Neocortical interpretation of haptic and visual events across brain states: Electrophysiological investigations in sensory information processing

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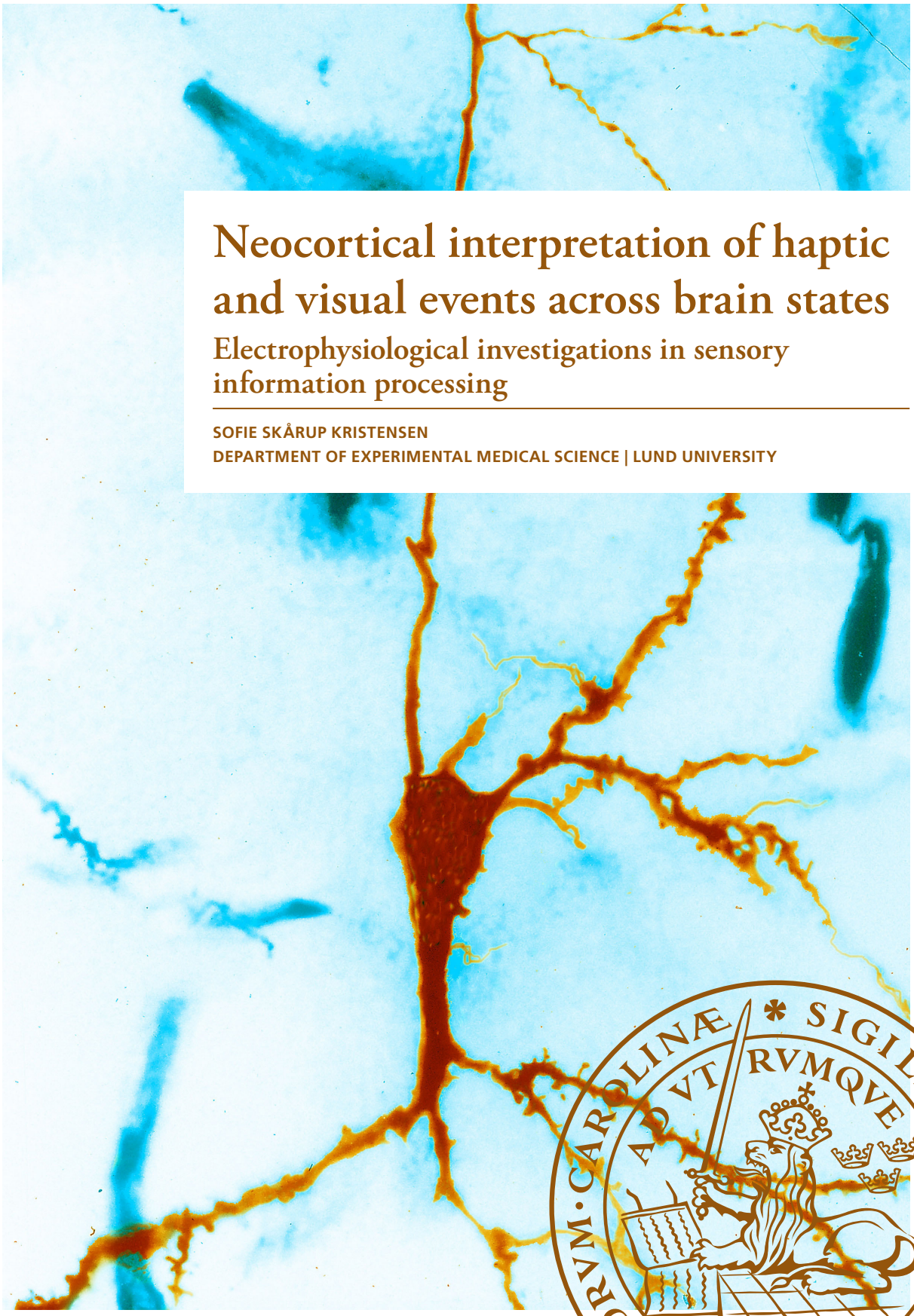

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Sofie Skårup Kristensen

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

This thesis delves into the complex architecture of dynamic sensory information processing in the neocortex. Specifically, it asks how primary sensory cortical regions are influenced by local and widespread cortical state changes. Central to this question is the exploration of two historically opposing information processing frameworks emphasizing a local and global information processing principle respectively, i.e. the principle that certain areas of the brain are dedicated to specific functions and the principle that individual functions are distributed over a large network.

Results were obtained through in vivo extracellular recordings in anesthetized rats while high-resolution spatiotemporal visual, tactile, and visuo-tactile input patterns were provided. Paper I showed that color input evokes rapid local state changes in primary visual cortex (V1) which result in unique temporal response patterns among neurons recorded within the same vertical axis, thereby challenging the historically popular idea of columnar organization. Paper II used field potential recordings as estimates of changes in the widespread and local cortical state and showed a significant differential effect on individual neuronal responses to haptic input in the primary somatosensory cortex (S1). In paper III, spontaneous activity among S1 neuron populations was defined as a high-dimensional state space that was found to shift in different ways when providing tactile, visual, and visuo-tactile input, questioning the idea of unimodal cortical regions.

Together, the results suggest that both local and widespread internal brain states can impact processing of sensory information in primary sensory regions. It is concluded that the functional localization model cannot fully explain what we and other researchers have observed about cortical sensory information processing and that brain state dependence on the neuronal representation of sensory input is more likely a result of coordinated activity across multiple, interconnected brain regions.

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Preface

This thesis aims to elucidate how time-varying internal brain states are studied and manipulated and how they affect neocortical representation of haptic and visual information.

The introduction starts with an exploration of the concept of brain state dependence on perception, along with some theoretical frameworks that provide insight into this phenomenon. This is succeeded by an overview of the tactile and visual information processing pathways, from the eyes and skin to the neocortex. The last part of the introduction is a presentation of the use of electric potential recordings in studying brain functionality, highlighting the method's advantages and limitations compared to other techniques.

Next, a methods section presents the experimental and analysis methods used in the three papers included in this thesis, followed by a presentation of the results. Paper I explores the local brain state mechanisms in primary visual cortex (V1) in response to spatiotemporal color input. Paper II uses different field potential recordings as estimates of local and widespread cortical states and investigates their effect on neuronal response to haptic input in primary somatosensory cortex (S1). Paper III defines spontaneous activity among S1 neuron populations as a high-dimensional state space and explores how the state space shifts when providing tactile, visual, and visuo-tactile input.

The results section is followed by a discussion comparing the results from the three papers with other research findings. The discussion focuses on methodology and information processing frameworks. It culminates in an evaluation of the effect of local and widespread cortical state changes on the interpretation of sensory input in primary sensory regions.

List of original papers

I. **Sofie S. Kristensen** and Henrik Jörntell. Differential encoding of temporally evolving color patterns across nearby V1 neurons. *Frontiers in Cellular Neuroscience, 2023, 17.*

II. **Sofie S. Kristensen** and Henrik Jörntell. Local field potential sharp waves with diversified impact on cortical neuronal encoding of haptic input. *Manuscript.*

III. **Sofie S. Kristensen**, Kaan Kesgin and Henrik Jörntell. High-dimensional cortical signals reveal rich bimodal and working memory-like representations among S1 neuron populations. *Manuscript.*

Important abbreviations

S1	Primary somatosensory cortex
V1	Primary visual cortex
LGN	Lateral geniculate nucleus
VPL	Ventroposterior lateral nucleus
CNS	Central nervous system
EEG	Electroencephalogram
ECoG	Electrocorticogram
MRI	Magnetic resonance imaging
fMRI	Functional MRI
PET	Positron emission tomography
CO	Cytochrome oxidase staining
AP	Action potential
LFP	Local field potential
SPW	Sharp wave
PSTH	Peristimulus time histogram
ISI	Interspike interval
KDE	Kernel density estimation
PCA	Principal component analysis
kNN	k-nearest neighbors
MI	Multisensory integration
DSS	Dissociative somatoform symptoms

Abstract

This thesis delves into the complex architecture of dynamic sensory information processing in the neocortex. Specifically, it asks how primary sensory cortical regions are influenced by local and widespread cortical state changes. Central to this question is the exploration of two historically opposing information processing frameworks emphasizing a local and global information processing principle respectively, i.e. the principle that certain areas of the brain are dedicated to specific functions and the principle that individual functions are distributed over a large network.

Results were obtained through *in vivo* extracellular recordings in anesthetized rats while high-resolution spatiotemporal visual, tactile, and visuo-tactile input patterns were provided. Paper I showed that color input evokes rapid local state changes in primary visual cortex (V1) which result in unique temporal response patterns among neurons recorded within the same vertical axis, thereby challenging the historically popular idea of columnar organization. Paper II used field potential recordings as estimates of changes in the widespread and local cortical state and showed a significant differential effect on individual neuronal responses to haptic input in the primary somatosensory cortex (S1). In paper III, spontaneous activity among S1 neuron populations was defined as a high-dimensional state space that was found to shift in different ways when providing tactile, visual, and visuo-tactile input, questioning the idea of unimodal cortical regions.

