought is what inspired me to choose the quote at the beginning of this thesis, originally said in various forms by Daniel J. Boorstin and in the form presented

here attributed to Stephen hawking: *The greatest enemy of knowledge is not ignorance; it is the illusion of knowledge.*

Populärvetenskaplig sammanfattning på svenska

När vi vidrör ett objekt med ett finger så aktiveras ett stort antal receptorer som finns i huden på fingret. Exakt vilka receptorer som aktiveras och sättet de aktiveras på beror på en rad olika faktorer, såsom objektets form och material, hur kraftigt man tryckte och vilken del av fingret som vidrörde objektet. Aktiviteten i receptorerna skickas till nervceller där den omvandlas till en elektrisk signal som skickar vidare den så kallade taktila informationen om beröringen till hjärnan.

På vägen från receptorerna till hjärnan så passerar informationen olika strukturer i ryggmärgen och hjärnstammen innan den når en struktur i den inre delen av hjärnan som kallas för talamus, som sedan skickar vidare informationen till hjärnbarken som är det översta skiktet av hjärnan.

Exakt hur hjärnan bearbetar informationen som den får så att vi upplever att vi exempelvis rör vid ett objekt har forskare funderat på i tusentals år, men man vet fortfarande inte riktigt, dock så finns det gott om teorier. Den allra vanligaste teorin kallas för funktionell lokalisation, som säger att varje del av hjärnan ansvarar för en specifik funktion. Den säger då att om du rör något med ditt högra pekfinger så skulle den informationen bearbetas på en specifik plats i hjärnan, men om du istället använder ditt högra långfinger eller vänstra pekfinger så skulle informationen istället bearbetas på en annan specifik plats.

En annan teori brukar kallas för global informationsbearbetning och säger ungefär det motsatta som funktionell lokalisation, att informationen som skapas då ditt högra pekfinger rör ett objekt istället bearbetas utspritt över en stor del av hjärnan, och att samma sak skulle gälla för ditt högra långfinger, synen från vänster öga och alla andra funktioner du kan tänka dig.

Den här avhandlingen innehåller fyra vetenskapliga studier som har genomförts för att försöka avgöra vilken av de två nämnda teorierna om hur hjärnan bearbetar information som är mer trolig.

Den första studien kollade på hur taktil information från ett finger går att hitta i båda hjärnhalvor. Vanligtvis brukar man säga att informationen från vänster hand framförallt bearbetas i höger hjärnhalva och vice versa. Studien visade dock att informationen från både vänster och höger hand verkar finnas representerad i båda hjärnhalvor i liknande detaljgrad.

Den andra studien kollade på hur en stroke i en del av hjärnan skulle påverka närvaron av taktil information i en annan del av hjärnan. Det visade sig att en stroke i en del av hjärnbarken som enligt teorin om funktionell lokalisation inte skulle vara relevant för taktil informationsbearbetning påverkade nervceller i den del av hjärnbarken som teorin säger ska vara ansvariga för taktil information, så att de blev sämre på att skilja mellan olika typer av simulerad beröring.

I den tredje studien kollade på hur taktil information fanns representerat i talamus. Teorin om funktionell lokalisation säger att även talamus är indelad, så att taktil information färdas genom ett specifikt område av talamus, och att informationen från ett visst finger färdas genom en liten del av det området. Studien visade dock att taktil information från ett finger finns representerad i detalj över stora delar av talamus.

Den fjärde och sista studien kollade på hur nervceller som ligger precis bredvid varandra i talamus beter sig i förhållande till varandra. Nervceller får information från ett stort antal andra nervceller, som nervcellen är kopplad till genom strukturer som förgrenar ut sig från nervcellen kallat dendriter, och som lämpligt nog brukar kallas nervcellen dendritträd. Två nervceller som ligger precis bredvid varandra kan antas ha dendritträd som överlappar till stor grad, vilket betyder att de skulle ta emot ungefär samma inkommande information. Om de skulle ta emot samma information skulle man kunna anta att de skulle bete sig på ungefär samma sätt relativt varandra. Dock så visade studien på att olika par av intilliggande nervceller hade helt olika inbördes beteende, vilket tyder på att nervcellerna i ett närliggande par antingen i grunden har olika egenskaper, eller att de genom inlärning har valt att prioritera olika delar av den inkommande taktila informationen.

Sammantaget så visar de fyra genomförda studierna att teorin om global informationsbearbetning verkar vara mer trolig än den om funktionell lokalisation. Detta stödjs av ett stort antal andra studier som har visat på att olika funktioner verkar vara utspridda över stora delar av hjärnan, samt av studier som visar på ett stort antal möjliga kopplingar mellan olika delar av hjärnan som ger information ett enkelt sätt att ta sig från vilken plats i hjärnan till vilken annan plats som helst.

Avhandlingen avslutas med en diskussion angående olika begränsningar i metoder som ofta används då man vill studera hjärnan, och hur det är viktigt att vara medveten om de begränsningarna då man försöker tolka resultaten från en studie.

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The experimental animals

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Thalamocortical interactions and the nature of higher function

Anders Wahlbom graduated from Lund University with a Master of Science in Engineering Nanoscience in 2016 and has since then pursued his PhD studies in the lab Neural Basis of Sensorimotor Control at the Department of Experimental Medical Science of Lund University. His research has been centered around the flow and processing of tactile sensory information in the neocortex and thalamus, through neurophysiological experiments.

The thesis in your hand contains a stepwise presentation of the tactile sensory system from the commonly accepted viewpoint of functional localization, but at each step findings suggesting other functional principles are presented. This is followed by a discussion about different functional principles, and how the choice of experimental and analytical methods might bias results and conclusions.

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