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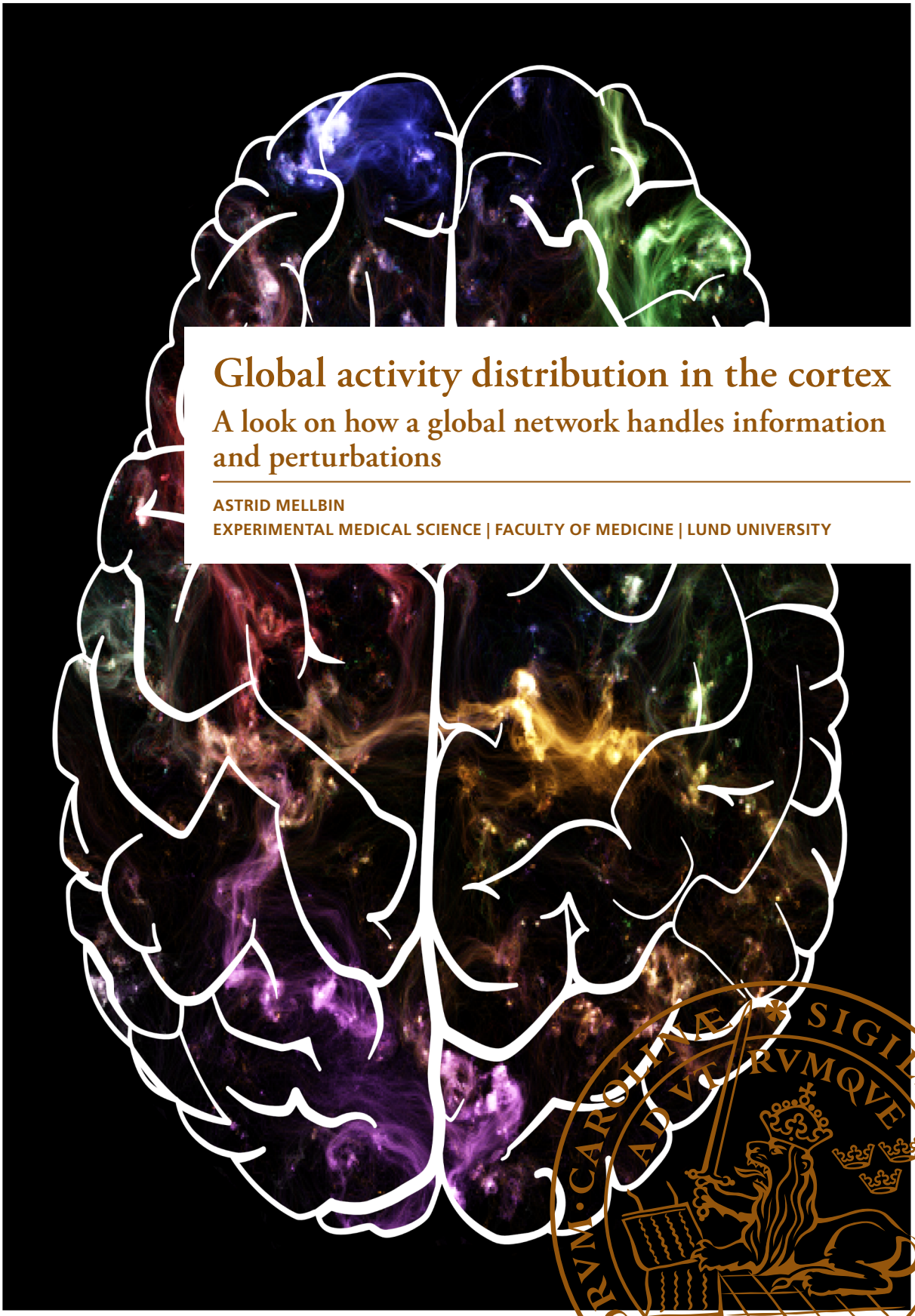

Global activity distribution in the cortex

A look on how a global network handles information and perturbations

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EXPERIMENTAL MEDICAL SCIENCE | FACULTY OF MEDICINE | LUND UNIVERSITY

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Global activity distribution in the cortex

Astrid Mellbin graduated from the medical program at Lund University in 2020. After this she began full time PhD studies at the lab Neural basis of sensorimotor control. Here she has investigated cortical activity and how it reacts to sensory stimulation and pharmacological perturbations.

In this thesis you will find an introduction to the neural basis for the sensation of touch and how we study cortical activity. Results from investigations on how the cortical network processes sensory stimulation and pharmacological interventions is presented as well as a discussion on the best way to study activity in the cortical network. And in the final part, what such studies may tell us about cortical processing of sensory information.

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Abstract:

Studies on cortical function have been a cornerstone in research trying to understand our brains for a long time. For many years now a basic feature of cortical processing has been the idea of a functional localization, with different areas or even neurons in the cortex having clear, individual, functions. This idea has been challenged from the outset, and with new methods to study the cortex the idea of functionality in the cortex depending on a globally interconnected network has gained support.
In this thesis both modern and more traditional analysis methods were used to examine how cortical activity is distributed across multiple cortical areas during the processing of somatosensory stimulus. Investigations were also made on how the distribution was affected by D-amphetamine. For this, an experimental set-up using anesthetised rats was used in which neural activity was recorded using Electrocorticograms (ECoG) in eight cortical areas simultaneously. Data during spontaneous activity, during sensory skin stimulation, and after D-amphetamine administration, was analysed with methods for dimensionality reduction, classification learning and more traditional frequency analysis.
It was observed that ECoG data from spontaneous activity and activity during stimulation could be separated based on its activity distribution. This separation persisted when data containing an evoked field potential from the stimulation was excluded. Based on the analysis of activity distributions, ECoG data could also be separated based on if D-amphetamine had been administered or not. Finally, investigations found that there appear to be set internal ranges of globally preferred frequencies in the cortex. These remained consistent during external sensory stimulation but could be disrupted by D-amphetamine. These results are discussed in the context of a globally interconnected network in the cortex, where the processing of external inputs is distributed across several cortical areas.

Key words: Somatosensory, Tactile, Distributed information processing, Neocortex, Function

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To my daughters
You are the true wonders of this world

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Preface

This thesis aims to give insight into how a cortex with a globally interconnected network and a global functionality and processing of stimulation can be studied and how such a network operates during spontaneous activity in comparison to during somatosensory stimulation and pharmacological intervention.

The first section of the thesis serves as an introduction, containing a brief overview of the pathway from touch receptors to the cortex. After that follows a summary of the cortical structure and the ideas of a localized and a global functionality in the cortex. It then moves on to explain how activity distributions can represent cortical activity and the role of oscillations in cortical activity. In the last part of the first section an overview of the effects of amphetamine on the central nervous system and different ways to study the cortical activity is presented.

In the second section of this thesis, a brief overview of the methods that were used in the included papers is presented. The third section contains a brief summary of the aims and results of each of the original research papers that are included in the thesis. For more information on the main methods that were used, please refer to paper II, as this methodology papers contains step-by-step instructions for the methods that were used in paper I and is the basis of the method for paper III as well. For further information on the three original research papers, please refer to paper I, III and IV.

The fourth and last section of the thesis contains a discussion of the results from the three original research papers and their implications. It also contains a discussion of the methods that were used. This section touches on some of the problems in studies of the cortex. It also presents possible interpretations of the results and their place in relation to other findings. The thesis concludes with a discussion on hurdles to overcome for brain research and potential future lines of investigation.

List of original papers

I. **Astrid Mellbin,** Udaya Rongala, Henrik Jörntell, Fredrik Bengtsson. ECoG activity distribution patterns detects global cortical responses following weak tactile inputs. *iScience, 2024, 27 (4), 109338.*

II. **Astrid Mellbin**, Udaya Rongala, Fredrik Bengtsson. Protocol for extracting and evaluating activity distributions in rat electrocorticograms with principal component analysis and k-nearest neighbor. *STAR protocols, accepted for publication*

III. **Astrid Mellbin**, Henrik Jörntell, Fredrik Bengtsson. D-amphetamine alters the dynamic ECoG activity distribution patterns in the rat neocortex. *Manuscript*

IV. **Astrid Mellbin**, Oscar Tuvesson, Fredrik Bengtsson. Possible preferred global frequencies in the cortex are affected by D-amphetamine but not by sensory stimulation. *Manuscript*

Abbreviations

ECoG	Electrocorticography
CNS	Central nervous system
VPL	Ventral posterolateral nucleus
S1	Primary somatosensory cortex
M1	Primary motor cortex
A1	Primary auditory cortex
V1	Primary visual cortex
fMRI	functional magnetic resonance imaging
EEG	Electroencephalography
kNN	k-nearest neighbour
PCA	Principal component analysis
PC	Principal component
CWT	Continuous wavelet transform
FFT	Fast Fourier transform

Abstract

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In this thesis both modern and more traditional analysis methods were used to examine how cortical activity is distributed across multiple cortical areas during the processing of somatosensory stimulus. Investigations were also made on how the distribution was affected by D-amphetamine. For this, an experimental set-up using anesthetised rats was used in which neural activity was recorded using Electrocorticograms (ECoG) in eight cortical areas simultaneously. Data during spontaneous activity, during sensory skin stimulation, and after D-amphetamine administration was analysed with methods for dimensionality reduction, classification learning and more traditional frequency analysis.

It was observed that ECoG data from spontaneous activity and activity during stimulation could be separated based on its activity distribution. This separation persisted when data containing an evoked field potential from the stimulation was excluded. Based on the analysis of activity distributions, ECoG data could also be separated based on if D-amphetamine had been administered or not. Finally, investigations found that there appear to be set internal ranges of globally preferred frequencies in the cortex. These remained consistent during external sensory stimulation but could be disrupted by D-amphetamine. These results are discussed in the context of a globally interconnected network in the cortex, where the processing of external inputs is distributed across several cortical areas.

Introduction

Research on the brain is a field in steady movement and progress. With advances in our ability to record from specific neurons and study specific receptors we are constantly learning more about how different parts of the brain reacts to various conditions. But it is important to remember that each individual neuron is a part in the larger, complex, brain network. Developing new ways to study and analyse the whole network is still a process. Given a network of the size and complexity as the brain it is currently not possible to record activity in the whole network with both a high temporal and spatial resolution. At the same time there is a risk of overlooking important nuances when extrapolating on general functionality from information gathered from only part of the network. In this thesis I hope to present a case for why it is so important to consider the brain as a complete network, both when considering how external inputs are processed and when investigating the cause and effect of diseases and drugs that disrupt the internal network.

The path from touch to sensation

Before investigating the effect of touch on the cortical activity, it is good to understand how the signal goes from the periphery to the cortex. The pathway from the stimulation of the skin of the paw, to the reaction of the mechanoreceptors, to the dorsal column nuclei, thalamus and finally to the cortex (Fig. 1A).

Mechanoreceptors

In the glabrous skin we have four different mechanoreceptors reacting to touch and vibration in different ways. These four can be divided into having either rapid or slow adaptation, and either small or large adaptive fields (Abraira & Ginty, 2013; Knibestöl & Vallbo, 1970). Merkel disks and Ruffini corpuscles are slow adapting. Merkel cells have a small receptive field and react to indentation and touch, while Ruffini corpuscles have a large receptive field and react to the skin stretching (Abraira & Ginty, 2013; Brodal, 2010; Johansson & Flanagan, 2009; Knibestöl & Vallbo, 1970). The rapidly adapting mechanoreceptors are known as Meissner corpuscles and Pacinian corpuscles. The Meissner corpuscles have a

small receptive field reacting to skin movement and vibrations below 100 Hz, while the Pacinian corpuscles have a large receptive field and react to vibrations over 100Hz (Abraira & Ginty, 2013; Brodal, 2010; Johansson & Flanagan, 2009). Together, these four transmit the properties of the objects we touch, and send the information to nucleus cuneatus and nucleus gracilis via the dorsal columns (Abraira & Ginty, 2013).

The dorsal column and its nuclei

Fibres from the mechanoreceptors are the first-order neurons in this relay and join the fibres from the proprioceptors in the dorsal column. Entering through funiculus posterior fibres from the lumbosacral level will run in fasciculus gracilis and fibres from a cervical and thoracic level will run more lateral in fasciculus cuneatus. The fibres are thought to first organize themselves segmentally, and as they ascend, gain a somatotopic organization, running up to the dorsal column nuclei (Brodal, 2010; Johnson Jr. et al., 1968; Nord, 1967). However, segregation based on the modality appears to also occur, while having a rough somatotropic organization within each modality (Loutit et al., 2021; Niu et al., 2013; Uddenberg, 1968). The fibres will run ipsilateral to the stimulation until the medulla oblongata.

Once in the medulla, afferents from the lower limbs and trunk will end up in nucleus gracilis, while those from the upper limbs and trunk ends up in nucleus cuneatus. While first thought of as simple relay stations to the thalamus, they have later proven to be part of the processing of information (Loutit et al., 2021; Therman, 1941). Both nucleus cuneatus and gracilis have been found to have a role in sensorimotor integration, and individual neurons in nucleus cuneatus have been found to be able to differentiate varying stimulus, in support of stimulus processing starting at this level (Berkley et al., 1986; Jörntell et al., 2014). Processing of sensory stimuli have also been found to occur already in the dorsal column, indicating that pure relays of neural activity are few if any (Browne et al., 2024; Koch et al., 2018).

Thalamus

The thalamus is a group of nuclei positioned in the diencephalon. Most information passing between the body and the cortex will pass through and interact within different parts of the thalamus. Apart from being a relay for information between the cortex and the lower parts of the central nervous system (CNS) it also has a substantial influence on consciousness and attention, by affecting the general level of activity in the cortex. However, the thalamus is not simply projecting to the cortex, it also receives projections from the cortex to a high degree, establishing the basis of the thalamocortical loop (Brodal, 2010).

Following the signal from the mechanoreceptors, after reaching nucleus cuneatus and gracilis the first-order neurons carrying the signal will synapse with second-order neurons. These second-order neurons will cross the midline and run in the medial lemniscus to the ventral posterolateral nucleus (VPL) in the thalamus (Brodal, 2010). From VPL the information will then continue up to the primary somatosensory area (S1) in third-order neurons and is traditionally thought to synapse in layer IV of the S1. Similar to the dorsal column nuclei, the thalamus was long considered simply a relay station to the cortex (Jones, 2012). And again, like the dorsal column nuclei, that was later found to be a simplification, as cells in the thalamus have been found to be able to differentiate between different tactile stimulations, as well as receiving both recurrent information within the thalamus and descending information from the neocortex, which then modulate the ascending information (Adams et al., 2002; Alitto & Usrey, 2003; Sherman, 2016; Wahlbom et al., 2021). In addition to this, thalamus has been found to send information to several different layers of the neocortex, and nuclei like VPL project to multiple different primary sensory areas in the cortex (Constantinople & Bruno, 2013; Henschke et al., 2015).