Together, the results suggest that both local and widespread internal brain states can impact processing of sensory information in primary sensory regions. It is concluded that the functional localization model cannot fully explain what we and other researchers have observed about cortical sensory information processing and that brain state dependence on the neuronal representation of sensory input is more likely a result of coordinated activity across multiple, interconnected brain regions.

Introduction

We are only just beginning to understand how different regions in the brain and the activity of neurons correlate with the perception of sensory input. Central to this exploration is the idea of brain state changes, i.e. the underlying cortical circuitry algorithm by which perception arises. In this introduction, studies suggesting a relationship between the state of the brain and its interpretation of sensory input will be presented together with an overview of the visual and tactile processing pathways, and electrophysiological techniques to study these phenomena.

What is a brain state?

A crucial aspect of perception, and illusions in particular, is that the brain's response to sensory input not only is determined by the characteristics of the sensory input itself but also by expectations, prior knowledge, and the internal state of the brain when the input occurs. In psychology, this phenomenon is often referred to as 'top-down' processing. While 'bottom-up' processing refers to incoming sensory input working its way up, top-down processing refers to a cognitive approach where higher-level knowledge and expectations guide the interpretation of sensory information. The concept of top-down processing arose among 20th-century Gestalt psychologists who observed that perception of different ambiguous images can be primed, meaning that the brain's expectations can be manipulated to make sense of new information in a certain way (Gilbert & Sigman, 2007; Porter, 1954; Wertheimer, 1938).

A more biological perspective on the functional and computational basis of top-down influences is the notion of brain states. It posits that synaptic connections, shaped by experience, create constrained 'realms' of potential response combinations (Golub et al., 2018; Luczak et al., 2009) and the concept thus extends beyond the idea of just higher-order cognitive influence on sensory input. The idea developed with advances in different neuroimaging techniques which enabled neuroscientists to observe how brain state changes such as sleep patterns and levels of alertness alters how the brain processes the same sensory stimulus. For example, intracellular whole-cell recordings

have shown that S1 neuronal responses to whisker stimulation are highly correlated with spontaneous fluctuations in brain activity (Crochet & Petersen, 2006; Petersen et al., 2003; Poulet & Petersen, 2008) and that internal brain network dynamics result in different intracellular representations of the same tactile input (Norrlid et al., 2021). A global brain state can be defined as the combination of activity in all neurons in the brain (Spanne & Jörntell, 2015), whereas the summed activity in specific regions or networks within the brain can be referred to as a local state.

The extent to which the global state can modulate responsiveness or sensitivity in local brain regions and vice versa, if local states can feedback and influence the global brain state, is a debated topic in neuroscience. Historically, sensory information processing within the brain has been posited to follow a linear, hierarchical path, progressing from simpler lower-level processing to more complex higher-order functions. This perspective, known as hierarchical (or local) information processing, assigns distinct roles to different brain areas in the refinement of sensory data interpretation, a concept referred to as functional localization. In contrast, the parallel (or global) information processing theory posits a parallel processing paradigm, wherein the brain integrates sensory inputs through a complex, interconnected neuronal network. This approach advocates for a comprehensive, holistic interpretation of brain functionality, with an extreme postulation suggesting the involvement of each neuron, i.e. global involvement, in all brain circuitry operations.

Visual and tactile sensory processing

Visual pathway

The eye

Processing of visual information starts in the eye where light waves are transduced into electrochemical signals by photoreceptor cells. First, light is focused by the cornea and lens onto the retina at the back of the eye. The retina consists of several layers of neurons interconnected by synapses with the 'outer' and first surface layer consisting of rods and cones, which are photoreceptor cells. Both rods and cones contain light-sensitive proteins called ciliary opsins, which are subdivided into scotopsins (responsible for dim light vision) and photopsins (responsible for daylight vision) (Bear et al., 2016b). Because rods mainly consist of scotopsins they are said to be responsible for low light levels and contrast detections and not color discrimination. Cones on the other hand are said to be responsible for color vision because they consist mainly of photopsins,

which are wavelength sensitive. Humans have three types of cones divided by the different wavelength sensitivity of the opsins they contain: L-cones, M-cones and S-cones which have been shown to respond optimally to long wavelengths (reddish color), medium wavelengths (greenish color), and short wavelengths (bluish color) respectively. Humans are therefore said to have trichromatic vision, whereas rats are said to have dichromatic vision as they lack L-cones.

Because rats only have two types of cones, they were thought to be red color blind for a long time. Recent literature, however, has revealed that the different types of cones not only contain one type of opsin but different percentages of M-opsins and S-opsins (Wang et al., 2011), which in theory should diversify the color tuning among the cones beyond that defined by the individual opsin. Individual neurons of the retina network can thus create different combinations of individual photoreceptor inputs to dramatically increase the color information present in the retinal output (Yoshimatsu et al., 2021). Furthermore, it has been shown that at least in the rat, rods also have a degree of color tuning (Wang et al., 2011) and could thereby contribute to color opponency in an advanced processing network.

Both in humans and rats, rods and cones project to bipolar cells which pass information to the retinal ganglion cells (RGC) directly or indirectly (via amacrine cells). Retinal ganglion cells (RGC) make up the 'inner' and second surface layer of the retina.

The lateral geniculate nucleus

Most of the ganglion axons project to the dorsal lateral geniculate nucleus (dLGN), a structure in the thalamus. When staining the dLGN of the macaque monkey, it becomes visible that it is composed of larger cells and smaller cells organized in six layers (Hubel, 1988). The smallest cells (the koniocellular layer) are innervated by axons from K ganglion cells, the slightly larger cells (the magnocellular dLGN layers) by axons from M ganglion cells, and the largest cells (the parvocellular dLGN layers) by axons from P ganglion cells (Bear et al., 2016a).

Initially, the distinct and segregated input to the LGN layers led to the belief that this brain region functions predominantly as a passive relay station. According to this view, the LGN simply forwards visual information from the retina to the visual cortex without significant processing, maintaining the separation of information streams from the parvocellular, magnocellular, and koniocellular pathways, respectively. Several studies, however, indicate that the LGN plays a more preliminary role in actively processing visual information. For example, an fMRI study has shown that attention can modulate activity in the human LGN by enhancing neural responses to attended stimuli (O'Connor et al., 2002), and cellular studies have shown that individual dLGN

neurons encode visual parameters in unique ways, suggesting some kind of learning mechanism (Gollisch & Meister, 2010; Marshel et al., 2012; Petersen et al., 2013).

In addition to input from the retina, the dLGN also receives input from multiple brain regions, including the primary visual cortex. In fact, about 80% of its input is from excitatory V1 neurons (Bear et al., 2016). This corticothalamic interaction has been studied and discussed extensively in several papers (Briggs & Usrey, 2007; Sherman, 2007; Sillito & Jones, 2002) all of which argue that the relationship between the LGN and V1 is complex and that the feedback from V1 to the LGN plays a crucial role in the dynamic modulation of visual information processing. Hence, many studies indicate that a great variety of signals is being sent to this thalamic structure, suggesting that the dLGN is involved in tuning information from the retina, contrary to being a passive relay structure.

The primary visual cortex

From the LGN, the neurons give rise to axons projecting to the primary visual cortex (V1), located in the occipital lobe of the brain. Like the rest of the neocortex, V1 is divided into six horizontal layers, with the majority of the thalamic efferents projecting to layer IV (Livingstone & Hubel, 1984) but with some direct connectivity also found to the superficial V1 layers I and II (Cruz-Martín et al., 2014). Input from the two eyes is segregated in columns across the horizontal layers called ocular dominance columns first discovered by (Hubel & Wiesel, 1962) who were pioneers in studying the primary visual cortex. Ocular dominance columns were argued to have some important functionality for integrating input from the two eyes. Horton & Adams (2005), however, question this because only the koniocellular neurons, and not the parvocellular neurons and the magnocellular neurons, are segregated both by layer (Chatterjee & Callaway, 2003) and by column (Hendry & Yoshioka, 1994). Furthermore, while having the same visual skills as humans, both the tree shrew and squirrel monkeys lack ocular dominance columns, suggesting that this organization might not serve any function (Casagrande & Harting, 1975; Hubel, 1975).

Columnar functional organization has also been suggested in relation to line orientations (Hubel & Wiesel, 1962; Kondo et al., 2016; Ohki et al., 2006) and motion direction (Palagina et al., 2017) because when penetrating the horizontal layers with an electrode perpendicular to the surface, the neurons have been found to respond similarly, forming columns of neurons with similar input preferences. Several studies, however, challenge this notion of functional columnar organization by reporting findings where the neurons are often broadly tuned in their orientation selectivity (Albus, 1975; Blasdel & Salama, 1986; Hetherington & Swindale, 1999; Ringach et al., 2002).

Also, a cylindrical vertical organization of neurons with increased CO content has been reported from several different layers (Horton & Hubel, 1981; Wong-Riley & Carroll, 1984). The structures were named 'blobs' by Livingstone & Hubel (1984) and have later been identified with other labeling techniques due to the increased content of neurotransmitters, receptors, and structural proteins (Carder, 1997; Carder & Hendry, 1994; Hendrickson et al., 1981; Horton, 1984; Wong-Riley et al., 1998). Several functional properties of blobs have been suggested, for example, that they are dedicated to a single type of color opponency but not orientation (Landisman & Ts'O, 2002; Livingstone & Hubel, 1984; Ts'o & Gilbert, 1988). Other studies, however, find that the blob cells indeed are orientation selective but fail to find a relationship with color tuning (Lennie et al., 1990) whereas others report no color tuning and no orientation preferences (Leventhal et al., 1995).

Tactile pathway

The skin

Touch input starts when mechanoreceptors in the skin are activated mechanically. Traditionally, mechanoreceptors are divided into four types based on their sensing properties and morphological appearance. The largest ones, the Pacinian corpuscles, lie in the deeper layer of the skin, the dermis, and have been found to respond to vibrations (Abraira & Ginty, 2013; Johansson & Flanagan, 2009). The Meissner corpuscles are about one-tenth the size and have, in the same studies, been found to be located mainly in the ridges of the glabrous skin where they respond to movement of the skin. The Merkel's disks, located in the outer layer of the skin, the epidermis, have small receptive fields and are said to respond to indentation such as edges and points. Finally, the Ruffini endings with large receptive fields are found in all layers of the skin and are said to respond to stretching of the skin (Abraira & Ginty, 2013; Johansson & Flanagan, 2009; Knibestöl & Vallbo, 1970). The cells are further divided into slow-adapting (Pacinian and Meissner corpuscles) and fast-adapting (Merkel's disks and Ruffini endings), because they have been found to continue to respond when there is a long-lasting stimulus or only to the onset of a stimulus, respectively. Whether the mechanoreceptors should be categorized like this can, however, be questioned as their response profiles have been shown to overlap significantly under some conditions (Johansson et al., 1982). In line with this, Hayward (2011) argues that individual receptors are dependent on their biomechanical context meaning that a receptor response is not just a simple, isolated event but dependent on the overall mechanical interactions and conditions that are present. This is supported by the finding that even basic skin-object contacts, like finger tapping, engage numerous mechanoreceptors

across a broad region, encompassing much of the hand and multiple fingers (Shao et al., 2016, 2020).

The cuneate nucleus and the ventroposterior lateral nucleus

The mechanoreceptor primary afferents enter the spinal cord through its dorsal roots, ascend along the dorsal column, and terminate in the cuneate nucleus in the brainstem. Here, information is forwarded from first-order neurons to second-order neurons, which cross to the contralateral side and form efferent connections to the ventroposterior lateral nucleus (VPL) in the thalamus. Both the cuneate nucleus and the VPL have classically been described as relay stations, meaning that incoming information is forwarded without any type of interpretation or learning. Multiple studies, however, suggest otherwise, for example, Bengtsson et al. (2013) showed that neurons in the cuneate nucleus are dominated by 4–8 primary afferent inputs with large synaptic weights even though other studies suggest that they receive input from hundreds of primary afferents (Jones, 2000). This is an indication of a learning mechanism in cuneate nucleus neurons where the strength of synaptic connections changes in response to sensory input patterns. In support of this, Jörntell et al. (2014) demonstrated that individual cuneate nucleus neurons could separate different types of tactile input, and that neurons with similar receptive fields had highly unique response patterns to the same tactile input. This was later also found to be true for thalamic neurons with direct afferent input from the cuneate nucleus (Wahlbom et al., 2021), and even for thalamic neurons with longer response latency times although at a lower performance. The latter is an indication of descending input from the neocortex, which, together with recurrent connections within the thalamus itself also have been shown to modulate ascending somatosensory information (Alitto & Usrey, 2003; Jones, 2002; Sherman, 2007, 2016), suggesting that the thalamus is not just a simple relay center.

The primary somatosensory cortex

The somatosensory information is forwarded from the VPN to the primary somatosensory cortex (S1). The receptive field of the first-order sensory neurons is commonly thought to be segregated through the cuneate nucleus and the VPL all the way to S1 which has been shown to result in an orderly map of the body in the cortex. This was first shown by direct stimulation of different areas of the S1 in neurosurgical patients (Penfield & Boldrey, 1937) who named this topographic brain map of the body along the postcentral gyrus the sensory homunculus. The body has also been mapped in the rat somatosensory cortex by stimulating different body parts and recording the responding neuron activity (Chaplin & Lin, 1984) although most of what we know about rat somatotopy comes from the whisker-dominated posteromedial barrel fields (Feldmeyer, 2012). However, multiple studies have shown that efferent

connectivity from different thalamic nuclei terminates in various cortical areas (Cappe et al., 2009; Hunnicutt et al., 2014), and other studies have shown that somatosensory cortical neurons in the forepaw region of the second digit in rats with high accuracy can separate different types of input provided to the first digit (Enander & Jörntell, 2019), and decode contralateral and ipsilateral input patterns to comparable extents (Genna et al., 2018). Similarly, the conventional model that tactile information spreads from the thalamus to layer L4 and from there to L2/3 and L5/6 (Feldmeyer, 2012; Gilbert & Wiesel, 1979), can be questioned. Measurements of reconstructed thalamocortical axons show direct innervation to L5/6 (Oberlaender et al., 2011) and neurophysiology in vivo recordings show that L5 neurons sometimes respond faster than neurons in L4 (Constantinople & Bruno, 2013).

Visuo-tactile integration

When you grasp an object, you do not experience the sight of the object and the haptic sensation as separate events. Your brain integrates information from spatiotemporal activation patterns of photo -and mechanoreceptors into a single percept and your experience becomes holistic and continuous. Within the hierarchical model of sensory processing, cortical multisensory integration (MI) is thought to occur only in secondary heteromodal areas, after unimodal processing in primary cortical regions (Felleman & Van Essen, 1991). Early neuroanatomical studies indicated almost no interconnections between unimodal cortical areas which contributed to this notion (Kuypers et al., 1965). Since then, other anatomical studies have found the substrate for MI to be present in these cortical areas (Cappe & Barone, 2005; Falchier et al., 2002; Rockland & Ojima, 2003), and several studies have shown that neurons in primary sensory regions also respond to sensory input from other modalities (Enander et al., 2019; Koelewijn et al., 2010; Wallace et al., 2004). Following these findings, it has even been suggested that all of the neocortex may be multisensory in the organization of its processing (Ghazanfar & Schroeder, 2006).

Studying electric potential in the brain

Action potentials

Neurons communicate via action potentials (APs) which are initiated when the membrane potential reaches a critical threshold due to depolarization. In sensory neurons, depolarization happens if the sensory receptor is activated by light, touch, or

sound etc., and within the central nervous system (CNS) it happens via synaptic input from another neuron. APs can be recorded with an electrode in the extracellular medium and give insight into the information a neuron sends out to other neurons. Several characteristics of the APs such as frequency, latency, or temporal patterns of activation are used to study how different types of information is represented in different parts of the brain.

One of the most fundamental questions the APs can answer is whether or not a neuron responds to a certain type of stimulus. For example, this is the question asked when defining the receptive fields in cortical neurons in vision studies (Gilbert, 1977; Hubel & Wiesel, 1962; Palagina et al., 2017) and mechanoreceptors in the skin (Abraira & Ginty, 2013; Knibestöl & Vallbo, 1970) both of which were in used to make interpretations about functional organization. To determine if a neuron responds to a stimulus or not, one has to first define a baseline, a threshold, a critical factor by which the threshold should be exceeded, and a time window within which this should occur. These predefined values might vary from paper to paper, and are sometimes not even reported, for example, a concrete definition is lacking from all of the above-mentioned studies in this paragraph.

Because of an interest in describing neuronal preferences, tuning, and selectivity to different parameters, another commonly asked question is with which intensity a neuron responds to a stimulus. Also here, different definitions exist, for example, the number of APs fired within a predefined time window or how fast the AP is fired (Johansson et al., 1982). Unfortunately, because some studies are unclear about how they define a response, their equations for calculating tuning and selectivity are hard to compare (Abraira & Ginty, 2013; Hubel & Wiesel, 1962; Knibestöl & Vallbo, 1970; Kondo et al., 2016; Palagina et al., 2017). And while these are valid questions to ask, they fail to take into account the temporal dimension of neuronal responses.