Neocortex

The neocortex makes up the majority of the grey matter in the cerebrum, and is traditionally thought of as being divided into areas, each with a specific functionality (Brodal, 2010). The theory of a brain divided into functional subunits is often attributed to Broca's observations on patients with aphasia (Broca, 1861). It has since then gained huge traction and many observations and studies in support of it has been made, which speak of a brain where input and output of different modalities arrive and arise in very specific areas. In this manner the neocortex is divided into the primary somatosensory, visual, auditory and motor area, as well as associative areas. These areas are often considered to be further divided by which part of the body it relates to, or the specifics of the stimulation (Desmurget & Sirigu, 2015; Felleman & Van Essen, 1991; Penfield & Boldrey, 1937). Brodmann postulated an additional division of the neocortex based on the histology of different areas, with 52 specific subareas, commonly known as Brodmann's areas (Broodmann & LJ, 2006). As an example of this, the S1 can be divided into Brodmann area 1, 2, 3A and 3B, with area 1 and 3B being considered as mainly involved in the processing of signals from skin receptors, specifically mechanoreceptors. Area 2 and 3A are instead considered to mainly deal with information from proprioception. As well as being divided into these distinct functional and morphological areas, the neocortex is also considered to be comprised of six different layers based on its morphology (Broodmann & LJ, 2006). Based on the cells in each layer some thoughts on their individual roles exists. Layer II and IV appear to mainly receive afferents, while layer III and V contain mainly efferents, with layer III primarily being connected to other parts of

the cortex and layer V to subcortical nuclei. Layer VI also contain mostly efferents, connected to the thalamus (Brodal, 2010).

The division of functional subunits and layers in the cortex was in a way combined by Mountcastle, who proposed a system where columns, small sections of the neocortex spanning all six layers, share a receptive field and functional properties. This led to the idea that such columns made up the basic functional unit in the cortex (Mountcastle, 1955; Mountcastle, 1957). If the cortex in fact can be divided into columns with distinct functional properties have been debated however, and a specific microcircuit that would correspond to a cortical column has not been found (Douglas & Martin, 2004; Horton & Adams, 2005).

In this view of the neocortex, information is considered to be processed by being relayed to new areas, with new responsibilities, integrating information from several areas and becoming more complex as it moves along. Thus, the traditional view of somatosensory processing is of afferents from thalamus being received in layer IV of the S1, and what specific part of the S1 which receives it will be dependent on the type, properties and location of the original stimulus. In the S1 the information will start being processed and then relayed to other areas. From layer II and III projections will go to the primary motor cortex (M1), the secondary somatosensory area (SII) and Brodmann's area 5 and 7. Area 5 and 7 will further the information to motor areas, while SII will relay the information to the amygdala, hippocampus and temporal lobe. Some information will also go via layer V from the SI to the insula for integration with other sensory modalities (Fig. 1B). This shows how the traditional view of information processing starts with very specialized areas to then continue to new areas with their own specialization.

Such a division of functional localization has long been the leading theory for how the neocortex, and the brain as a whole, operates. However, parallel to this, other theories have existed and have recently grown in prevalence.

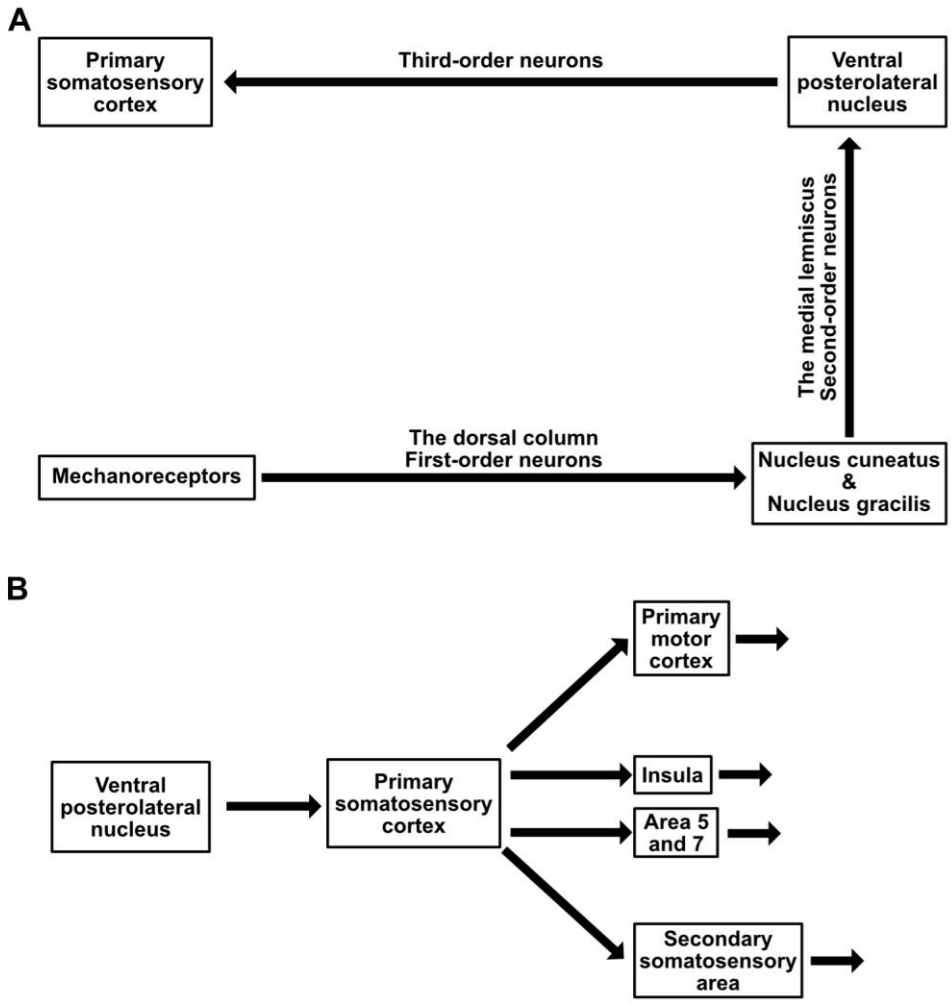

Fig 1. Schematics of connective paths
A) Schematic showing the path from mechanorecptors to the primary somatosensory cortex. The axons of first-order neurons run in the dorsal column from the mechanoreceptors up to the dorsal column nuclei. There they synapse and cross over the midline to the contralateral side, before the information continues in the axons of second-order neurons up to the ventral posterolateral nuclei in the thalamus. There they synapse with third-order neurons that continue up to the primary somatosensory cortex. B) Schematic showing the traditional hierarchical view of the functional path for somatosensory information. Signals arrive from the ventral posterolateral nucleus to the primary somatosensory cortex. From there signals are relayed to the secondary somatosensory cortex, the primary motor cortex, Brodmann's area 5 and 7 and the insula. Each of these areas then transmit the signal further to other cortical areas where integration with other modalities occures.

A brain with a globally interconnected network

As research on the brain moves forward and our understanding of it has evolved, there has been a shift of our fundamental understanding on how the brain operates. With this, the view of the brain as an organ with a functionally localized organisation has been challenged, as more and more studies point to the brain being an organ with a globally interconnected network and a globally integrated processing. In line with this, tactile input has been observed in several parts of the thalamus and sensory nuclei in the thalamus have been found to project to several different primary sensory areas (Henschke et al., 2015; Wahlbom et al., 2021). Studies have found that groups of neurons are better at decoding input than a single neuron and that neurons will decode both ipsilateral and contralateral input but at different timescales (Enander et al., 2019; Genna et al., 2018). Furthermore, calcium imaging has shown widespread cortical activity during motor tasks, learning and visual tasks (Nietz et al., 2022; Stringer et al., 2019). Similarly, other methods have shown responses to visual input, vestibular activation and sensory stimulation across the cortex (Findling et al., 2023; Frostig et al., 2008; Rancz et al., 2015).

This is not only a new idea, historically there have long been arguments made for a less functionally divided cortex. Brown-Séquard argued against the idea of Broca's area being responsible for language, as he had observed aphasia in patients with lesions in several different areas (Brown-Séquard, 1877). The idea of the brain relying on schemas to function and those schemas being unable to function with a change in the network after lesions was raised in 1911 (Head & Holmes, 1912). And in 1917, Franz argued that the fact that function could be regained with rehabilitation was evidence against a strict localized functionality (Franz, 1917).

More recent evidence also supports that in a brain with a globally interconnected network the effect of local perturbations would be wide-spread. Stroke in a distant area has been shown to affect the processing of sensory information (Wahlbom et al., 2019). Less destructive perturbations in the brain will also have an effect, as remote electrical perturbations have been seen to influence the response to tactile input, likely due to changing the internal state of the network (Etemadi et al., 2022).

The idea is of a network with a global functionality, where function is the result of the processing in an integrated network as whole, rather than a network with a localized functionality. This means that rather than a signal following a set path between specific regions in a hierarchical manner as described above (Fig. 1B), widespread areas of the cortical network are connected in a distributed manner. However, this does not have to mean that each individual neuron is involved in every single process in the brain. Indeed, that would most likely be a huge drain of

energy and lead to redundancy. Another, perhaps more likely explanation is that while not all neurons are involved in every process, each process is, to a varying extent, distributed across the cortex, with hubs or regions carrying a higher computational load but still relying on integration with other areas. Studies utilizing diffusion tensor imaging (a technique employing magnetic resonance imaging to reconstruct traces of white matter in the brain) have identified hub regions that are highly connected (van den Heuvel et al., 2012). These hubs, detectable by methods of graph theory used to summarize the network, have been suggested to be central to communication and integration in the brain. They also appear to be involved across a wide range of cognitive functions (van den Heuvel et al., 2012; van den Heuvel & Sporns, 2013). However, with the high connectivity and being central in the network functionality they would become susceptible to causing disconnection and dysfunction if altered or damaged. Indeed, abnormalities in hub regions, as well as a reduction in integration across the cortical network have been found in patients with schizophrenia (Lynall et al., 2010; van den Heuvel et al., 2010). These findings of functional connectivity have been to some degree correlated with the presence of white matter tracts, but these structural connections do not fully explain the functional connections and their ability to shift (Bullmore & Sporns, 2009; van den Heuvel & Hulshoff Pol, 2010). Another approach to quantifying and describing the perplex system of neural networks like the cortex is to use a vector field analysis with high dimensionality to allow for the inclusion of a high number of network properties. This allows for the circumvention of the problems that arise when using dimensionality reduction on a highly complex network (Szeier & Jörntell, 2025).

Signal frequencies in the cortex

Oscillations on different levels in the CNS appears to be one of the basic principles of operations in the network (Lampl & Yarom, 1997; Pisarchik & Hramov, 2023; Stark et al., 2022). Oscillations can be found across membranes or in the synchronous activity of groups of neurons. The oscillators in the brain appear to have features of both harmonic and relaxation oscillators. Thus, it gains the advantage of the predictable long-term behaviour of harmonic oscillators, which output sinusoidal signals, at a macroscopic level. While at the same time allowing synchronisation through the spiking at a neuronal level which resembles that of relaxation oscillators, which can abruptly change the output resulting in a saw tooth or square waveform in the signal (Glass, 2001; Somers & Kopell, 1993). The frequencies of brain oscillations can be measured and perhaps tell us something about the network operations. Thus, examining the frequency of cortical activity might help the understanding of how different parts of the nervous system interact and how they process stimuli.

At the neural level, individual neurons have been found to have resonance frequencies, based on membrane properties, which affect how the neurons will respond to different sensory stimuli (Binini et al., 2021; Gupta et al., 2000; Marshall et al., 2002; Puil et al., 1994; Thomson & West, 2003). Such an inherent resonance on a neuronal level could shape responses and act as a gate-keeping mechanism, giving rise to a band-pass filtering effect. In line with this idea, cortical interneurons have been suggested to be involved in shaping cortical frequencies via such band-pass filtering effects, as interneurons have been found to have inherent preferred frequencies shaping their responses to stimulation (Buzsáki & Chrobak, 1995; Buzsáki & Draguhn, 2004; Gupta et al., 2000; Thomson & West, 2003). At a network level, intracortical circuits have also been shown to favour certain frequencies, and the thalamocortical loop as well as nucleus cuneatus might be part of shaping the frequencies present in the cortex (Hahn et al., 2014; Jörntell et al., 2014; Pisarchik et al., 2019; Rongala et al., 2018; Steriade, 2000; Vanneste et al., 2018).

With so many mechanisms working together to shape the frequency content in the cortex, and resonance mechanisms appearing to exist at most levels of organisation, the idea of a cortical resonance frequency is tantalizing (Manuylovich et al., 2024; Pisarchik & Hramov, 2023; Roach et al., 2018; Stark et al., 2022). Global cortical activity frequencies and different aspects of resonance have been suggested as an important mechanism for the connection of different cortical areas in an interconnected cortical network. A theory has been proposed of global slow wave frequencies synchronising more local, faster frequencies, thus allowing for the integration of processing and information from widespread areas (Csicsvari et al., 2003; Sirota et al., 2003). It could be that the number of band-pass filtering mechanisms present in the CNS serves to keep the global cortical frequency at these slow wave frequencies to allow such synchronization.

A different perspective on the possibility of a global resonance is that it cannot exist due to the inherent complexity of the brain rhythms. There appears to be a lack of individual clear rhythms on a global scale, with the global activity instead consisting of complex waves being made up of oscillations of several different frequencies (Steriade, 2001). It is also possible that the neuronal network utilize a system of stochastic resonance to increase global signalling as needed, where a specific level of noise correlates with peak processing ability and robustness of the network (McDonnell & Abbott, 2009).

How amphetamine affects the network

Amphetamine is known to have effects on several monoaminergic neurotransmitters, such as noradrenaline, dopamine and serotonin, as well as on

acetylcholine. By directly interacting with monoaminergic cells it can increase the levels of monoamines (Carvalho et al., 2012; Cunha-Oliveira et al., 2008; Sulzer, 2011). Amphetamine also increase the release of acetylcholine in the cortex (Arnold et al., 2001). These neurotransmitters are present throughout the cortex and thalamus (Stratmann et al., 2018; Tohyama & Takatsuji, 1998). Thus, disruptions of these systems will have a widespread effect in the CNS.

Amphetamine has a use in the treatment of several conditions, for example ADHD and narcolepsy. In ADHD it improves executive function and enables more focused attention, likely due to an effect on both noradrenergic and dopaminergic systems (Arnsten, 2006). However, it also carries the risk of dependency. When used as a drug it can cause symptoms like ataxia, paranoia, and increased sympathetic stimulation among others, showing that it affects several different modalities (Connell, 1966; Heal et al., 2013). Long-term exposure also causes a dopamine depletion and has been suggested to be associated with the development of Parkinson's disease (Cunha-Oliveira et al., 2006; Garwood et al., 2006). Studies have shown that amphetamine modulates synaptic plasticity in the motor cortex affecting the learning of motor tasks and recovery after brain lesions. Other studies have shown that while amphetamine increased short-term neuronal excitability, it in fact supressed long-term plasticity (Bütefisch et al., 2002; Gilmour et al., 2005; Ziemann et al., 2002). Amphetamine has also been observed to reduce both REM and non-REM sleep, as well as reducing low frequencies in EEG activity (Authier et al., 2014).