Field potentials

Whenever there is current going into a neuron it creates an electric field in the surrounding extracellular space, which is called a field potential. Because of electrical activity from thousands of neurons in the brain, we can only detect field potentials if they have a sufficient amplitude. They can be studied from the scalp with electroencephalography (EEG) or directly from the brain surface with electrocorticography (ECoG), which captures the activity of large populations of neurons. These methods are often used to record field potential oscillations (brain rhythms) in studies of sleep patterns or to diagnose neurological disorders.

The local field potential

The local field potential (LFP) is a specific type of field potential that is recorded from inside the brain tissue. It originates from the combined electrical activity within a smaller, more local neuronal population, and has been found to reflect synchronous excitatory postsynaptic potentials, inhibitory synaptic input, and afterpotentials of somatodendritic action potentials (Buzsaki & Kandel, 1998; Hasenstaub et al., 2005). The magnitude of the field potential will vary depending on the distance to the electrode and the size of the current, which can be used to estimate where the LFP originates from. Where some studies have reported the LFP to occur within approximately 200-400 µm of the recording electrode in the cortex (Katzner et al., 2009; Xing et al., 2009), other studies have reported it to spread laterally up to 600-1000 µm (Berens et al., 2008) and up to 2-5 mm (Kreiman et al., 2006; Leski et al., 2013; Nauhaus et al., 2009; Wang et al., 2005). The latter studies, however, record evoked local field potentials which can be very large, thus, the spontaneously occurring LFPs are still thought to be extremely local.

The hippocampal sharp wave

Recordings from the hippocampus have reported a field potential signal with a relatively distinct neurophysiological signature. The hippocampal sharp wave (Hipp-SPW), as it has been named, is reported within the frequency range 50:150 (Buzsáki, 2015; Liu et al., 2022; Petersen et al., 2022) and is often superimposed by higher frequency components, ripples. The Hipp-SPW has been associated with many high-level brain functions, such as replay and recall (Buzsáki, 2015; Kanamori, 1985; Leonard & Hoffman, 2017; Liu et al., 2022), and it also been linked to activity changes in the neocortex in different ways (Logothetis et al., 2012; Mölle et al., 2006; Siapas & Wilson, 1998; Sirota et al., 2003). For example, Hipp-SPWs can trigger corresponding EEG-SPWs as demonstrated for the prefrontal cortical region (Mölle et al., 2006). Although the overall occurrences of Hipp-SPWs are often not analyzed in detail in the literature, raw data illustrations indicate that their rate of occurrence is more than 1 Hz (Kanamori, 1985) and up to 2 Hz (Mölle et al., 2006).

Comparison with other techniques

Recordings of electric potential have a very high temporal resolution which makes it suitable for studying when things are happening in the brain, in other words, how the brain functions. Other techniques have a higher spatial resolution, meaning that they are accurate at locating neural structures in the brain.

At the cellular level, calcium imaging and two-photon calcium imaging are some popular techniques for studying the brain's functions. When a neuron is depolarized, there is a rapid influx of calcium ions, which can be visualized by injecting calcium-sensitive fluorescent dye into the neurons. Both methods have much lower temporal resolution than electrophysiology recordings, but the big advantage of two-photon calcium imaging is that it allows imaging in three dimensions, i.e. the spatial resolution is higher.

The above-mentioned techniques are invasive which is why methods such as Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI) often are preferred to study brain function in humans. In PET, the metabolic activity in neurons is recorded with radioactive tracers, and fMRI detects changes in oxygenated blood. Both metabolism and blood supply to neurons happen at a much slower rate than changes in membrane potential and as a result, the temporal resolution in PET and fMRI is quite low compared to non-invasive electrophysiology recordings. However, because of the high spatial resolution of the methods, they are preferred in studies investigating both function and structure.

Cytochrome oxidase (CO) staining is an example of a technique measuring changes in metabolism at the cellular level. It is performed in vitro and is most suitable for studying structure but can also be used to study function, for example by correlating micrographs with real-time mapping from two-photon calcium imaging. Many more microscopic techniques exist, each with its advantages and limitations, one of which is the fact that they are all invasive to some extent. Non-invasive structural imaging techniques such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are therefore used in clinical settings to study structures in the brain.

Methods

This section provides an overview of the experimental methods and the most important analysis methods used in the three papers included in this thesis. If the reader would like a more detailed description of specific methods or an in-depth explanation of the motivation for using certain methods, please see the method sections provided in the individual papers.

Experimental

Animal research

Adult male Sprague-Dawley rats were used in all papers included in the thesis. All use of experimental animals was reviewed and approved by the Local Animal Ethics Committee in Lund/Malmö. All studies were conducted in accordance with the local legislation and institutional requirements.

Anesthesia

Rats were under general anesthesia in all experiments. Anesthesia was induced with a mixture of ketamine (40 mg/kg) and xylazine (4 mg/kg), administered intraperitoneally after initial sedation with isoflurane gas (3%) for 1-2 minutes. Continuous anesthesia during the experiment was maintained through an intravenous catheter in the right femoral vein, delivering a mixture of Ringer acetate and glucose mixed with ketamine and xylazine (20:1 ratio) at a rate of approximately 5 mg/kg/h. Throughout the procedure, the anesthesia level was closely monitored to ensure a light yet sufficient anesthetic depth (as confirmed by the regular absence of withdrawal reflexes upon pinching the hind paws). Additionally, the irregular occurrences of synchronized brain activity, a sign of deep sleep (Niedermeyer & da Silva, 2005), were continuously observed to confirm the appropriate anesthesia level. The choice of anesthetic was based on its known property of preserving patterns of sequential neuron activity recruitment

across diverse forms of UP states (Luczak & Barthó, 2012). Following the completion of the experiment, the animals were euthanized with an overdose of pentobarbital.

Surgery

First, the head of the animal was fixated using a stereotaxic frame. The skin was cut open, and tissue covering the skull was removed. In paper I, craniotomy was made over the binocular region of V1 (V1b), where input from the two eyes converge, and in paper II and III craniotomy was made over the somatosensory forepaw cortical area. Craniotomy in all papers were made contralateral to the stimulated eye or paw illustrated in Figure 1A. Size of craniotomy varied depending on whether it had to the Neuropixel probe or the patch pipette and an ECoG electrode.

Recordings

Neuropixel

In paper I and paper III spiking activity was recorded with Neuropixel silicon probes. The probe recorded from the lower (first) 384 channels but only the top 180 channels of these were used for analysis as they were located within the approximately 1.8 mm deep cortex. Neuropixel recordings were digitized (30 us sampling time per channel).

Patch clamp

In paper II, extracellular recordings of individual neurons were made with patch clamp pipettes in the loose-patch current clamp recording mode. Borosilicate glass capillaries were used to pull the patch pipettes to 10–30 MΩ using a Sutter Instruments (Novato, CA, USA) P-97 horizontal puller. Pipettes were filled with an electrolyte solution composited of (in mM) potassium-gluconate (135), HEPES (10), KCl (6.0), Mg-ATP (2), EGTA (10) titrated to 7.35–7.40 pH using 1 M KOH. The pipette was inserted into the cortex with an electrical stepping motor at a rate of 0.002 mm/s and neurons were recorded between cortical layers III and V. Unfiltered patch electrode recording data was digitized at 100 KHz using CED 1401 mk2 hardware and Spike2 software (CambridgeElectronic Design, CED, Cambridge, UK).

ECoG

In paper II, electrocorticographic (ECoG) recordings were made from the surface of the cortex. The silver ball electrode (Ø 250 µm at the cortex contact surface; no filters were applied, amplifier cut-off 50 kHz) was placed at the caudal end of the craniectomy, approximately 4 mm laterally and 3 mm caudally to the bregma.

Stimulation

Tactile

Tactile stimulation was used in paper II and paper III and was delivered as spatio-temporal patterns of electrical skin activation through four pairs of intracutaneous needle electrodes (see Figure 1B). The patterns mimic tactile afferent activation patterns for four different types of mechanical skin-object interactions (Oddo et al., 2017). The needle electrodes were inserted into the volar side of the second digit of the forepaw with 2-3 mm distance between each pair and 1 mm or less within the pair. The stimulation patterns were delivered as pulses with intensities of 0.5 mA and durations of 0.14 ms (DS3 Isolated Stimulator, Digitimer, UK). The pattern durations were between 200 ms and 340 ms. They were delivered in pre-defined random order and were separated by about 1.8 s (random intervals).