Beyond the direct effects on individual cells and specific parts of the thalamocortical loop, amphetamine has also been shown to affect the connectivity of areas beyond the cortex and thalamus. It has been found to increase the functional connectivity between the nucleus accumbens and medial frontal regions of the cortex, between the putamen and the left inferior frontal gyrus, and cause an auditory-sensorimotor-thalamic functional hyperconnectivity (Avram et al., 2024; Weafer et al., 2020). But amphetamine also appears to reduce the functional connectivity in the cortico-striatal-thalamic network, the default mode network and in the salience-executive network (Schrantee et al., 2016). It also appears to reduce the functional connectivity between nucleus accumbens and several other areas, the basal ganglia, the medial prefrontal cortex, the temporal cortex and the subgenual anterior cingulate cortex (Ramaekers et al., 2013; Weafer et al., 2020).

Given the number of neurotransmitters affected, the wide range of symptoms after administration and the many areas affected, amphetamine truly has a great impact on the network of the brain, which makes it a good candidate for the study of global effects on the cortical network.

Brain activity can be visualized as activity distributions

A wide range of methods have been used to record and describe patterns and trends in activity across several areas in the cortex. One such method is to visualise the activity distributions of the cortical activity.

Activity distribution as the term is used in this thesis describes the dispersion of cortical activity in a multidimensional space, based on the recorded activity from each area. A comparable approach to study cortical activity at the level of individual neurons is to examine the elicited response patterns found when repeating a stimulus. These two methods could allow for analysis on how activity during sensory stimulation might differ from spontaneous activity. They also have the potential to allow for investigation into how underlying states of the cortex might affect different types of activity.

In the case of response patterns, studies on intracellular single cells recordings during peripheral electrical stimulation of the skin have shown that there appear to be a set of specific response patterns to a specific pattern of stimulation. These response patterns appeared to depend on the state of the subnetworks related to the recorded neuron. This is supported by the finding that new response patterns could be induced by electric cortical perturbations in remote areas (Etemadi et al., 2022; Norrlid et al., 2021).

For activity distributions, studies on a population level using electrophysiological recordings and calcium imaging have found that there appears to exist set activity distributions during spontaneous activity. These activity distributions shift during sensory stimulation to inhabit a subset of the activity distribution of the spontaneous activity (Luczak et al., 2009; Stringer et al., 2019). This might be a reflection of the response patterns mentioned above, that when recorded from many neurons at once they change the activity distribution from that during spontaneous activity.

Interestingly, another study observed that the change in activity distribution can remain after the end of the stimuli, in a manner similar to working memory (Kristensen et al., 2024). This could be an indication that a change in activity distribution is not only caused by the firing of individual neurons in specific patterns as a response to sensory stimuli but also represent a lasting change in firing patterns or network organization.

Studies like these may provide an insight into the most common and preferred activity distributions in the cortex. It is possible that the most common activity distributions reflect the normal processing of the cortex, where variations of these distributions might relate to spontaneous activity, different sensory input or motor output. Less common activity distributions could then be signs of pharmacological

perturbations or relate to neurological diseases that affects the normal cortical processing.

Recording cortical activity

In order to match the aims of a specific investigation when studying the neural activity of the brain, one needs to consider what level of resolution is required in relation to what extent the recorded data should represent network activity. The basic principle however remains, that what is measured is the degree to which neurons in the network are active. The available methods vary and come with their own advantages and limitations.

Single cell recordings

At the level of single cell recordings, measurements can range from the movement of ions across the membrane in a single ion channel with patch clamp technique, to recording the number of action potentials generated using extracellular electrodes (Hubel, 1957; Kodirov, 2023; McNaughton et al., 1983; Neher & Sakmann, 1992).

While recordings from individual neurons using patch clamp will give a high resolution, there are limits to the number of neurons that can be recorded from simultaneously without damaging the brain tissue. Using such techniques will thus only give insight into a small part of the network. Thus, these techniques are very useful when investigating neuronal properties and activity, but less so when investigating the integration and distribution of signals across the cortex. A recent advance in single cell recordings is the development of probes that allows for a single recording electrode to register from thousands of neurons simultaneously with the same resolution as in classical single cell recordings (Jun et al., 2017). This is a significant advancement for the recording and understanding how groups of neurons interact and process stimuli together. However, in the vast network of the cortex, the recorded neurons will still only represent a small fraction of the whole.

Global recordings

With global techniques, it is often a case of sacrificing either temporal or spatial resolution in return for an increase in the other. Both calcium imaging and functional magnetic resonance imaging (fMRI), two common methods for investigating activity in the brain as a whole, have a very high spatial resolution, but a lower time resolution. Electroencephalography (EEG) and ECoG instead have a lower spatial resolution, as they will collect data from a bigger area in a

single recording trace. Instead, they offer a higher temporal resolution. What is recorded also differs between these methods.

Functional magnetic resonance imaging

A common way to study global cortical activity in humans is fMRI. The principal behind this method is the fact that all process of signalling in the brain depend on the use of energy. When increasing the energy requirement more oxygen will be needed. As oxygen stored in the nearby capillaries is consumed the vessels will dilate. This increases the local blood flow in the area and changes the concentration of oxygenated blood, both of which can be detected using magnetic resonance imaging (MRI). Most fMRI are based on the latter mechanism, the change in oxygenation level, as this has a higher degree of sensitivity (Glover, 2011).

However, the analysis of the resulting signal can be difficult, as it contains noise, sometimes larger than the signal that is to be investigated. Thus, statistical analysis are needed to examine the effects and several steps of pre-processing are required for the final analysis (Glover, 2011; Worsley et al., 2002).

fMRI is useful for its spatial resolution, which is relatively high and for being non-invasive. It also allows for the recording of activity in deeper brain structures. However, it suffers from a low temporal resolution due to measuring the comparatively slow change in blood oxygenation level, as well as a need for more pre-processing, which risks changing minor but important parts of the signal.

Calcium imaging

A fairly recently developed technique for measuring cortical activity is calcium imaging. It is a method for visualizing neural activity by using fluorescent molecules that respond to calcium. As calcium is involved in many aspects of neuronal signalling, monitoring the concentration allows for the investigations on neuronal activity. With improvements of genetically encoded calcium indicators, calcium imaging has become a viable method for *in vivo* studies on a mesoscopic level, known as wide-field calcium imaging.

As with the fMRI technique, calcium imaging has a high spatial resolution, but a lower temporal resolution, as it depends on the kinetics of the calcium indicator. Analysing the recorded calcium imaging data can be challenging as even defining the recorded regions can pose a challenge (Nietz et al., 2022).

Electroencephalography and electrocorticography

EEG and ECoG are two methods that are similar in principle and execution, although there are some differences. EEG is non-invasive with electrodes placed on the scalp and ECoG is invasive with electrodes placed directly on the surface of the cortex. In contrast to fMRI and calcium imaging, these techniques measure the

electrical activity created by neuronal activity directly. The extracellular changes in potential caused by ions moving across membranes of many neurons in concert create what is known as local field potentials. The potentials measured with EEG/ECoG electrodes are versions of local field potentials, modified by the distance from the source, and in the case of EEG by the conductance across the tissues between the brain and the electrodes (Buzsaki et al., 2012; Müller-Putz, 2020). A common analysis method for signals recorded with EEG/ECoG is frequency analysis. Such investigations have correlated different signal frequencies to different functions and states. During spontaneous EEG/ECoG the state of the network has been correlated to the prominent frequencies. While alpha (8-13 Hz), beta (13-30 Hz) and gamma (>30 Hz) oscillations are associated with various levels of wakefulness and alertness, delta (<4 Hz) and theta (4-8 Hz) oscillations are typically associated with levels of sleep and drowsiness (Müller-Putz, 2020).

EEG and ECoG both have low spatial resolution, as the recorded data will be a combination of all neurons firing within the recording range of the electrode. Thus, there are limitations to how much EEG and ECoG recordings can tell about the details of the network structure and its interconnectivity. Instead, it can provide information about how the network as a whole operates with a high temporal resolution, which is of interest when examining the response in a short time window following a short sensory stimulus.

Methods

Overview of the study design

All experiments were performed in an experimental set-up with anesthetised rats. The same recording set-up and basic stimulation protocol was used for all data collection (papers I, III-IV). In paper III and IV, part of the data was recorded after the administration of D-amphetamine. The recording set-up is described in the methodology paper (paper II) in this thesis. The analysis method described in paper II is the one used in paper I to investigate activity distributions. The data analysis in paper III is, with the exception of the frequency analysis, based on the same method. Paper IV instead focuses on signal processing to analyse the frequency content of the cortical activity across all eight recording electrodes. Details for the methods can be found in each paper, and a step-by-step protocol for the method in paper I can be found in the related methodology paper, paper II.

Experimental set up

Animal surgery

Adult male Sprague-Dawley rats were used for the three original research papers. Data collection was executed in such a way as to allow the data to be used in more than one paper to reduce the number of animals needed.

Anaesthesia was initially established using isoflurane (3%, mixed with air) for 60-120s. After initial anaesthesia, it was maintained using a ketamine/xylazine mixture. The animals remained anaesthetized for the full duration of the experiment and were euthanised upon completion of the experimental protocol. A femoral vein catheter was surgically inserted to enable a continuous IV drip of the ketamine/xylazine mixture (ketamine:xylazine ratio of 20:1, initial ketamine dose of 5mg/kg). In the experiments including D-amphetamine administration a second femoral vein catheter was inserted on the opposite side, to allow for drug injection without interrupting the flow of anaesthetics. The level of anaesthesia was continuously monitored throughout the experiment.

After the preparatory surgery, the rats were mounted in a stereotaxic frame to immobilize the head. After accessing the skull, four 5x5mm craniotomies were performed to give access to the eight recording areas. The craniotomies were performed bilaterally. Craniotomies were placed over the sutura coronaria to give access to M1 and S1, and rostrally of the sutura lambdoidea to give access to the primary visual cortex (V1) and the primary auditory cortex (A1) (Fig. 2A). To avoid the tissue drying, a cotton and agar pool was built around the skull and filled with 37°C paraffin oil. The dura was cut so that it would lie flat and cerebrospinal fluid could escape, aided by cotton drains. After recordings were completed, the animals were euthanized using a lethal dose of pentobarbital. Death was confirmed by the lack of brain activity and sustained loss of breathing.

Recordings

The ECoG recordings were made with silver ball electrodes (Ø 250 µm). Two were placed in each craniotomy, one on the surface of each recording area. In total, eight recording electrodes were used, four on each hemisphere. Two grounding electrodes were placed in the neck muscle. The signal was passed through CED 1401 mk2 hardware to Spike2 software (Cambridge Electronic Design (CED), Cambridge, UK) via a Digitimer NL844 pre-amplifier with low frequency cut off at 0.1Hz and gain x1000 and a NL820 isolator (Neurolog system, Digitimer) with gain x5, which digitized the data at 1kHz. Recordings were all kept under 8 hours from initial anaesthesia to the animal being euthanized.

Pairs of intracutaneous needles inserted in the skin of the left forepaw and right hind paw were used for electrical stimulation (Fig. 2B). Periods of stimulation consisted of a single pulse train (pulse intensity 0.5mA, pulse duration 0.14 ms) lasting for 5 minutes at a time, with varying frequencies of 0.3, 0.5, 1-6 Hz. Periods with stimulation frequencies of 0.3-5Hz were used for paper I and III, while all stimulation periods, including those with a stimulation frequency of 6Hz, were used in paper IV. Electrical skin stimulation will activate the mechanoreceptors in a more synchronous manner than natural somatosensory stimulus. However, due to the conduction velocities of the different fibres not matching, the synchrony will be broken already at the level of nucleus cuneatus (Abraira & Ginty, 2013; Bengtsson et al., 2013; Oddo et al., 2017).

The stimulation was applied alternately to the forepaw and hind paw, with each frequency applied once to each location. Each period of stimulation was separated by 2 minutes of spontaneous activity (Fig. 2C). For the experiments used in paper III and IV the stimulation protocol was performed in the exact same manner before and after the administration of D-amphetamine. The pulse intensity for the stimulation was chosen to be between the activation threshold of tactile afferents and the threshold for pain fibres (Bengtsson et al., 2013; Ekerot et al., 1987).

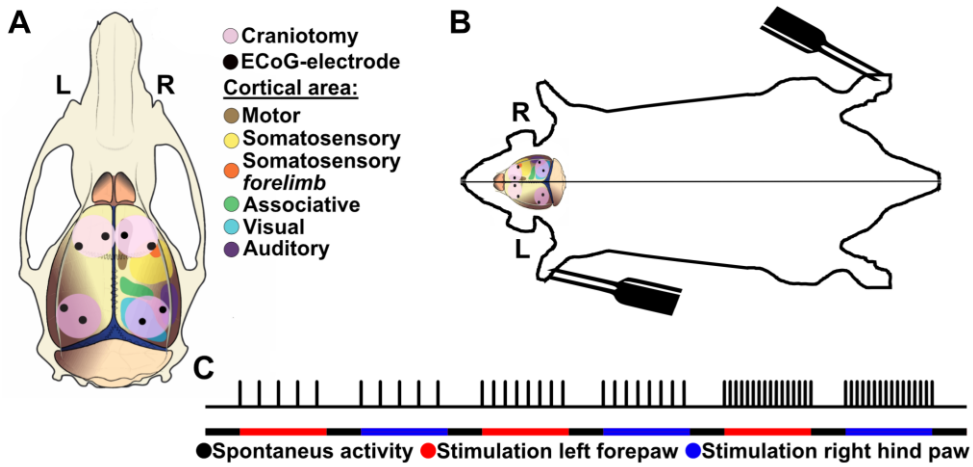

Fig 2. Set-up for recordings
A) Overview of the skull and brain of the rat. The primary areas of the cortex are indicated with different colours, and indicated with a pink shadow and black dots are the positioning of the craniotomies and the eight recording electrodes. B) Rat outline showing the positioning of the two stimulation electrodes. C) A simple schematic showing the basis for the stimulation protocol used. The schematic does not accurately display the frequency and number of impulses used.

Drug administration

In paper III and IV, D-amphetamine was administrated halfway through the experiment. D-amphetamine sulphate solution (Sigma-Aldrich, SE) with a salt weight of 1mg/ml and a vehicle of 0.3ml of 0.9% saline solution was used. A dose of 0.25mg/kg was injected intravenously 15 minutes after the last period in the stimulation protocol. After injection of the D-amphetamine a wait of 15 minutes was had to allow for the distribution before the stimulation protocol was re-run. The level of anaesthesia was monitored especially carefully after the injection to ensure the level of anaesthesia did not decrease, and the flow of anaesthesia was increased if needed.

Data analysis

Post processing

All ECoG data was imported from Spike2 to MATLAB (MATLAB Release 2021a, The MathWorks, Inc. Natick, Massachusetts, United States) (Fig. 3A). When data recorded during the exact time of the stimulation impulse was included in an analysis, artifact removal was performed to ensure that any potential artifacts

would not influence the results. Artifact removal was executed using linear interpolation between two times steps from just before and after the stimulation pulse. Before frequency analysis was performed, the raw ECoG data was filtered to reduce noise. In paper III this was achieved by applying a Savitzky-Golay filter with a window size of 20 ms. In paper IV the raw ECoG signals underwent high-pass filtering, to increase the signal quality and remove any low-frequency drift, using a fourth-order Butterworth filter, with a cut-off frequency of 0.3Hz. This also ensured that any direct current components were removed, without removing relevant neural activity.

PCA

Principal component analysis (PCA) is a method for dimensionality reduction, calculating the eigenvectors and their corresponding eigenvalues for the data. This summarizes the variations in the original data into a new set of vectors, the eigenvectors, where each new vector is one of the principal components (PC). The PCs are ordered after the size of their corresponding eigenvalues, with the first having the largest eigenvalue, thus containing most of the variance in the data (Fig. 3B). Every subsequent PC will be orthogonal to the one before and contain a decreasing amount of the variance in the data. Each point of data will be described in the new coordinate system and will be given a new coordinate value correlating to its position in the new PC axis, which are uncorrelated to the original axis (Fig. 3C). The variance in data explained by all eigenvectors will add up to 100%.

PCA was used to extract information about variation in the neuronal activity across all the eight recorded ECoG traces. The raw ECoG data was Z-scored to highlight temporal profiles before the PCA was performed on the whole ECoG dataset (both spontaneous activity and activity during stimulation, and both with and without D-amphetamine for the drug trials) using the inbuilt MATLAB function "*pca*". This created eight principal components (PCs) vectors that created a multidimensional space in which activity distributions could be examined.

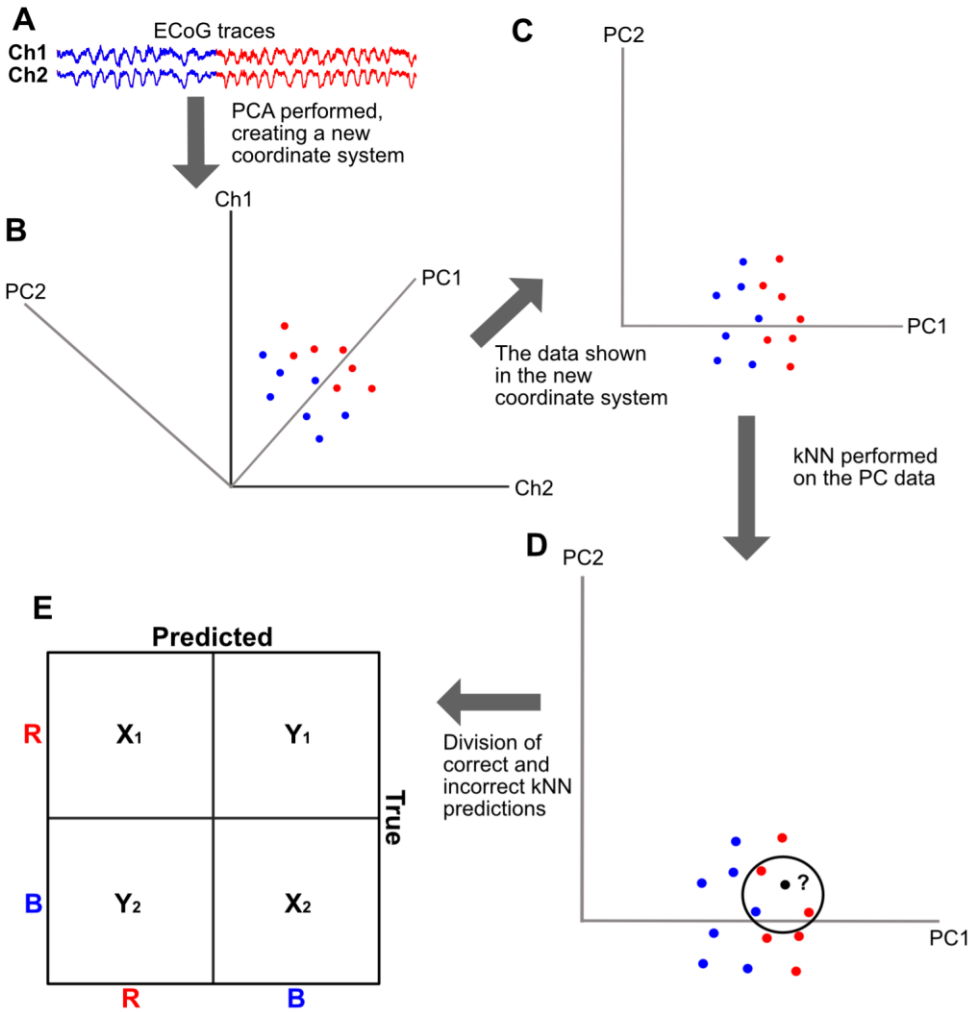

Fig 3. The process of going from ECoG traces to kNN accuracy
A) Example of two of the eight recorded ECoG traces, which will be analysed togheter using PCA. B) Showing how the data might look when each time step is plotted based on the values from two channels. Note that in this graph if an individual point is blue or red (representing different periods of the recorded trace) can not be determined by looking at the coordinate on only one axis. Grey axes show how the new vectors are placed in relation to the original. C) The new coordinate system after PCA. Please note that now the colour of each point can be determined with only the PC1 coordinate, despite the points not moving in relation to each other. D) Visualisation on the basic of how kNN works. After training on one set of data, it will predict the colour of points based on a number of the closest neighbours, in this example set to three. E) Based on the kNN's predictions and each points true class all predictions can go in one of the four squares. kNN accuracy will then be calculated as what precentage of all predictions were correct, in the manner of $Acc(\%)=(X_1+X_2)/(X_1+X_2+Y_1+Y_2)$.

kNN

k-nearest neighbour analysis is a classification method to analyse if groups of data can be separated by the classification of their closest neighbours (Fig. 3D). kNN gives an objective value of the separation between groups, in the form of a percentage indicating how often its prediction of a data points group affiliation was correct (Fig. 3E). It also allows for comparison in a multitude of dimensions simultaneously. In paper I and III, kNN was used to compare the activity distributions for different subsets of the data, using all eight dimensions acquired from the PCA. The kNN was performed using the MATLAB classification learner toolbox. N=5 nearest neighbour and five-fold cross validation was used. Before the kNN the full time series of PC coefficients were normalized between 0-1 as a method of feature scaling.

For all kNN analysis, activity during stimulation was defined as a window of 190ms from 5ms post stimulation pulse to 195ms post stimulation pulse. This window ensured that any artifacts from the stimulation pulse were excluded and that no overlap between post pulse activity occurred for the 5Hz stimulation periods. A window of this size also included more than a potential evoked response, which typically would last for 20-50ms, thereby ensuring that an evoked response would not be the only differentiator.

To avoid skewing the kNN results in cases when the spontaneous period data contained more data points than the period during stimulation, a shorter time series of spontaneous data was randomly selected to match the size of the two compared groups. This time series was also randomized again with every 10^{th} iteration of the kNN to ensure that the results were not the result of a lucky or unlucky randomization. In total each comparison with kNN was repeated 100 times, which together with the five-fold cross validation gave a total of 500 randomisations of test and training data. The mean kNN accuracy for these 100 repetitions was then calculated to represent the accuracy of that specific comparison. This process was repeated for every single pair of data subsets being compared.

The significance of the resulting kNN accuracy was validated by performing a randomization test, which is variant of the permutation test. This consists of a shuffling process, were the data from the subsets that were compared had their labels shuffled and then went through the kNN process as above, creating a distribution curve of kNN accuracies that the kNN accuracy of the correctly labelled data can be compared to as a way to determine significance.

Frequency analysis

Frequency analysis was performed using either MATLABs continuous wavelet transform (CWT) function, "*cwt*", for paper III, or its fast Fourier transform (FFT) function, "*fft*", for paper IV.

Continuous wavelet transform

CWT is a newer signal processing tool that allows for the investigation on the variation in frequency over time. In CWT, the signal will be compared to a wavelet. This will occur when varying the scale factor and thus dilating or compressing the wavelet allowing for the investigation into both fine details and coarser trends of the signal. The wavelet will also be shifted along the signal that is studied, thus allowing for a representation of the frequency content at varying time points (Najmi et al., 1997).

In paper III, CWT was applied to the summed-up data of all eight ECoG traces, both to the whole two-hour periods before and after D-amphetamine administration, and to the spontaneous activity and activity during stimulation separately for each condition. This was done to allow for further insights in the results from the PCA and kNN. After this the power was calculated for the frequency bands defined as: Delta <4Hz, Theta 4-7Hz, Alpha 7-12Hz, Beta 12-30Hz and Gamma >30Hz.

Fast Fourier transform

FFT is a method for calculating the discrete Fourier transform, thereby allowing the identification of the different frequencies that are present in the signal, and the amount of the signal consisting of each frequency. Based on the principle that all signals can be described as a sum of a number of sinusoid waveforms, the FFT will calculate which of these waveforms make up the analysed signal and the amplitude of each waveform. However, FFT only reveals what frequency components are present and not how these components vary over time in the analysed period (Lynch et al., 2016).

In paper IV, FFT was performed on each individual ECoG trace and applied to the separate periods of spontaneous activity and activity during stimulation, both before and after D-amphetamine administration. Frequencies below 0.3Hz were excluded from this analysis, to be consistent with the filtering that was used. The frequency with the highest amplitude (referred to as “peak frequency” throughout this thesis) was extracted for each ECoG trace and each period. Additionally, the frequency with the largest positive difference in amplitude between the activity during stimulation and the spontaneous activity immediately preceding it was calculated as well, for the pre- and post-D-amphetamine condition both.

Ethical consideration

The results reported in this thesis were acquired from analysis of data recorded from animals. All animal experiments were in accordance with local laws and

guidelines, as well as ARRIVE guidelines, and all experiments were performed after approval from the local animal ethics committee in Lund/Malmö.

Unfortunately, models of neural networks are not yet of a quality that allows them to replace *in vivo* experiments. Thus, we have focused on reducing and refining the experiments necessary for our studies. To do so, we have designed the experiments to maximize the number of possible analyses and recorded data per experiment. This allowed different aspects of the collected data to be used in more than one study. To minimize the stress, discomfort and pain for the animals, rats in all our experiments were handled as little as possible before the initial anaesthesia. During anaesthesia, vital signs, ECoG recordings and the response to a noxious pinch to the hind paw was used to monitor the level of anaesthesia. This was done to ensure that the animal remained under deep anaesthesia until the experiments were terminated.

The methods of recording and analysis employed in this thesis carry the potential to be developed to use in human EEG studies in the future. This would allow for future studies to be performed with consenting human participants instead of animals. However, such studies would likely include more complicated data and more confounders than the present studies performed in anesthetized animals. Thus, pilot studies on animals could be necessary to allow for a better understanding and developing of the methods. Of course, studies on humans comes with its own set of ethical considerations, in this case about the protection of personal data as well as the risk of incidental finding of aberrant cortical activity.

Results

Paper I: ECoG activity distribution patterns detects global cortical responses following weak tactile inputs

Neuronal decoding and information about sensory input have been observed beyond the corresponding neocortical regions and across the cortex. If this holds true and sensory input changes the brains activity distribution, one should be able to observe these changes across the cortex more or less simultaneously (Enander & Jorntell, 2019; Enander et al., 2019; Etemadi et al., 2022; Findling et al., 2023; Luczak et al., 2009; Nietz et al., 2022; Stringer et al., 2019). Exactly how a sensory evoked change of the neural activity will move through the cortical network will depend on several internal factors. Likely with an extreme number of different permutations given the number of neurons in the brain (Enander et al., 2019; Etemadi et al., 2022; Nietz et al., 2022; Norrlid et al., 2021). Despite this, there may still be patterns of activity distributions that are more common, reflecting spontaneous cortical activity. These could then potentially be differentiated from less common activity distributions caused by external input or internal perturbations.

In paper I we wanted to investigate if a low-resolution method could be used to detect and differentiate different distribution patterns of cortical activity. We also asked if this was possible using only a few recording sites, even when only using a mild perturbation in the form of brief sensory input from the skin. We also wanted to investigate if this was possible even when excluding the data from the main receiving sensory area.

To do this, we used the experimental set-up described in methods. Eight recording ECoG electrodes were placed in different primary cortical areas, and mild electrical stimulation was applied to the skin of the paws. PCA and kNN was then applied to the recorded data. This allowed for an analysis of the data from all eight recording electrodes simultaneously and for detection of changes in the activity distributions.

Visualising the recorded data in a three-dimensional space after having applied PCA, we found that the activity preceding and during stimulation had different, but overlapping, distributions when projected in the principal component space (Fig. 4A). When we examined the data just before and after a single stimulation

impulse it could at times be observed that the stimulation caused a transition of the position in the principal component space. That is to say, the data immediately following the stimulation impulse moved away from the spontaneous data, only to return to the same activity space after about 200ms (Fig. 4B).

However, since we are limited to visual inspections in three dimensions, any differences present across more than three dimensions will be hard to detect. Therefore, to enable the detection of differences across all eight dimensions we applied kNN. As described previously, kNN allows for the classification of individual data points based on the class of the nearest neighbours, thus providing a measure of the level of separation between groups of data. We decided to use kNN to examine the separability between spontaneous data and data during stimulation in four different permutations.

To begin with, we simply examined one group of spontaneous activity to one group of activity during stimulation, including data from all eight recording electrodes. In this analysis we found a clear difference between the two types of activity, with a kNN accuracy of 72.71% compared to the chance level of 50% (Fig. 4C). Following this we compared the activity during stimulation to the spontaneous activity immediately before and after stimulation as two separate groups. This resulted in an accuracy well above the chance level of 33%, indicating that our stimulation did not permanently shift the activity distribution.

We also examined the global distribution of the response by removing the data from the only recording electrode in an area with an evoked response to the stimulation (the right S1 electrode) before performing kNN between activity during stimulation and a single group of spontaneous activity. (Fig. 4D). We also investigated the accuracy when removing the data from all four recording electrodes on the side with the evoked response. We found that while reducing the number of included traces reduced our kNN accuracy, we were still well above the chance level of 50%.

When investigating the effect of the different variations of the stimulation, we found that the localization of the stimulation (left front paw or right hind paw) had no effect on the separation between the spontaneous activity and the activity during stimulation. However, the frequency of the stimulation did have an effect on the separation. Frequency stimulations of 0.3, 0.5 and 1Hz showed a larger separation between spontaneous activity and activity during stimulation than frequencies between 2 and 5Hz.