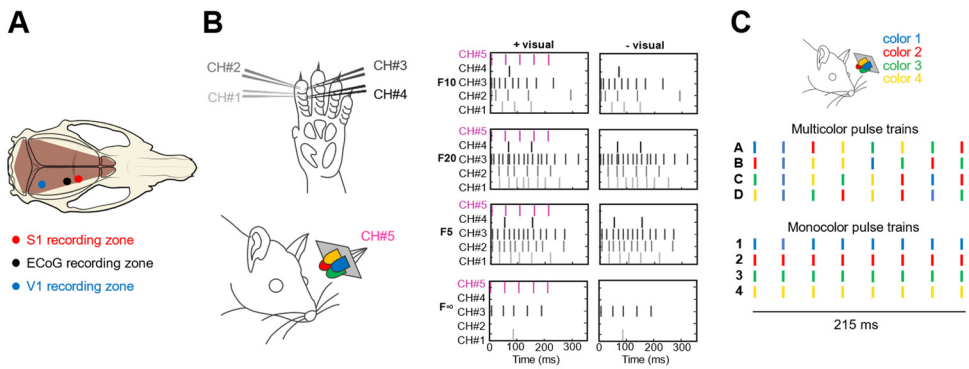

Figure 1. Experimental setup for recording and stimulation
A) Schematic showing of recording zones. B) Tactile and visuo-tactile stimulation patterns. C) Visual stimulation patterns.

Visual

For visual stimulation, a custom-made apparatus with four adjacent 7000 mcd LEDs (red, blue, green, and yellow) was used (see Figure 1C). The apparatus was positioned at a 30° angle from the midline of the animal (sagittal plane), 4–5 cm from the left eye. Stimulation patterns were delivered as multicolor pulse trains (at 1 mW) comprising sequences of colored light pulses in a pre-defined random order. Each sequence included each color, repeated twice, each with a 5 ms duration and a 25 ms interval until the onset of the next pulse. This approach allowed for a set of four different visual stimulation patterns, each with a total duration of 215 ms. Visual stimulation patterns were repeated in randomized order with 1.8 s intervals. The visual patterns were used in paper I and paper III and were similar except the order of the colors.

Visuo-tactile

The visuo-tactile stimulation patterns in paper III consisted of visual pulse trains of simultaneous activation of all four colors and tactile stimulation patterns (see Figure 1B). Here, a visual pulse train consisted of five flashes where all four LEDs would light up in each flash (i.e. these were non-patterned visual stimuli). The pulses had 5 ms duration and a 50 ms interval until the onset of the next visual stimulation pulse. The visual pulse trains started simultaneously with the tactile stimulation patterns and were similar across all tactile patterns.

Analysis

Event detection

Spikes

For patch clamp recordings, spikes were detected using a waveshape transform approach, which is related to the continuous wavelet transform approach but uses a fixed waveshape rather than a wavelet. A spike waveshape vector was extracted in individual recordings, and the waveshape vector was multiplied with the vector of the time continuous patch recording data, with a stride of 50 data sample points (0.5 ms) across the entire recording.

For Neuropixel recordings, spikes were detected using the Kilosort2.5 Matlab package for spike sorting. Units were visually inspected in the Phy library, focusing on spike shape, frequency, and amplitude. Units with spike firing frequencies below 0.8 Hz or those confused with the stimulation artifacts were manually deselected. Units that had more than 1% of their inter-spike-intervals (ISI) within 2 ms were considered non-isolated due to refractory period violations. Units were split or deselected based on ISI plot analysis.

Sharp waves

Local field potential sharp waves (LFP-SPW) and ECoG sharp waves (ECoG-SPW) were also identified using a waveshape transform approach, which is illustrated in Figure 2. An LFP-SPW waveshape (left Figure 2B) was based on visually identified LFP-SPWs, which had a latency to peak of 10-15 ms and a duration of 20-30 ms. The LFP waveshape vector was multiplied with the vector of the time continuous patch recording data, with a stride of 500 data sample points (5 ms), across the entire recording (typically 30-60 mins). At each stride, we used the dot product of the

transform to define if an SPW was present by setting a threshold. The threshold for the dot product was set manually for each neuron recording in order to detect as many events as possible without including other, less structured variations in baseline activity. The same method was used to detect ECoG-SPWs in the ECoG recording, except that here we used two waveshape templates: one with a positive voltage deflection and one with a negative voltage deflection (see left Figure 2C). Here, the waveshapes were multiplied with a stride of one data sample point (1 ms).

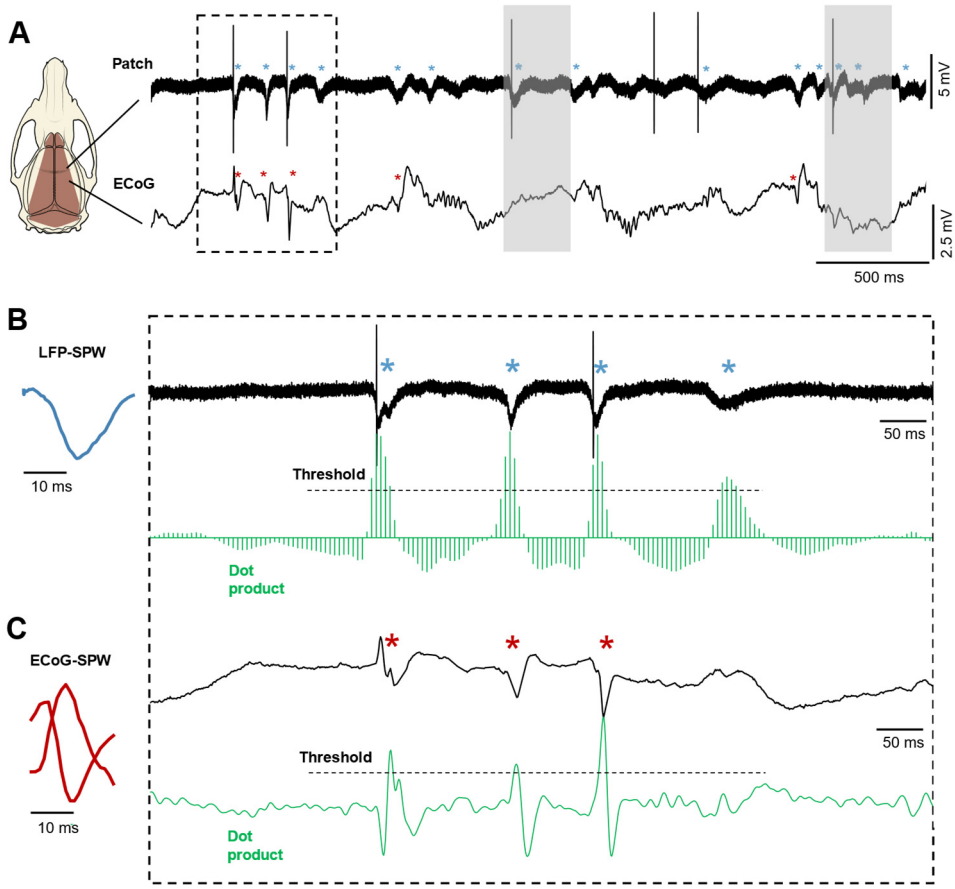

Figure 2. Waveshape transform approach

A) Left: LFP and ECoG recording sites inside and outside the forelimb S1 region, respectively. Right: Raw recording data from a sample experiment. The asterisks indicate LFP-SPWs (blue) and ECoG-SPWs (red), respectively. Grey shading indicates periods of skin stimulation on the second digit. (B) Left: LFP-SPW template. Right: Zoom-in on a segment of the raw patch trace in A. Below, in green, is the equivalent dot product trace obtained by multiplying the template with the raw recording with a stride. The SPW-detection threshold is indicated as a black dashed line. (C) Same as B, but for the ECoG recording.

Responsiveness

In paper I and paper III, we did an initial analysis of responsiveness to the visual and tactile stimulation to discard non-responsive neurons. Peristimulus time histograms (PSTHs) of evoked responses to the stimulation patterns used in the given paper were generated with 5 ms (paper I) and 2 ms (paper III) time bins. The baseline activity was obtained for individual neurons by calculating the mean spike frequency in a prestimulus time window of 200 ms (paper I) and 300 ms (paper III). If the spike frequency exceeded the baseline activity by two standard deviations (SDs) for two consecutive time bins in a poststimulus time window of 400 ms (paper I) and 300 ms (paper III), the neuron was considered responsive to the stimulation, and was included in the analysis.

In paper I, we also used the PSTH generated for the monocolor pulse trains to evaluate response latency. The time point where the PSTH exceeded baseline activity by 2 SDs was defined as the latency time.