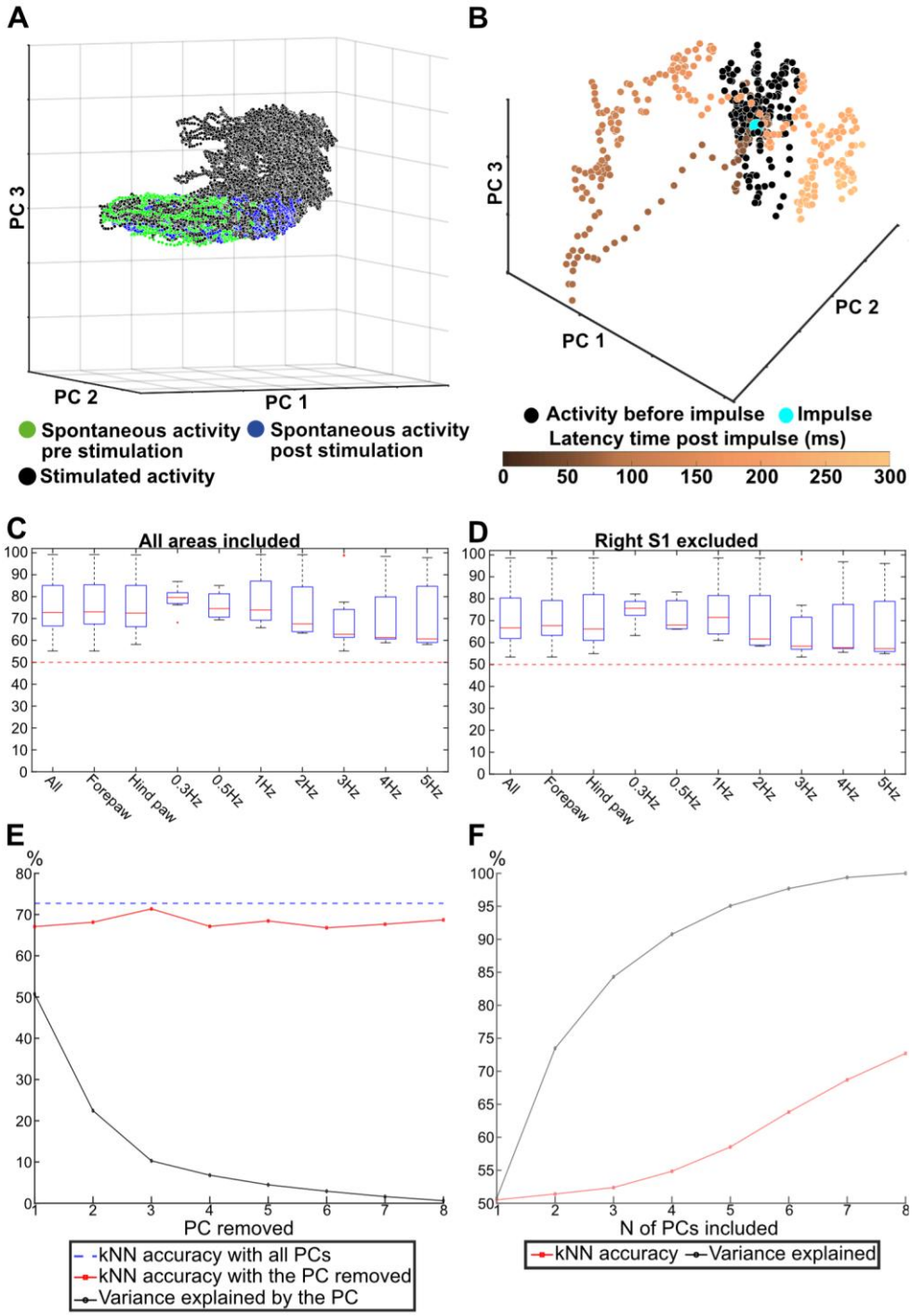
A
PC 3
PC 2
PC 1
Spontaneous activity pre stimulation
Spontaneous activity post stimulation
Stimulated activity
B
PC 3
PC 2
PC 1
Activity before impulse
Impulse
Latency time post impulse (ms)
0 50 100 150 200 250 300
C
All areas included
D
Right S1 excluded
All
Forepaw
Hind paw
0.3Hz
0.5Hz
1Hz
2Hz
3Hz
4Hz
5Hz
E
%
PC removed
kNN accuracy with all PCs
kNN accuracy with the PC removed
Variance explained by the PC
F
%
N of PCs included
kNN accuracy
Variance explained

Fig 4. Summary of the results in paper I
A) 3D-plot showing the activity distribution of one period of activity during stimulation (black) togheter with the period of spontaneous activity immediately before (green) and after (blue) it. This visualises the separate but overlapping distributions. B) Brown dots show the movement of the activity distribution in the PC space immediately following a stimulation pulse (cyan), and its return to the pre-stimulation activity distribution (black). C) Box plot showing the median, quartiles and outliers of the kNN accuracies when comparing activity during stimulation to one group of spontaneous activity with all recorded traces included in the analysis. The dotted red line shows the chance level. D) Similar to C) but for the kNN results when the trace recorded from the right S1 was excluded from the analysis. This was the only trace in which an evoked response to the stimulation was recorded. E) Plot showing how much of the kNN accuracy is lost with each individual PC being excluded one by one from the kNN, compared to how much of the variance each PC explains. F) Plot showing how the kNN accuracy varies depending on the number of PCs included, compared to how much of the variation the included PCs explains.

Finally, we repeated our first version of the kNN analysis, but this time we altered the number of PCs included from one up to eight. We also performed the kNN with each PC excluded one by one. In this analysis we found that each individual PC had about the same effect on the accuracy when they were excluded. The reduction in accuracy caused by a single PC was not correlated to how much of the variance in the data that specific PC explained (Fig. 4E). When we increased the number of PCs included in the analysis a similar lack of correlation was found. While the first few PCs had the smallest effect on the resulting accuracy, they contained most of the explanation of the variance in the data. Instead, the accuracy had a larger increase only when around four to five PCs were included, with the accuracy rising for each one added, all the way up to eight, while each of the later PCs only explained a few percent of the variance in the data (Fig. 4F).

Paper III: D-amphetamine alters the dynamic ECoG activity distribution patterns in the rat neocortex.

Amphetamine is known to affect several neurotransmitters, such as noradrenaline, dopamine, acetylcholine and serotonin, which means that, given the spread of these in the cortex, it will impact most if not the whole cortex (Arnold et al., 2001; Berridge & Morris, 2000; Stahl et al., 1997; Stratmann et al., 2018; Tohyama & Takatsuji, 1998). As it is a known treatment of narcolepsy and ADHD, several studies on how it might affect the cortex have been performed. These have often examined its effect on the link between the cortex and subcortical areas using fMRI (Avram et al., 2024; Ramaekers et al., 2013; Schrantee et al., 2016; Weafer et al., 2020). However, when it comes to studying changes in the activity dynamics between neurons, the higher temporal resolution of electrophysiological recordings can be an advantage (Kristensen et al., 2024).

In paper III we set out to examine how the activity distribution patterns reported in paper I and the separability between the spontaneous activity and activity during stimulation might be affected by the administration of D-amphetamine.

Recordings were performed as described in the methods section, but with the administration D-amphetamine after the stimulation protocol had been run once, before running the same stimulation protocol again. PCA and kNN was again used to analyse the activity distributions, but for different sets of data (Fig. 5A).

First, we compared the same type of activity (either spontaneous or during stimulation) before and after the D-amphetamine administration and found that kNN could separate them based on if D-amphetamine had been administered or not (Fig. 5B). For this comparison of the same type of activity before and after D-amphetamine administration, a control was run to ensure that any difference did not consist only of the rat having been anaesthetized for two hours. We found that the control had a significantly lower separation of the activity distributions than when comparing activity with or without D-amphetamine having been administered.

Following this, a comparison similar to that in paper I was performed. We compared one group of spontaneous activity to one group of activity during stimulation. This was performed on data from before and after the administration of D-amphetamine, and we found that the separability between the activity distribution of the two types of activity was significantly reduced after the administration of D-amphetamine. However, the accuracy after D-amphetamine administration was still above chance level, indicating that the difference is smaller but still present (Fig. 5C).

In this study, two investigations into the dimensionality were performed. Firstly, the dimensionality when comparing the same type of activity, with or without D-amphetamine having been administered was investigated. For both the spontaneous activity and activity during stimulation each PC still contributed about equally to the resulting accuracy when removing one at a time. When increasing the number of included PCs one by one from one to eight, we found that the spontaneous activity and activity during stimulation had a similar increasing accuracy for each PC.

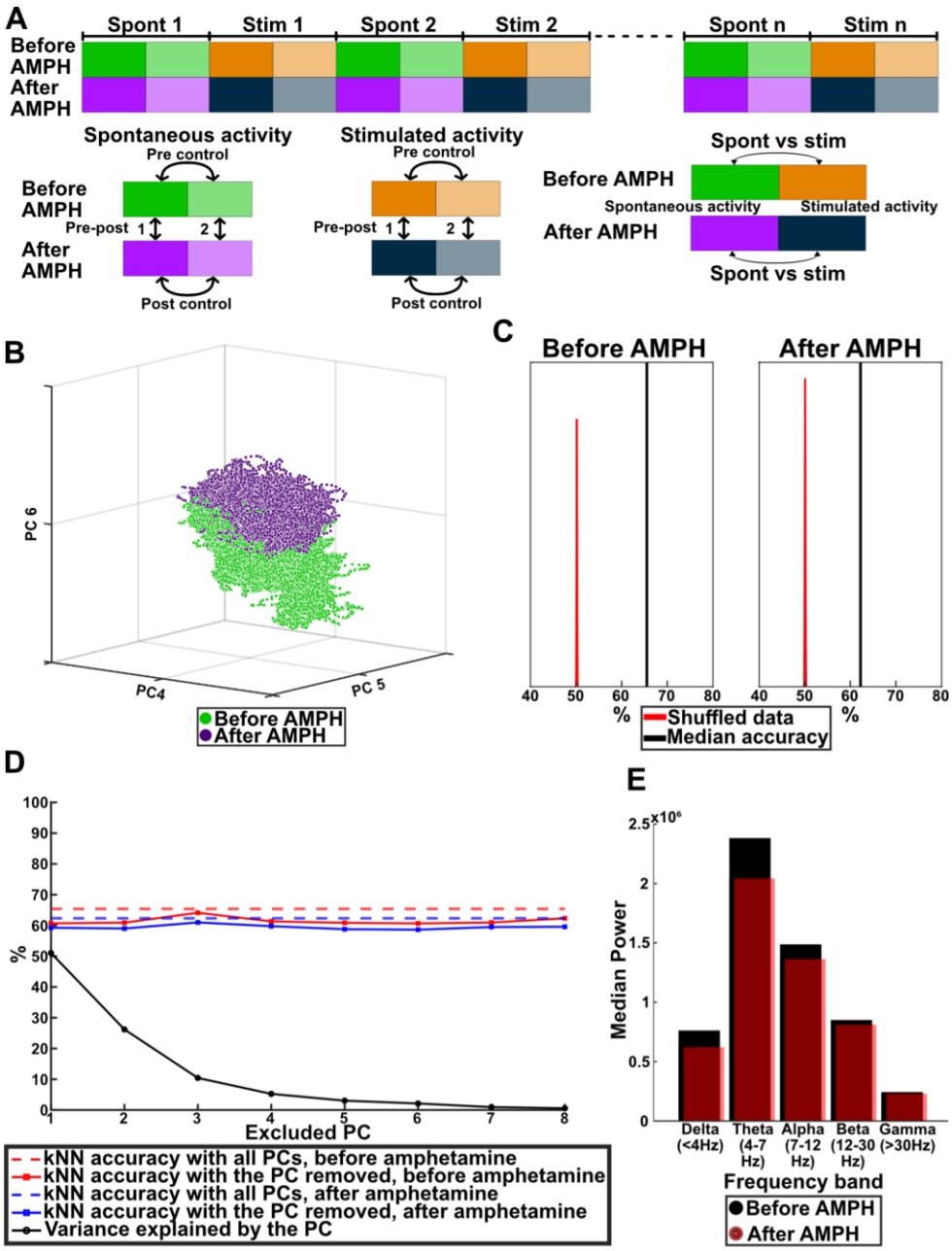

Fig 5. Summary of the results in paper III

A) Diagram describing the timeline of the recorded activity and how it was analysed using kNN. Comparisons between the same type of activity with and without D-amphetamine having been administered were performed with matching parts of the experimental protocol. To investigate the

separability of spontaneous activity from activity during stimulation before and after D-amphetamine administration, the recorded activity was divided into parts so that each period of activity during stimulation was compared to the spontaneous activity in connection with it. B) 3D-plot showing how the addition of D-amphetamine can cause the activity distribution of spontanoeus activity to shift its position in the PC space. C) Graphs showing the median kNN accuracy and the chance level determined by data shuffling for the separabilty of spontaneous activity and activity during stimulation with or without D-amphetamine. This shows the higher kNN accuracy before D-amphetamine administration (left) compared to after (right), but with both being well above the chance level. D) Plot showing the reduction in kNN accuracy depending on any single PC being excluded from the analysis. This shows that the pattern of how much each individual PC contributes to the total accuracy remains similar after the administration of D-amphetamine to what it was before. Here shown for the comparison between spontaneous activity and activity during stimulation. E) Example of how the median power in each frequency band is affected by the administration of D-amphetamine during spontaneous activity, with a general lowering across all bands.

We then also investigated the dimensionality when comparing spontaneous activity to activity during stimulation. When removing a single PC at a time, the reduction in accuracy was similar for all PCs, both before and after D-amphetamine administration. This indicates that any differences in separability between the two types of activity before and after D-amphetamine administration are evenly distributed across the dimensions (Fig. 5D). However, the effect of adding additional PCs was reduced when looking at the separability of spontaneous activity and activity during stimulation after D-amphetamine administration as compared to before D-amphetamine administration. This could indicate that the structure of the activity distribution is made less separable overall by D-amphetamine, with less information in each dimension adding up to a lower overall separability. The fact that none of the comparisons had a single PC contribute to the accuracy to a higher degree indicates that neither D-amphetamine nor sensory stimulation drives a change in activity distribution in one specific dimension. Rather, the change in activity distribution remains spread across the eight dimensions. Just as in paper I the contribution to the kNN accuracy was uncorrelated to how much of the variance in data each PC explained in both types of comparisons.

Finally, we examined the power across the different frequency bands before D-amphetamine administration compared to after. For this we used continuous wavelet transform, which identifies the frequencies present in a signal at specific times. We compared the power in each frequency band during both spontaneous activity and activity during stimulation. In this analysis, a general decrease in power was found across all frequency bands after D-amphetamine administration (Fig. 5E).

Paper IV: Possible preferred global frequencies in the cortex are affected by D-amphetamine but not by sensory stimulation

The idea of resonance as a way for the cortical network to optimize its performance is intriguing, and not wholly without basis. Some aspect of resonance can be found in many parts of the CNS (Hahn et al., 2014; Lampl & Yarom, 1997; Pisarchik & Hramov, 2023; Stark et al., 2022). In individual neurons, membrane properties have been found to cause frequency preferences in the neurons response to sensory input. Frequency preferences have also been observed in both intracortical circuits and in the thalamocortical loop (Binini et al., 2021; Brunel & Wang, 2003; Hutcheon & Yarom, 2000; Izhikevich, 2002; Puil et al., 1994; Steriade, 2000). In addition to this, brain-wide frequencies of activity might shape communication across cortical areas (Fries, 2005; Pisarchik et al., 2019). Resonant features have been found in the auditory and vibrissal sensory system, but if this occurs across many cortical areas simultaneously is not known (Andermann et al., 2004; Johnson et al., 2024).

In paper IV we wanted to investigate if external activation, in the form of somatosensory stimulation, could interact with resonance properties and enhance the sensory evoked response in distributed areas of the cortex based on the stimulation frequency. We also wanted to examine if changes in the internal properties of the cortical network modulated the resonance mechanisms. We therefore investigated the effects of D-amphetamine, known to have a widespread effect on many different neurotransmitters.

Like in the previous investigations, ECoG data was recorded as described in methods. The frequency analysis was performed using fast Fourier transformation (FFT), transforming the recorded signals from the time domain to the frequency domain. FFT was used to find the frequencies that were present in the recorded signal and to evaluate their power. That is, how much of any given frequency there was in the signal, of all different frequencies present in the recording. The frequency with the highest power in the recorded data was defined as the peak frequency.

We found that across all eight recorded areas a clear majority of the peak frequencies could be found between 1-2Hz. The distribution of peak frequencies was largely unchanged when comparing spontaneous activity and activity during stimulation (Fig. 6A). After the administration of D-amphetamine there was a difference in the distribution of peak frequencies. The number of peak frequencies in the 1-2Hz range were reduced, with more peak frequencies below 1 Hz occurring. The majority remained in the same range however (Fig. 6B). During stimulation after D-amphetamine administration there was an increase of the

number of peak frequencies in the 1-2Hz range compared to during spontaneous activity (Fig. 6B). However, the increase in peak frequencies between 1-2Hz was not sufficient to reach the same percentage as recorded before D-amphetamine administration. Globally, the mean peak frequency was lower after D-amphetamine administration for both types of activity (Fig. 6C). The percentage of peak frequencies above 2Hz remained fairly consistent across both types of activity before and after D-amphetamine administration.

Inside of the 1-2Hz range some regional clustering could be observed in the mean peak frequency. The right S1 consistently exhibited a higher mean peak frequency compared to other areas.

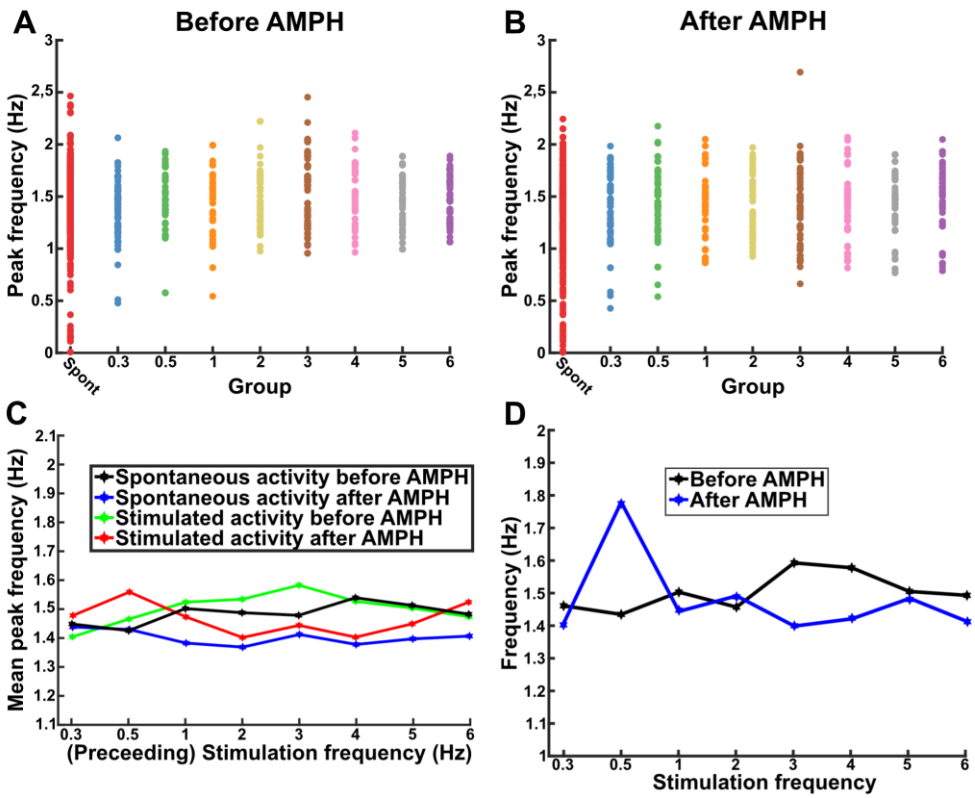

Fig 6. Summary of results in paper IV
A) Scatter plot showing the distribution of peak frequencies in all eight recorded areas before administration of D-amphetamine. In the graph data was placed in one of nine different groups, one for spontaneous activity and one for each of the eight stimulation frequencies used. Values above 3 Hz where excluded for visual clarity. No outlier was above 5 Hz. B) As in A) but now for the data recorded after D-amphetamine administration. C) The mean peak frequencies for spontaneous activity and activity during stimulation before and after the administration of D-amphetamine. On the x-axis it is shown what stimulation frequency was used during stimulation, and the stimulation frequency of the preceeding stimulation for the spontaneous activity. Here we can see a significant reduction in mean peak frequency after D-amphetamine (blue and red) compared to the same type of activity before D-

amphetamine administration (black and green). We can also see how stimulation raises the mean peak frequency after D-amphetamine administration (red), while not reaching the previous mean peak frequencies during stimulation before D-amphetamine administration (green). D) Plot showing at which frequencies the largest increase in amplitude was recorded during stimulation before and after D-amphetamine administration

When examining how stimulation impacted the amplitude of different frequencies, we found that the largest increase in amplitude during stimulation before the D-amphetamine administration occurred in frequencies not significantly different from those that were the mean peak frequencies, both during spontaneous activity and activity during stimulation. After the administration of D-amphetamine the frequencies with the largest increase in amplitude were different from the mean peak frequencies during spontaneous activity but matched the higher mean peak frequencies from activity during stimulation (Fig. 6D).

Interestingly, the frequency of the peripheral skin stimulation consistently appeared to matter little or not at all to the peak frequency during stimulation.

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Discussion

This thesis includes four papers with a common goal of increasing our understanding of the basic principles of how cortical activity at a global level reacts to sensory stimulation and pharmacological disruptions and how these results can be used to interpret cortical functionality. Paper I, III and IV are original research papers, presented under Results. Paper I and III used a similar methodology, and paper IV used a different analysis method, performed on data from the same experiments. Paper II is a methodology paper. In it, step-by-step instructions on how to perform the experiments as well as the analysis methods from paper I and III are presented. In paper I we showed that even mild sensory input from the skin changes the activity distribution in the whole cortex. This was true even when data from the primary area thought to be responsible for processing the stimulus was excluded. Paper III built on this and showed that the administration of D-amphetamine caused a shift in the activity distribution and at the same time reduced the difference between activity distributions for spontaneous activity and activity during stimulation. In paper IV we investigated the frequency content of the cortical activity during peripheral skin stimulation and at rest. Here we found that the cortex, in our experimental set-up, appears to have a clear range of preferred frequencies that remained unaffected by the peripheral skin stimulation. But the preferred frequency range was found to shift with the administration of D-amphetamine. Below follows a discussion of possible explanations and implications of these findings. This is followed by a discussion on the choice of methods and finally a discussion on how these results fit with our understanding of the brain.

Activity distributions place in interpreting the brain

There is no perfect way of recording activity in the CNS. Thus, there will always have to be some aspect of compromise in all recording techniques. One of the most common ways to study and interpret neuronal activity is to examine the number of spikes in relation to a stimulus and then interpret an increase or decrease in spiking as a sign of that particular neuron or ensemble of neurons being involved in the processing of the stimulus. However, spiking in a single neuron does not reveal how that particular signal is received in the rest of the

network. With information from only a single point in the network it will also be hard to draw conclusion on what has led to the shape and location of the recorded response. And while recording from larger parts of the nervous system reveals more about the activity of the network, other issues occur. Features like temporal or spatial resolution are compromised, introducing a risk that important nuances of responses are lost given the complex and fast working dynamics of the brain. And regardless of what the choice of recording method is, in the end, the resulting data must be interpreted.

Studying activity distributions is one way to widen our interpretation of recorded neuronal and cortical activity. By projecting the activity across several recorded areas or neurons in a multidimensional space, activity distributions can be found and studied. Investigating how these activity distributions change under different conditions could then be used to interpret how the network operates, as the activity in different areas and neurons varies and changes (Luczak et al., 2009; Stringer et al., 2019).

In paper I and III we found, using PCA for cross-channel analysis and kNN to allow for higher dimensionality in the classification analysis, that even small perturbations could change the activity distribution. However, although the difference was clearly detectable, there was still an overlap between the activity distributions for each condition. This is in line with previous results investigating activity distributions under different conditions using recording and analysis methods that were different from the ones used here (Luczak et al., 2009; Stringer et al., 2019). This suggests that the cortex is unlikely to have completely separate states for the handling of the different conditions.

While the difference can be detected, what this change in activity distribution means in functional terms is not easy to understand. During stimulation it would be easy to assume that the change in activity distribution is related to our perception of the stimulus. But what about when we introduce D-amphetamine? Do even low doses, as in our experiment, change the perception of the environment?

Perhaps more likely, the change in activity distribution is related to a change in internal processing. This is the most basic explanation for the change in activity distribution, that different pathways in the cortical network are activated during different conditions. But without the ability to record exactly which pathways are activated and their role, suggestions on the functional significance of a finding will be based on the correlation between the recorded data and observed behavior during the recording.

The dimensionality of the brain

One issue when studying the brain is the complexity of it. In the neocortex alone there are billions of neurons all connected in an enormous network. This is a problem when you want to analyse how activity is distributed in a large part of the network. Even from a theoretical point of view it is impossible for a human to properly comprehend such a vast network. One way to circumvent this is to use methods for dimensionality reduction. One such method is PCA.

PCA will attempt to capture the maximum amount of information in the fewest number of dimensions possible. In this analysis method the principal components can combine information from several of the original vectors into each of the new vectors. Thus, the activity distribution in the PC space builds on the combined information from all our recorded channels. This maximizes the information present in each dimension. However, finding a difference between activity distributions after dimensionality reduction can be harder to interpret, as we will not necessarily know what specific feature of the original data led to these differences. All that it tells us is that there is a difference between the data sets.

Another common discussion when it comes to dimensionality reduction is what number of dimensions are needed to properly explain the recorded cortical activity. There have been studies indicating that very few dimensions, that explains the majority of the variance in the data, contain all the information of interest (Saleem et al., 2013; Stringer et al., 2016). However, in paper I and III we saw that even the dimension that explained the smallest amount of the variance in our data contributed about equally to the ability to separate two types of activity. This is in part in line with findings that the activity distribution during stimulation is in some parts situated in dimensions orthogonal to the dimensions that the spontaneous activity distribution inhabits, thus increasing the dimensionality (Stringer et al., 2019).

In addition to this, we found that the number of dimensions that were compared appeared to matter more to the ability to differentiate activity types than what specific dimensions were included. This could indicate that in addition to being a high dimensional system, the cortex has also minimized redundancy, as all dimension carried information. Thus, it is unlikely that the cortex is a system where every neuron is involved in all processing, as that would likely carry a high level of redundancy. It might also be in opposition to a cortex with a very localized functionality, as redundant dimensions would then likely have appeared in our analysis. An interesting question would be how many recording electrodes we could use, thus increasing the number of dimensions, before we start having redundant dimensions in our PCA. And if this could tell us something about what portion of the network is involved in the processing. Studies using independent component analysis, a method of dimensionality reduction based on similar

principles as PCA, on fMRI data found that around 150 dimensions were needed for optimal reliability in test-retest results, indicating that with eight in our studies we are still a long way from contending with redundancy (Ma & MacDonald Iii, 2021).

Frequency content and resonance

Another, more well-established way to investigate how the cortex works on a large scale is to study the frequency content of its activity. Different frequencies of activity in the cortex have been linked to different states of consciousness and activity.

From the perspective of the cortex as a globally interconnected network, inherent features like rhythmical firing of neuronal ensembles, filtering and resonance mechanisms might allow for synchronization between different cortical areas. This might represent a mechanism that allows for greater integration and processing of information across the brain (Buzsáki & Draguhn, 2004).

In paper IV we found that the cortex appears to prefer frequencies in the 1-2 Hz range in our experimental set-up. This specific range might reflect the effects of the ketamine/xylazine anaesthesia. Ketamine/xylazine anaesthesia has been observed to induce a state similar to slow-wave non-REM sleep, during which thalamic neurons are known to oscillate at around 0.5-4Hz (Chauvette et al., 2011; Dworak et al., 2011; McCormick & Pape, 1990; Steriade et al., 1993). Other studies have found prominent low frequency EEG rhythms in rats under ketamine/xylazine anaesthesia, with a peak at 1.6Hz (Sharma et al., 2010). However, low frequency oscillations have also been observed as global frequencies used by the brain to synchronize distant areas during waking and natural sleep (Csicsvari et al., 2003; Sirota et al., 2003). Other studies have shown that sensory stimulation is transmitted to the cortex under ketamine/xylazine anaesthesia, indicating that the lack of change in cortical frequency content in response to stimulation is not due to the anaesthesia blocking signals from the peripheral stimulation from reaching the cortex (Zandieh et al., 2003). Interestingly, in paper I we found that stimulation frequencies below 2 Hz appeared to have a greater effect in differentiating the activity during stimulation from the spontaneous activity. This could indicate that stimulation matching the preferred frequencies in the cortex affects the network to a higher degree, having a higher impact on the resulting activity distribution.

Importantly, while the specific frequency range we observed in paper IV is likely an effect of the anaesthesia, that it is global and largely unaffected by the external stimuli could indicate that the cortex works with oscillations in specific frequency ranges, perhaps determined by the level of arousal and other internal states.

Having an internally set frequency range that external input is adjusted to fit within could be an effective way of ensuring optimal communication and processing in the cortex and hamper the ability for external input to disrupt internal processes. This may be a way to prevent self-resonance. If an external input of the correct frequency was able to cause an uncontrolled resonance effect, the network could potentially fall into an unstable self-resonating epileptic state.