Spike response decoding

In paper I, the main goal was to estimate the uniqueness with which individual neurons responded to the multicolor input patterns (shown in Figure 1C). To conduct this analysis, all spike trains were first convolved into a time-continuous vector with a Gaussian kernel of 5ms. Convolved spike trains were z-scored before being randomly split into a test and a train data set with equivalent numbers of spike train responses evoked by each stimulation condition.

Principal component analysis (PCA) was used to extract PCs explaining 95% of the variance across time bins of all temporal, z-scored responses in the training set. This resulted in a set of principal component vectors (PCs) with the same length as the temporal responses. To determine the location of individual temporal spike responses in PC space, we calculated the score for each PC relative to each of the z-scored responses, i.e., the scalar product between each response temporal vector and each PC temporal vector.

A k-nearest neighbor (kNN) classification algorithm using nine neighbors was trained on the scores from the training set before classifying scores from the test set as belonging to one of the stimulation conditions. We repeated the training/test split and the kNN decoding analysis 50 times. Responses evoked with multicolor pulse trains and responses evoked by the monocolor pulse trains were analyzed in this way separately and resulted in one 4x4 classification matrix (average of all 50 decoding analyses) per neuron.

Decoding accuracy

As a measure of the decoding accuracy of the matrices, the F1 score was used. Precision and recall values were calculated with true positives, false positives, and false negatives:

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

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

With the precision and recall parameters calculated for the matrix, the F1-score was calculated:

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

As a control, chance level decoding performance was estimated by performing the decoding analysis with shuffled labels.

Neighboring neurons analysis

To explore the uniqueness of the spike responses to the multicolor pulse train inputs between neighboring neurons, we performed a decoding analysis for selected groups of four neurons recorded within 10 channels (equivalent to neurons being located within a distance of 0.1mm). For each group of neurons, we performed the decoding analysis with responses to all four input patterns, resulting in a 16×16 classification matrix for each group.

To verify that spike responses to multicolor patterns would not only be separable among neighboring neurons but also among remotely located neurons, the decoding analysis was also performed for three control groups consisting of four neurons recorded from far apart channels (distance between each pair of neurons >0.25mm).

Color opponency analysis

In paper I, we also calculated the differences in neuronal responses between different pairs of monocolor inputs. To do this, we used PSTHs binned at 20 ms generated for each monocolor input. All PSTH activity below the mean plus two standard deviations of the baseline activity (calculated from the 200 ms prestimulus data) was then removed from the PSTHs. Next, the 400 ms poststimulus part of the PSTHs evoked by the individual monocolors were subtracted from each other, bin-by-bin, in six combinations (blue-yellow, blue-red, blue-green, red-yellow, red-green, yellow-green).

If a neuron responded more strongly to blue than to yellow, it would have a positive value for the blue-yellow pair and vice versa.

Once the color with the stronger response, and hence the resulting sign of the comparison (positive or negative) had been obtained for the color pair, we made another round of the bin-by-bin subtraction but this time keeping the absolute of the resulting value for each bin. This analysis design was motivated by that in terms of color opponency, i.e., the ability to use the signal of a neuron to deduce which color was activating the retinal cells, the timing of the response would be as important as the magnitude and by using the absolute values bin-by-bin we could also take the differences in response timing into account. Hypothetically, a neuron could have equal overall magnitude PSTHs to two different colors, but two totally different temporal response profiles, and this would not have been captured by a regular subtraction. Next, the sum of the absolute differences was divided by the sum of the values for the color that evoked the strongest response in the pair to express the result as multiples of that response.

Covariance pattern decoding

In paper III, the main analysis was based on the activity distributions across the neuron population during spontaneous activity compared with evoked activity. First, spike responses from individual neurons were split into spontaneous (300 ms prestimulus time windows) and evoked (300 ms poststimulus time windows). Then responses were binned at 1 ms and averaged across 50 sequential responses resulting in time-continuous signals. The averaging was performed to avoid potential classification errors caused by infrequently spiking neurons. The resulting responses were finally convolved with a 10 ms Gaussian kernel, which was motivated by that 10 ms is close to the apparent spike time resolution under similar experimental conditions (Oddo et al., 2017). A section of the convolved signals for three example neurons is shown in Figure 3A.

The PCA+kNN decoding analysis used in paper III was different from the one used to analyze the temporal neuronal responses in paper I. Here, the PCA was used to identify the covariance patterns in the activity distribution rather than variance across individual responses and was only performed on the spontaneous data, which would be a total of 5 or 10 minutes depending on the experiment.

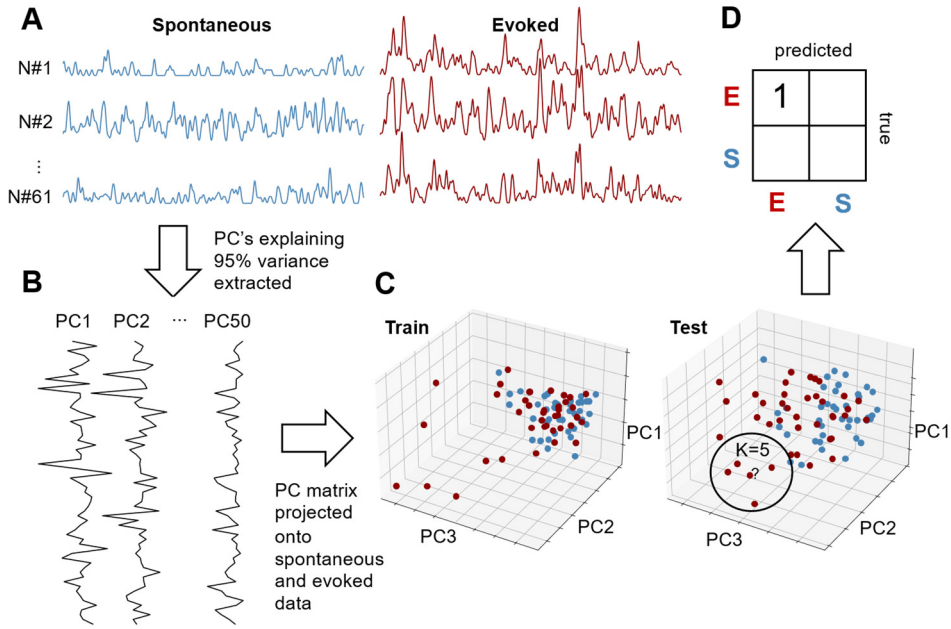

Figure 3. PCA+kNN approach in paper III
A) Time continuous vectors of spontaneous activity (blue) and tactile evoked activity (red) from three example neurons. B) Three example principal components derived from the full spontaneous data set. PCs explaining 95% of the variance resulted in 50 PCs with a length of 61 (equivalent to the number of neurons in this example experiment). C) Example visualization of the placement of data points from the spontaneous data (blue) and the tactile evoked data (red) in a three-dimensional PC space, after splitting all the data into a training set and a test set. D) Example result of the kNN estimation for one data point (question mark in C) after training.

To determine if tactile, visual, and visuo-tactile evoked activities would be placed differently in the high-dimensional spontaneous PC space (explaining 95% variance) compared to the spontaneous data, the location of data points was compared using k-Nearest Neighbor analysis (kNN) with 5 neighbors (see Figure 3C). Data points were split into training and test sets (50/50), and the kNN analysis was repeated 50 times, each time with a new random training/test split. The average result was reported as the decoding accuracy (i.e. the values shown in the confusion matrices, Figure 3D).

Sharp wave impact on spike responses

Evoked spike responses

To analyze the effect of LFP-SPWs on the evoked spike responses for individual neurons, we first defined a time prestimulus time window of 100 ms in which an LFP-SPW event could occur. For each neuron, a set of responses would be preceded by an LFP-SPW in this time window, and a set of responses would not be preceded by an

LFP-SPW. To compare the evoked responses to the stimulations for these two groups of traces, the number of spikes occurring in the 30 ms post stimulation time window was counted for each trace in each group. As the number of spikes in this time window could be either 0, 1, or 2, this resulted in two distributions of ordinal data. The Mann-Whitney U test was used to test for a statistical difference between the two groups of traces (traces preceded by and traces not preceded by an LFP-SPW) for individual neurons. If the test result was significant, and the difference was negative, the neuron was classified as being 'depressed' by the preceding SPW and 'excited' if the difference was positive and significant. If the test result was non-significant, the neuron was classified as having 'no effect' from the preceding SPW on the evoked response. Effect size was calculated with: $r = z\sqrt{n}$

The same method was used to compare evoked responses preceded by LFP-SPWs which either did or did not coincide with an ECoG-SPW. Also here, neurons were classified as 'depressed', 'excited', or with 'no effect' depending on the significance of the test. In this case, depressed would indicate that the coinciding ECoG-SPW reduced the evoked response and vice versa for excitation. Only neurons that had 15 or more traces per category were included in this analysis.