That the recorded frequency range shifted with the administration of D-amphetamine is in line with this theory. D-amphetamine, with its widespread effect in the CNS, could be expected to change the internal state of the network, thus changing the preferred frequency range. Interestingly, the external input had a greater effect on the mean peak frequency after D-amphetamine administration. This suggests that D-amphetamine disrupts some of the mechanisms adjusting the external input to the internal frequency range. Such a reduction in the ability to synchronize external input to internal processes could perhaps be part of the problem with altered cortical rhythms and synchronization in diseases and states like Parkinson's and ADHD, where monoaminergic systems are known to be involved in the underlying changes in the network (Arnsten, 2009; Franzen & Wilson, 2012; Hammond et al., 2007).

The effect of D-amphetamine

In paper III we saw a change in activity distribution for activity before and after administration of D-amphetamine. We postulated then that this could possibly be caused by a reduction in the structure of the cortical activity. We also observed a reduction in power across all frequency bands after D-amphetamine administration which could possibly be due to a reduction in network synchronization. In paper IV meanwhile, we found that a global change in mean peak frequency occurred during peripheral skin stimulation only after D-amphetamine administration. Thus, the smaller difference between the activity distribution of spontaneous activity and activity during stimulation observed after D-amphetamine in paper III can not be explain solely by a change in the frequency content during both spontaneous activity and activity during stimulation, or by a reduction in the transmission of information via the thalamus.

These results together suggest that there is a change in network organisation rather than a destabilisation. This is in line with the studies on functional connectivity following D-amphetamine administration in humans, where both hyper- and hypoconnectivity is observed. D-amphetamine did reduce the connectivity from unimodal areas of the cortex down to the thalamus, and from the thalamus up to multimodal areas. But it also strengthened the connectivity from the thalamus up

to unimodal areas, and from multimodal areas down to the thalamus. It also modulated connectivity between different cortical areas (Avram et al., 2025; Avram et al., 2024).

The findings that sensory skin stimulation had an increased effect on the cortical frequency after D-amphetamine administration are in opposition to a reduction in real-world input relayed from the thalamus being the cause of the reduced difference between activity distributions for spontaneous activity and activity during stimulation following D-amphetamine administration. However, the decreased connectivity from the thalamus to the multimodal cortical areas could indicate that the reduction in difference between the two activity distributions is because fewer parts of the cortex receive the information from the thalamus. A lack of information to multimodal areas could also mean a lack of contextualization of the sensory stimulation, thus reducing its impact on the activity distribution. Simultaneously, the increase in connectivity from the thalamus up to unimodal areas might be part of explaining the change in mean peak frequency in response to sensory skin stimulation after the administration of D-amphetamine.

Another contradiction to the theory that D-amphetamines simply reduce the cohesion in the cortex is that it is thought to have a calming and stabilizing effect when used as a treatment in ADHD (Arnsten, 2006; Harris et al., 2022). This might be another sign that rather than causing a general loss of cohesion, it is more likely that D-amphetamine modulates the cortical responsiveness, in a widespread and not yet fully understood manner. A widespread effect encompassing the whole network would be unsurprising given amphetamines effect on a multitude of neurotransmitters present throughout the cortex and thalamus (Stratmann et al., 2018; Tohyama & Takatsuji, 1998). A widespread effect that modulates the network structure without reducing said structure is also in line with the findings of a remaining high dimensionality after the administration of D-amphetamine, as was observed in paper III.

In the experiments in paper III and IV we used a comparatively low dose of D-amphetamine. And as in other pharmacological interventions, there might be dose-dependent effects. In the case of D-amphetamine there are varying reports on the effective dose. Some studies have found that there were no effects of D-amphetamine on the measured outcomes unless a larger, repeated dose was administered (Stahl et al., 1997). In other studies doses lower than the ones we used in paper III and IV were reported to affect the slow-wave activity in the forebrain (Berridge & Morris, 2000). Thus, it is possible that there is a dose-dependent effect to what changes in the cortical activity and network can be observed following D-amphetamine administration. Possibly a high enough dose of D-amphetamine would reduce the dimensionality or cause a degradation of the cortical network rather than modulating the cortical activity. Another interesting property of amphetamine is that it has a stabilizing effect in ADHD, while

arguably having a de-stabilizing effect when used as drug (Arnsten, 2006; Connell, 1966). Dopamine have been found to work on an inverse U-curve in studies on working memory and cognitive control, where both a lack of dopamine and an overabundance will lead to negative effects (Cools & D'Esposito, 2011). A similar system has been suggested for noradrenaline (Aston-Jones & Cohen, 2005). If an inverse U-shaped curve explains the relation between levels and functionality for both dopamine and noradrenaline, a similar pattern might exist for other neurotransmitters. It could also be that the modulation by amphetamine on those neurotransmitters will move where on the curve the levels fall. Thus, it could have a stabilizing effect when neurotransmitters are at a suboptimal level. While at the same time having a de-stabilizing effect on the network if modulating neurotransmitters that are at an optimal level.

Global processing in the cortex

As discussed above, our findings in paper I that the activity distribution during stimulation is distinct from, but partially overlapping with, the activity distribution of spontaneous activity is in line with results from other studies (Luczak et al., 2009; Stringer et al., 2019). What makes our study unique is that we examine this effect across large areas of the cortex simultaneously rather than focusing on one area or a specific population of neurons.

The separation between the two types of activity, regardless of the presence of an evoked field potential response suggests that the separation is not merely the effect of a local response to the stimulus but rather caused by a global shift in the activity distribution. Another finding in favor of this interpretation is that the separation of activity distributions remained even with the removal of the only area that contained an evoked field potential response. The separation remained even when that whole hemisphere was excluded from the analysis. The finding that the stimulation to one side of the body produced a separation in activity distributions within the ipsilateral hemisphere is in line with previous findings that tactile stimulation is decoded both ipsi- and contralateral to the stimulation (Genna et al., 2018).

These results supports the theory of cortex as an interconnected network with a global functionality (Harris & Shepherd, 2015). More specifically, they indicate that the cortex is a network where neuronal responses to specific sensory stimulation has a global spread. These findings are consistent with previous findings that support a theory of global functionality, demonstrating that perturbations to remote areas of the cortex can influence responses to sensory stimulation, and that evoked sensory responses are distributed across large parts of the cortex (Enander & Jorntell, 2019; Enander et al., 2019; Etemadi et al., 2022;

Findling et al., 2023; Frostig et al., 2008; Rancz et al., 2015; Wahlbom et al., 2019).

When considering the cortex as a network with global processing mechanisms, all afferent signals will always have to be interpreted in the context of and integrated with the intrinsic properties of any cortical subnetworks that it comes in contact with (Norrlid et al., 2021; Stringer et al., 2019). The modulatory influence of spontaneous activity on sensory responses has, in fact, been shown before (Arieli et al., 1996; Chen et al., 2020; Steriade et al., 1993). The results from paper I show that peripheral stimulation also changes the spontaneous activity in the cortex, as even weak sensory stimulation caused a shift in the global activity distribution.

That D-amphetamine would have an effect across the majority of the cortex was expected, given the number of neurotransmitters it affects and their distribution in the brain (Stratmann et al., 2018; Tohyama & Takatsuji, 1998). An interesting result from paper III when considering global cortical processing of sensory information was that the high dimensionality remained after D-amphetamine had been administrated. This indicates that whatever its exact effect is, it did not reduce processing in the cortex to fewer dimensions. This could indicate that the processing remained widespread across the cortex. However, the difference between the activity distributions for spontaneous activity and activity during stimulation was reduced after D-amphetamine had been administered. If this is indeed an effect of the reduction in connectivity going from the thalamus to multimodal cortical areas as postulated above, this could also support the theory of global processing. If the cortex had a functional localization and D-amphetamine increase the connectivity between the thalamus and unimodal cortical areas, an increase in the difference between the spontaneous activity and activity during stimulation distribution would be expected. However, what we saw was the opposite, meaning that the response to the sensory stimulation in the S1 is not the reason for the separation in activity distribution. Instead, the reduction in separation between the two activity distributions could be due to a lack of processing in other areas, which would be in line with the reduced connectivity from the thalamus to multimodal cortical areas (Avram et al., 2024).

Another finding supporting the theory of a globally integrated network is in paper IV, where we observed a globally preferred frequency range. Changes to this preferred range occurred globally, indicating that a global synchronization of cortical rhythms exists. This might be a mechanism to aid in communication between areas, thus supporting global processing in the network (Buzsáki & Draguhn, 2004).

Interpreting results during anaesthesia

All experiments were performed in animals under anesthesia. It is therefore important to consider how anesthesia might affect the recorded activity and thus the results. In a previous part of this thesis, I discussed how ketamine/xylazine anesthesia might affect the cortical frequencies. As we are examining the effect of stimulation and D-amphetamine on the cortical activity, an important question is "how can we be certain that we are not just measuring an arousal effect".

In paper I we compared the activity distribution of the activity during stimulation to spontaneous activity immediately preceding and following it separately. This showed that there was a separation between activity during stimulation and the spontaneous activity just following it. This indicates that our stimulation did not cause a long-term change in the activity distribution via arousal.

Arousal has also been reported to correlate with PC 1, that is the principal component explaining the majority of the variance (Stringer et al., 2019). In paper I and III we found that PC 1 could be excluded from the kNN analysis without it affecting the resulting accuracy in classifying the type of activity any more than the exclusion of any other PC. This also indicates that it is not just the level of arousal that we are measuring.

The question of arousal might be even more important in paper III when we administered D-amphetamine, which is known to have effects on the level of arousal. For example, D-amphetamine has been shown to reduce both REM and non-REM sleep, and reduce the time of emergence from several types of anesthesia (Authier et al., 2014; Kato et al., 2021; Kenny et al., 2015; Moody et al., 2020). During ketamine anesthesia it appears that this effect is less pronounced (Kato et al., 2021). This might reflect an effect of ketamine releasing dopamine in the prefrontal cortex, which could interfere with some of the effects of D-amphetamines (Lorrain et al., 2003; Moghaddam et al., 1997).

The differences between spontaneous activity and activity during stimulation observed in paper I should be apparent in the awake state as well. However, as anesthesia reduces neuronal activity generally, there are likely many more potential activity distributions of spontaneous activity during wakefulness. This would mean that while still present, the separation between spontaneous activity and activity during stimulation might be harder to detect. If so, increasing the number of recorded channels could be a way to circumvent this, as an increased number of dimensions could contain more information about the activity distributions.

Thoughts on the choice of methods

ECoG and other methods for recording cortical activity

There are many methods to choose from when studying activity in the brain. Different methods allow for study of the cortical activity at different levels of resolution and detail. High resolution methods that give very specific information about a small part of the network with a high resolution, like patch clamp recordings. Or global methods, with lower resolution. Methods like fMRI, calcium imagining or ECoG.

In order to get a holistic view of how the brain operates, the optimal solution would of course be to record from every single individual cell. However, this is of course impossible. Not least because the sheer number of electrodes that would be needed would destroy much of the tissue if they were to be inserted into the brain. But even if it was possible, it might not be helpful, as the amount of data gathered from recording every individual neuron would be enormous and possibly insurmountable due to the computational power needed to analyse it.

Historically, recording from single cells has been the first choice in many investigations because of the high resolution. However, on a global level it is very limiting to study the behaviour of a single or a few cells in the same area. Therefore, using a method that is able to record distributed activity across the cortex is favourable.

A limitation of this approach is that it becomes impossible to say what specific neurons contribute with and how specific microcircuits might alter activity. Despite this, ECoG traces, which have a higher temporal resolution than fMRI or calcium imaging, at the cost of a lower spatial resolution, have been shown to contain enough information about underlying brain processing to drive a speech synthesizer (Littlejohn et al., 2025). ECoG recordings also have the advantage of being methodologically close to non-invasive EEG. This means that methods developed with ECoG recordings could possibly also be used with the non-invasive EEG method. Thus, opening up for applications in humans.

PCA, kNN and analysing and interpreting recorded data

In the end, regardless of the recording method, interpreting the functional significance of the recorded activity carries inherent difficulties. The firing of a neuron has no set functional meaning. And in *in vivo* experiments it is never possible to fully control both the external and internal environment, and so there will always be a degree of confounders. As discussed previously in this thesis, in

order to interpret the functional background of recorded neuronal activity we must thus relate it to the circumstances during which it was recorded.

There is also always the risk that an important part of the functionality that was investigated was not recorded or is lost in the recorded data due to limitations in analysis methods. In an attempt to capture as much of the global information as possible we thus chose to use PCA, which will capture as much information about variations in the variables as possible from all recorded channels in a single vector. This allows us to more effectively find differences between periods of activity that might consist of small changes across several of the recorded channels, but no big changes in any single channel. While EEG spectrograms are common for analysing this type of data, it lacks the cross-channel analysis (Maloney et al., 1997). PCA also allows for finding trends in the data that are independent of the frequency content, as we use individual time steps in our data as the individual data points and PCA simply combines cross-channel information to explain as much of the variance in the data as possible in a single vector. Instead, when comparing different parts of the activity distribution in the PC-space we are looking for differences in how data in all eight recorded channels relate to each other.

While the combination of information from all eight channels being represented in each vector allows for more subtle cortical integration becoming more apparent, interpreting differences in the PC-space comes with its own challenges. The principal components do not translate to specific features of the recorded data, they are simply the vectors that contain the largest amount of the information on the variation in the data. Thus, the results are hard to interpret from a functional viewpoint but can provide insights into how the information across the eight channels has changed.

Another inherent disadvantage of PCA comes from its function as a dimensionality reduction method. Reducing the number of dimensions can cause the loss of information important to the process that is studied (Kristensen et al., 2024; Pellegrino et al., 2024). There is also a risk of underestimating how complex the network and processing actually is. In the present studies, this risk was avoided as all principal components were included in the analysis and thus the number of dimensions remained constant. However, as the number of dimensions increase, this may no longer be a possibility, depending on the method used, since data tends to have an increased dispersion with a high number of dimensions.

In order to get a quantitative measure of the difference between groups of data in the PC space we used kNN. kNN has an advantage in that it requires very little preprocessing and thus we reduce the risk of transforming our data and the information in it. It gives a fairly straightforward result, simply showing to what degree the data could be correctly classified only by where it was positioned the coordinate system in the relation to other data points. kNN also has the benefit of

being able to perform this classification in any number of dimensions, which is good when investigating a system with a high dimensionality, were the separation or removal of dimensions in the analysis might greatly change the results.

However, with an increase in the number of dimensions there is a risk of the data becoming too widespread, thus making the distance between all data points similar. This is why combining kNN with a dimensionality reduction technique like PCA can be beneficial, allowing high levels of information in fewer dimensions.

Some caution needs to be observed when using kNN as it is a very sensitive method, and the activity distributions even within a single type of activity is highly complex (Etemadi et al., 2022; Norrlid et al., 2021; Stringer et al., 2019). This is exemplified in paper III where when comparing a minute of activity to the following minute of activity, with the same type of activity under the same condition, we also saw a separation between the two activity distributions. This is likely caused by the ever-ongoing internal process in the cortical network and is likely also in some way time dependent.

If we consider the spontaneous activity distribution to inhabit a set activity space, created by all possible cortical states, the activity distribution moves around within this space in a time dependent manner with the changing cortical state. Shorter time segments being compared would thus result in a higher kNN accuracy, as they would be two different subsets of the larger activity distribution. With increasing time segments being compared, the two subsets being compared would eventually contain more overlap, as the activity distribution will move back to previous subspaces. Possibly a long enough time window would result in two activity distributions of a single type of activity no longer being separable with kNN, although the time window needed could possibly be in the range of many hours. This is why control groups were used for the comparisons of the same type of activity in paper III and why emphasis was put on ensuring that the test and control group used time periods of the same length in the kNN analysis.

A place for frequency analysis

While the above analysis methods have resulted in some remarkably interesting findings, there is still very much a need for the methods resulting in more concrete and specific information about the cortical activity. Thus, in paper III continuous wavelet transform was used to analyze the frequency content during periods of spontaneous and stimulated activity. This allowed us to analyze whether the change seen in activity distribution could be explained by neural oscillations.

CWT is highly useful for examining how the frequency content in a signal change over time, as it has a time component. This is in contrast to FFT that will output all frequencies that are present in the signal during the analyzed period with no

indication of when or for how long any given frequency was part of the analyzed signal. Wavelet transforms are also generally good at reducing the amount of noise in a signal (Ergen, 2012). However, it adds redundancy to the analysis and with that computational time. It can also be hard to find comprehensive sources on the theory behind it and on how to perform it (Aguiar-Conraria & Soares, 2010).

In paper IV the focus was on the frequency content of the cortical activity. This was analyzed using fast Fourier transformation. This allowed for an examination on how global processing in the cortical network may interact with the inherent rhythms and mechanisms present in the CNS to regulate oscillations. While FFT lacks the time component present in CWT as mentioned above, it is a well-established method with a much faster computational time.

Implications for our understanding of the cortex

In summary, the combined results from our investigations, that the separation of activity distributions is not dependent on the inclusion of the evoked response in paper I, the D-amphetamine not reducing the dimensionality in paper III and the presence of a globally preferred frequency range in paper IV, support the theory of cortex as an interconnected network with a global functionality. This is in accordance with studies showing that sensory decoding is improved in groups of neurons, that sensory input is processed bilaterally in the brain and calcium imaging studies that shows widespread changes in cortical activity during motor behaviours (Enander et al., 2019; Genna et al., 2018; Nietz et al., 2022). While the presence of central hubs with a high degree of connectivity was not investigated, the findings of a highly integrated network with such hubs is in no way contradictory to the results presented in this thesis. Rather, they both support a network with high levels of global integration of neuronal information (van den Heuvel et al., 2012).

In such a network information is processed not in a single cell, column or area, but by a larger part of the network. With a global functionality in the cortex, any responses to a stimulus in a single neuron or cortical area would need to be put in context with the activity in the rest of the network. The need of this can be exemplified by the studies that have shown that distant activity or perturbations impacts the local response to a stimulus (Etemadi et al., 2022; Rojas-Libano et al., 2018; Wahlbom et al., 2019).

That processing is widespread across the cortex implies that it might be impossible to relate functionality to an area based on histological or anatomical features. This is in line with the idea that the cortical columns do not constitute a functional unit (Horton & Adams, 2005). Some correlation between structural and functional connectivity has been found, where regions with higher levels of structural

connectivity also show higher levels of functional connectivity. However, specific structural connections are not the complete explanation for functional connectivity. In adult brains, there are no known fast, large-scale, fluctuations in structural connectivity. Meanwhile, the functional connectivity in the brain can change rapidly, both spontaneously and in response to perturbations (Bullmore & Sporns, 2009; van den Heuvel & Hulshoff Pol, 2010).

Another complicating aspect of trying to understand the processing of sensory information is that the networks that are involved in processing information do not exist solely on a cortical level. Processing of sensory stimuli from the body has been suggested to start as early as in the spinal cord (Browne et al., 2024; Koch et al., 2018). Sensorimotor integration and processing appears in the interneuronal networks of the spinal cord (Jankowska, 2008). Advanced processing also happens at the level of nucleus cuneatus and nucleus gracilis, as well as in the thalamus (Alitto & Usrey, 2003; Jörntell et al., 2014; Wahlbom et al., 2021). Thus, even if we were able to perfectly map and understand the cortical network and its processing, we would still be lacking a deeper understanding of how a sensory stimulus is progressively transformed at each stage of the sensorimotor system. This, as we still do not understand how networks at different levels, spinal, subcortical and cortical, interact to shape the final perceptual outcome.

The same is true when examining the changes caused D-amphetamine. Given intravenously it will have a systemic effect. As modulation of monoamines can affect spinal interneurons, as well as the fact that monoamines are present throughout the brain, it is likely that any effect seen with the administration of D-amphetamine is not isolated to the cortex (Hammar et al., 2004; Stratmann et al., 2018; Tohyama & Takatsuji, 1998).

We must also consider the fact that none of these networks will be static. As mentioned above, functional connectivity can change rapidly within the brain (Bullmore & Sporns, 2009). In addition, there are also plasticity phenomena throughout the different networks and learning and adaptation occur at all levels in response to our bodies interacting with the environment. As the plasticity in the CNS can lead to both long- and short-term changes, any description of the networks and their processing must make allowance for such changes, without a loss of stability and structure (Jirenhed et al., 2007; Pascual-Leone et al., 2005; Petersson et al., 2003; Steriade & Timofeev, 2003).

Findings like this show just how far we still have to go to properly understand how the cortical network works. It is still very common to study activity in individual cells or in small areas of the cortex when investigating how different stimuli are processed in the brain (Carrillo et al., 2019; Helmstaedter et al., 2007; Liu et al., 2025). While understanding the shape of the individual jigsaw pieces is important, looking at the whole puzzle is essential to understanding the image. Even if one uses methods that allow visualization of the whole cortex, the analysis must be

advanced and sensitive enough to consider changes throughout the whole cortex simultaneously. And also, how activity changes in different areas concurrently and how these changes relate to each other, rather than only focusing on key areas. Are areas with an increase or a decrease in activity more important for the processing? And of course, information about the processing could be concealed in how the areas surrounding a specific region reacts to a stimulus. Of course, this greatly increases the difficulty in investigating the cortical activity. However, this is a field in constant motion and development. New and different methods are being developed that allows for the modelling and study of larger networks (Nayak et al., 2018; Szeier & Jörntell, 2025).

Potential avenues of future studies

It would be interesting to use the analysis methods from paper I and III in investigations on epilepsy, stroke, schizophrenia or Parkinson's to see how such conditions affect the activity distribution. As part of such investigations, it would be of great interest to follow the progression of stroke in the cortex. To investigate activity changes from the healthy brain to the brain during the acute damage, and to the brain after rehabilitation and potential regain of function. It could also be of interest to study the effects of drugs targeting specific receptors, to investigate the effects of individual neurotransmitters on the cortical network and its processing.

There have been reports of lasting changes in activity distribution following stimulation (Kristensen et al., 2024). Thus, it could also be of interest to study if the separation between activities will increase with longer periods of spontaneous activity in between the periods of stimulation. This could be a way to investigate the timing of a cortical return to a resting state and how long effects of stimulation lasts in the cortex. Further investigations into the dimensionality of the brain and redundancy in the network would also be valuable, possibly establishing a baseline for the dimensionality needed to investigate cortical processing.

Another possible continuation of the current investigations would be to increase the number of recorded channels and potentially use the same analysis with EEG recordings in humans. Some such investigations have already been made, using PCA and a classifier on human EEG data to detect mental fatigue (Chai et al., 2016). PCA and kNN appear to have a high level of sensitivity for changes in the network structure. With experience and refinement, they could potentially allow for detecting early stages of degenerative neurological diseases or for monitoring neurological and psychiatric diseases such as epilepsy or schizophrenia.

Concluding remarks

In recent years, an increasing number of studies are reporting findings in support of a global functionality in the cortex, with the cortical network being globally interconnected and with distributed processing. In this thesis, investigations on the cortical network and how it handles the processing of somatosensory stimuli and pharmacological perturbations, are reported.

The findings in paper I indicate that spontaneous activity and activity during stimulation have overlapping but separate activity distributions, and that the separation is not dependent on the presence of an evoked field potential response. The method that was used in paper I is described in detail in paper II, which is a methodology paper. In paper III it is reported that while D-amphetamine changes the activity distribution, it does not do so by reducing the global integration or the dimensionality of the cortical processing. Finally, in paper IV it is reported that the frequency content in the cortex is kept at a specific preferred internal range that was affected by the administration of D-amphetamine but unaffected by external input.

It is argued that activity distributions have a place among the methods to study cortical activity, albeit with the caveat that their interpretation is not clear in functional terms. The considerations necessary around dimensionality when studying such a complex network are important, so as not to lose important information about the recorded activity. Thus, activity distributions with a higher number of dimensions are likely more helpful for investigating cortical activity than ones with fewer.

The fact that there appears to exist an internal range of preferred frequencies that are largely unaffected by external stimuli could be an indication that there are strict internal processes that keep the cortical activity at a certain level given specific internal and external circumstances. That D-amphetamine changes both the preferred frequency range and the activity distributions, while seemingly not reducing the global integration of activity, could be due to a modulation of neurotransmitters and change in functional connectivity causing a change in the network structure.

A highly interconnected cortical network, with integrated processing, implies that research needs to focus on global activity when examining cortical processing. The cortex is also connected to several subcortical networks that are part of the

processing of sensory stimuli. Thus, it is likely that subcortical activity must also be considered for a comprehensive understanding of the processing and perception of sensory stimuli in the cortex.

In the future, studies with drugs targeting specific receptors could be of great interest, together with studies on models of neurological or psychiatric diseases. Studies to further investigate the features of changes in activity distributions and the dimensionality of the brain could potentially help refine and establish baselines for the methods of analysis used. There is also a possibility to develop the methods of analysis that were used here in anesthetized animals for further studies on wake humans.

In conclusion this thesis supports the notion of the cortex as a globally interconnected network characterized by a global integration and processing of sensory input. Furthermore, our results suggest that the cortex has a rich variation in internal dynamics during spontaneous activity, while simultaneously having highly regulated internal processes that are largely unaffected by external input. However, internal perturbations such as by the administration of D-amphetamine appear to shift these internal processes while keeping the global integration of the cortical processing intact.

Populärvetenskaplig sammanfattning

Allt vi upplever och gör är på grund av vårt nervsystem. Högst upp i nervsystemet är vår hjärna. Trots många år av forskning vet vi fortfarande inte exakt hur hjärnan fungerar. När det kommer till hur hjärnan bearbetar intryck från våra sinnen har det länge funnits två teorier. Den ena är att känselinformation från kroppen kommer att nå ett litet område i hjärnan som är specialiserat på bearbetning av just den typen av information. Detta område kommer sedan bearbeta känselinformationen innan den kan sättas ihop med information från andra delar av kroppen, i ett annat område av hjärnan. Den andra teorin är att känselinformation från kroppen istället bearbetas samtidigt i många delar av hjärnan, och att nätverket av nervceller i hjärnan är mer komplext sammanlänkat än det skulle vara om varje område bara tog hand om en väldigt specifik funktion.

Då hjärnan består av flera biljoner nervceller är det svårt att studera vad som händer i stora delar av den samtidigt på ett bra sätt. Därför måste man försöka koppla ihop förändringar i aktivitet i hjärnan som man kan mäta med vad som hänt under tiden som man spelat in aktiviteten för att försöka lista ut vad som orsakar de förändringar man ser. För att studera hjärnan kan man spela in aktivitet från nervcellerna på olika sätt.

Man kan till exempel mäta signaler på utsidan av hjärnan som representerar den elektrisk aktiviteten från massor av nervceller. Man kan sen försöka förstå signalen genom att undersöka i vilken takt nervcellerna är aktiva, något som kallas frekvensanalys. Det innebär att man plockar ut olika svängningar som förekommer i signalen när många nervceller aktiveras samtidigt. Man kan också mäta aktiviteten på flera olika platser samtidigt för att se hur aktiviteten i de olika områdena hänger ihop och förhåller sig till varandra.

För att göra det enklare att förstå vad den aktivitet man har spelat in betyder kan man titta på hur den ändras när olika saker händer i omgivningen. På det sättet kan man koppla en viss förändring till en specifik händelse. Till exempel kan man jämföra hjärnans aktivitet under vila när inget händer med aktiviteten när man rör vid huden så att information från känselsinnet skickas till hjärnan. Man kan också ändra på förutsättningar inne i hjärnan, till exempel genom att ge kemiska substanser som påverkar hjärnan, eller genom att framkalla sjukdomstillstånd och jämföra aktiviteten före och efter stroke eller före och under ett epilepsianfall.

Den här avhandlingen består av tre vetenskapliga studier, och ett studieprotokoll som beskriver hur en av dessa studier gjorts. Målet är att öka förståelsen för hur hjärnan arbetar. För att uppnå detta har vi spelat in aktivitet från ostörd sömn, när vi simulerar beröring av en tass med hjälp av en elektrisk signal och efter att vi gett amfetamin, som påverkar många olika signalämnen i hjärnan. Studierna har gjorts på sövda råttor där vi gjort inspelningar från utsidan av hjärnan.

I artikel I såg vi att genom att undersöka aktiviteten i åtta områden av hjärnan samtidigt så kunde man särskilja aktiviteten när råttan sov ostört jämfört med när vi simulerade beröring på dess tass. Skillnaden syntes inte bara i inspelningarna från de områden som anses vara ansvariga för att hantera beröring av tassen, utan även i andra delar av hjärnan, vilket tyder på att känselinformationen även når till dem.

Artikel II går i detalj igenom hur studien i artikel I utförts, steg för steg.

I artikel III fortsatte vi titta på hjärnans aktivitet i de åtta områdena, men provade nu också att förutom att simulera beröring på tassen även att ge råttan amfetamin. Vi upptäckte då att även om amfetamin ändrade aktiviteten i hjärnan, så verkade det inte ha effekt på hur utspridd information om beröringen var i hjärnan.

I artikel IV tittade vi istället på vilka frekvenser som var vanligast i signalen från de olika områdena. Det visade sig att det fanns stora likheter i alla de områden i hjärnan vi spelat in från. När vi simulerade beröring av tassen var samma frekvenser vanligast i signalen, men det fanns nu mer av dem. När amfetamin gavs ändrades det dock lite vilka de vanligaste frekvenserna var. Detta kan vara ett tecken på att hjärnan tycker bäst om att jobba med signaler med en viss frekvens och därför har olika sätt att se till att signaler som kommer med information anpassar sig till detta, men att frekvenserna ändras om man ändrar på förutsättningarna inne i hjärnan.

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