All spike responses

To visualize the effect of SPWs on spontaneous and evoked spike activity LFP-SPWs and ECoG-SPWs were used as triggers in PSTHs with KDEs. The intensity and latency time of the spike activity that preceded the onset of the SPWs were used to define three distinct groups of neurons: Neurons with no preceding spike activity, neurons with short preceding spike activity, and neurons with longer preceding spike activity. To sort neurons into these groups, we calculated the normalized baseline KDE activity and its SD in a time window starting 100 ms to 20 ms in the pre SPW interval separately for each neuron. Note that these arbitrary definitions of preceding spike activity magnitude were estimated to visualize the difference between neurons and were not used for further analysis.

To statistically analyze if ECoG-SPWs evoked more spikes than LFP-SPWs, the amplitudes of KDEs were measured for each individual neuron in each group and compared with Welch's t-test. Before running the test, the distributions of the two groups were checked for normality by plotting histograms. Levene's test for homogeneity of variance failed which is why Welch's t-test was chosen instead of a paired student's t-test.

Results

Paper I: Differential encoding of temporally evolving color patterns across nearby V1 neurons

As discussed in the introduction, studies of V1 have focused on dividing neurons into topographically organized subpopulations based on their preferences for line orientation, motion direction, and color. In many of these studies, it is 'the tip of the iceberg' neuronal activity that is interpreted, for example, when correlating peaks in metabolism with peaks in calcium activity (Wong-Riley & Carroll, 1984). As a result, the computational operations performed by V1 neurons on color input, particularly the temporal dynamics, remain largely uncovered.

In paper I, we aimed to explore the encoding strategies of individual neurons in the primary visual cortex to different combinations of spatiotemporal inputs composed of four basic colors (see Figure 4A, top row). We used multi-electrode arrays to record extracellular signals from neurons in vivo, comparing multiple individual neurons located within 2 mm along the vertical axis of the V1 cortex of the anesthetized rat. Recording traces across eight channels is illustrated in Figure 4B. Out of 411 recorded neurons, 334 responded to at least one color, and 77 responded to all colors. The neurons responding to all colors were evenly distributed across all recorded depths.

We used PCA+kNN to evaluate how well individual neurons could separate spatiotemporal multicolor input patterns. We found that almost all neurons had unique responses to the multicolor patterns and could separate the patterns well above chance. Responses from one example neurons to the four multicolor patterns can be seen as PSTH in Figure 4A. Note that each pattern contained a blue pulse as the second pulse, and the lower part of the figure illustrates how the color of the preceding pulse impacted the subsequent phase of the response (here, a response delay of approximately 30 ms is taken into account).

We also found that adjacent neurons recorded within a distance of less than 0.1 mm had very different responses to the same input patterns This was shown by performing the decoding analysis on groups of four neurons (grouped by their small recording dist-

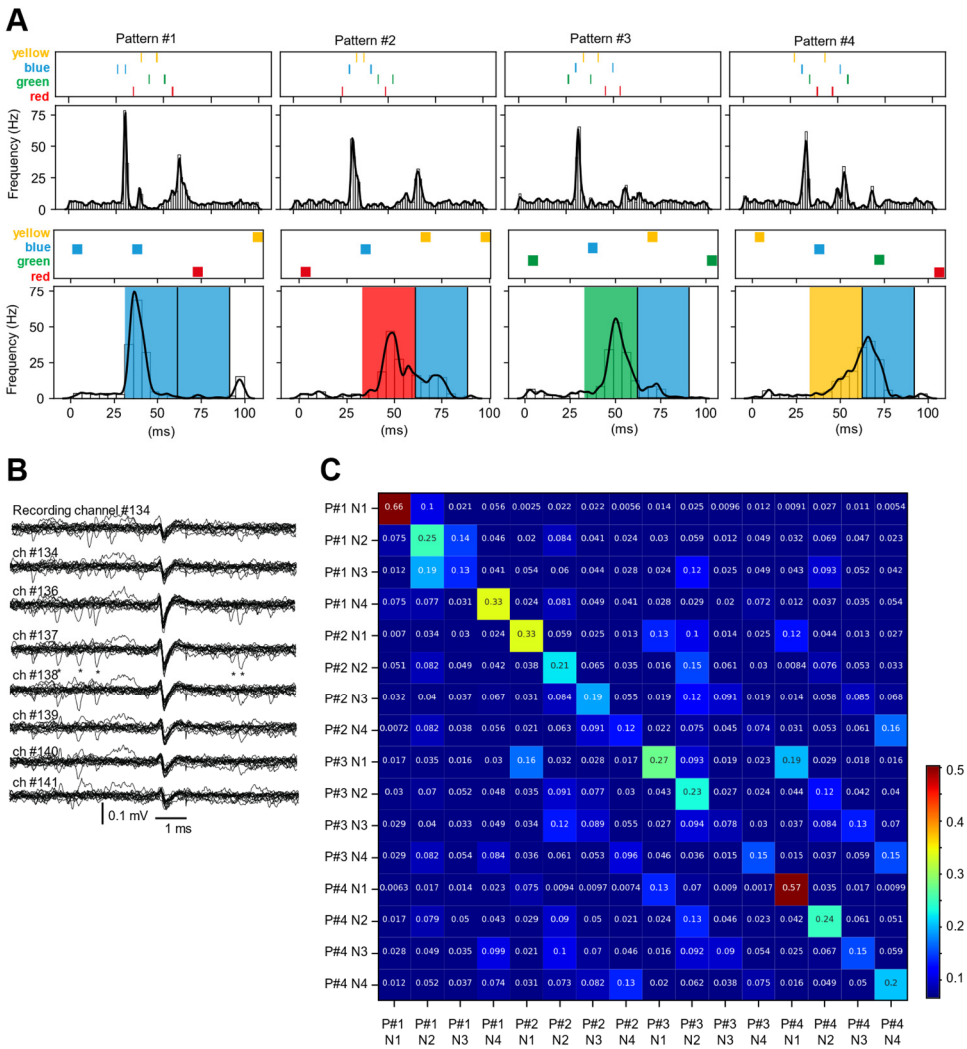

Figure 4. Summary of results from paper I.
A) Top: Stimulation patterns and corresponding responses for a sample neuron. The responses are represented as peristimulus time histograms (PSTH bar charts) and as a kernel density estimation (KDE, solid lines) of the same responses. Bottom: Zoom-in of the first 100 ms of the stimulation patterns and the neuron responses in the top part. The colored boxes superimposed on the PSTHs indicate the color input for the underlying response, given the apparent shortest response latency time of 30 ms evoked by any input. B) Example raw recording data from eight neighboring recording channels. Fifteen traces were aligned on the repeated occurrences of the spike of one unit. Asterisks indicate additional spike occurrences at very short intervals to the reference spike. C) Confusion matrix of neighboring neurons decoding analysis (four neurons and four patterns).

ance to each other) and calculating the F1 score from the resulting 16x16 matrix. An example matrix is shown in Figure 4C. All groups of neighboring neurons, despite depth, showed above-chance level decoding in this analysis, indicating a diversified

response strategy at the level of the local cortical circuitry. This finding is in opposition to the idea of hierarchical organization, which suggests that neurons in close proximity should receive more similar input than neurons far apart.

We employed the same analysis methods to evaluate how individual neurons responded to unicolor input. Essentially all neurons responding to all four colors also had highly unique responses to the monocolor input. To support this finding, we also performed a color opponency analysis, which revealed a surprising diversity and richness in color opponency across the four colors. Also, no color seemed to be standing out as evoking a stronger overall response, which was an unexpected finding, considering that rodent retinas express only two types of opsins and have been considered to be red-color blind.

This study shows that the decoding accuracy of both multicolor and monocolor input can be very high among V1 neurons, i.e. individual neurons carry information about the 'what' component of the input. The data indicates that local state changes affect the processing of incoming sensory stimuli, illustrated by the uniqueness of responses to multicolor input patterns which only varied in the order of the colors and nothing else. The fact that the same input patterns were encoded differently by neighboring neurons suggests that the V1 processing network is channeling information in parallel, potentially focusing on complementary aspects. In conclusion, we interpret these results as different individual V1 neurons being connected to different aspects of a local cortical processing network that perform abstract functionalities.

Paper II: Local field potential sharp waves with diversified impact on cortical neuronal encoding of haptic input

To investigate brain state dependence on neocortical interpretation of haptic events, biomarkers to estimate the brain state are needed. Since field potentials express the summed activity of populations of neurons they could be one such biomarker. Local field potentials (LFPs) can be argued to express the state of local cortical circuits, whereas field potentials recorded from the brain surface can be argued to express the state of a more widespread, global network of neurons.

In paper II, we recorded LFP-SPWs in the S1 neocortex with patch clamp electrodes to investigate their effect on neuronal responses to haptic input. We also recorded SPW events from the cortical surface (ECoG-SPWs), which had a similar shape and frequency as the hippocampal sharp wave (Hipp-SPW) reported in other papers (see *Introduction*). Both LFP-SPWs and ECoG-SPWs were detected with a waveform

approach (see *Methods*) and were found to be highly variable in shape, indicating that different synaptic activity combinations were responsible for individual events.

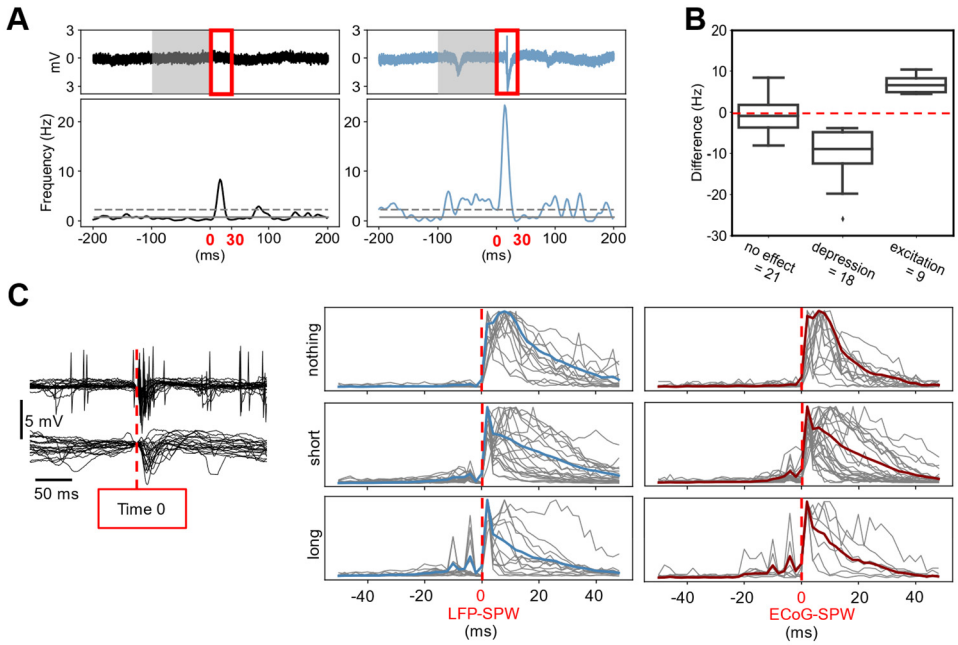

Figure 5. Summary of results from paper II.
A) Sample raw traces and KDE plots of the average evoked spike response for a neuron when it was preceded (blue) and not preceded (black) by an LFP-SPW. B) Summary of the statistical test of LFP-SPW impact on the tactile evoked spike responses for all neurons. C) Left: Superimposed raw data traces for a sample neuron illustrating spike responses around LFP-SPWs (top) and coinciding ECoG-SPWs (bottom). Right: Normalized SPW-triggered spike responses sorted by LFP-SPW trigger (blue) and ECoG-SPW trigger (red). Top-row shows neurons with an absence of a preceding spike response, middle-row neurons with a short preceding response (up to 7 ms), and bottom-row neurons with a long preceding response (up to 20 ms before the onset of the SPW). Individual neuron responses are shown as KDEs in grey.

LFP-SPWs were found to have considerable, yet diversified, effects on immediate neuronal responses to tactile inputs, some depressing and others enhancing the response. This is illustrated for one neuron in Figure 5A and for all neurons in 5B. When LFP-SPWs coincided with ECoG-SPWs, their effect on neuronal processing of haptic input was found to be further diversified, suggesting that the global state change signaled by the ECoG-SPW resulted in different widespread coordination of local cortical neuron activity. These results suggest a diverse relationship between individual neurons and population-level features in brain activity.

Plotting PSTHs of spikes with SPWs as the trigger revealed that SPWs elicited a massive spike response (see Figure 5C). Interestingly, a subset of our neurons had a build-up of activity starting before the occurrence of the SPWs, suggesting that they contributed to the onset of the SPWs (as has been suggested for hippocampal neurons for Hipp-SPWs

(Stark et al., 2015). This may suggest that the LFP-SPWs were a result of a rapid but gradual build-up of activity in recurrent excitatory loops that at least partly involved the local neurons. We also found the ECoG-SPWs in general evoked a more powerful spike response than the LFP-SPWs. In 34 out 48 neurons, the peak amplitude for the ECoG-SPW KDEs was higher compared to the amplitude for the LFP-SPW KDEs.

This study shows that local circuitry state changes, reflected by synchronous neuronal activity recorded within the S1, can mediate responses to haptic input in individual S1 neurons. The synchronous activity recorded from the surface of the cortex, reflecting a more widespread state, was shown to diversify the impact of the LFP-SPWs on the S1 neuronal responses, suggesting the involvement of ECoG-SPWs in global cortical signaling. Because the cortical SPWs had similar overall activity patterns as reported for hippocampal SPWs, this might reflect hippocampal-neocortical interactions.

Paper III: High-dimensional cortical signals reveal rich bimodal and working memory-like representations among S1 neuron populations

Complexity is important for flexibility of natural behavior and for the remarkably efficient learning of the brain. If the brain circuitry is considered a system with high complexity, then also its spontaneous activity should be characterized by high complexity, i.e. as a high-dimensional space. Being able to define the specific high-dimensional state of the cortical system at the moment of input is a way of understanding how neuronal interpretation of given sensory input is affected by the state of the network.

In paper III, we defined the high dimensional state space of the spontaneous activity of S1 neuron populations and considered the sensory inputs as potentially perturbing factors. The main question asked was whether the perturbation was sufficient to evoke detectable changes relative to that state space and whether different inputs caused different such changes. To answer this, we did multi-unit recordings with Neuropixel multielectrode arrays and used spatiotemporal tactile, visual, and tactile-visual input patterns (see illustration of stimulation patterns in Figure 1 in the introduction).

The high resolution of the stimulation and the recorded signal offered an advantage in capturing the complexity and high dimensionality inherent in brain circuitry. We used a PCA to define the high-dimensional space of the spontaneous activation patterns of populations of neurons rather than the temporal responses of individual neurons. The

idea behind this was that the complexity in a neural system can be expected to be at least as dependent on the activity distributions across the neuron population as it is on the complexity of the neuron signal. We found that the spontaneous activity of neurons was extremely high-dimensional which is illustrated in Figure 6A as a black line showing that more than 50 PCs were needed to explain 95% of the variance of the spontaneous data for that experiment. This suggests a complex and rich internal signal structure within the neuron population.

The main question asked was whether different types of sensory input could evoke detectable changes relative to the spontaneous state space. With this approach, we found that tactile input elicited coactivation patterns different from the spontaneous coactivation patterns in the S1 neuron population, which is illustrated in Figure 6A right side. Surprisingly, the neuron population retained information about the different tactile input patterns long after stimulations had terminated (illustrated in Figure 6D). The decoding analysis was performed separately for activity evoked in 10 ms time bins from -100 ms pre stimulus onset to 1000 ms post stimulus onset.

We also found that visual input shifted the high-dimensional spontaneous state space, although less than the tactile stimulation did (see Figure 6A orange line). This was a significant discovery as the S1 cortex is traditionally associated with tactile processing. Even more significant was the finding that the S1 neuron population could differentiate between fine nuances of visual patterns (Figure 6C), suggesting that the primary somatosensory cortex to some degree is involved in the interpretation of qualitative aspects of visual input.

Finally, we found that the activity elicited by tactile stimulation alone changed differently compared to the spontaneous activity when the tactile input was combined with visual input. The result from this analysis is shown in Figure 6B as a distribution of F1 scores (blue curve) way above the chance level (0.5). This suggests that neuronal responses to tactile input can be modified by visual input if the visual input is sufficiently strong. Interestingly, individual S1 neurons could not separate tactile and visuo-tactile conditions as effectively as the neuron population did, suggesting that the population activity contains more information than individual neuron responses. Results from the neuron-by-neuron analysis are shown in Figure 6B lower part as a grey distribution of F1 scores.

The findings in this study imply that cortical information processing is extremely high-dimensional and that it incorporates diverse modalities as well as long-lasting signals, reminiscent of a type of working memory, related to internal processing elicited by previous sensory inputs. It provides a different methodological approach where the naturally occurring local state changes, reflected in the spontaneous neuronal activity,

is taken into account when estimating the effect of sensory input, emphasizing that higher-order dimensions of brain circuitry representations can be missed with excessive dimensionality reduction.

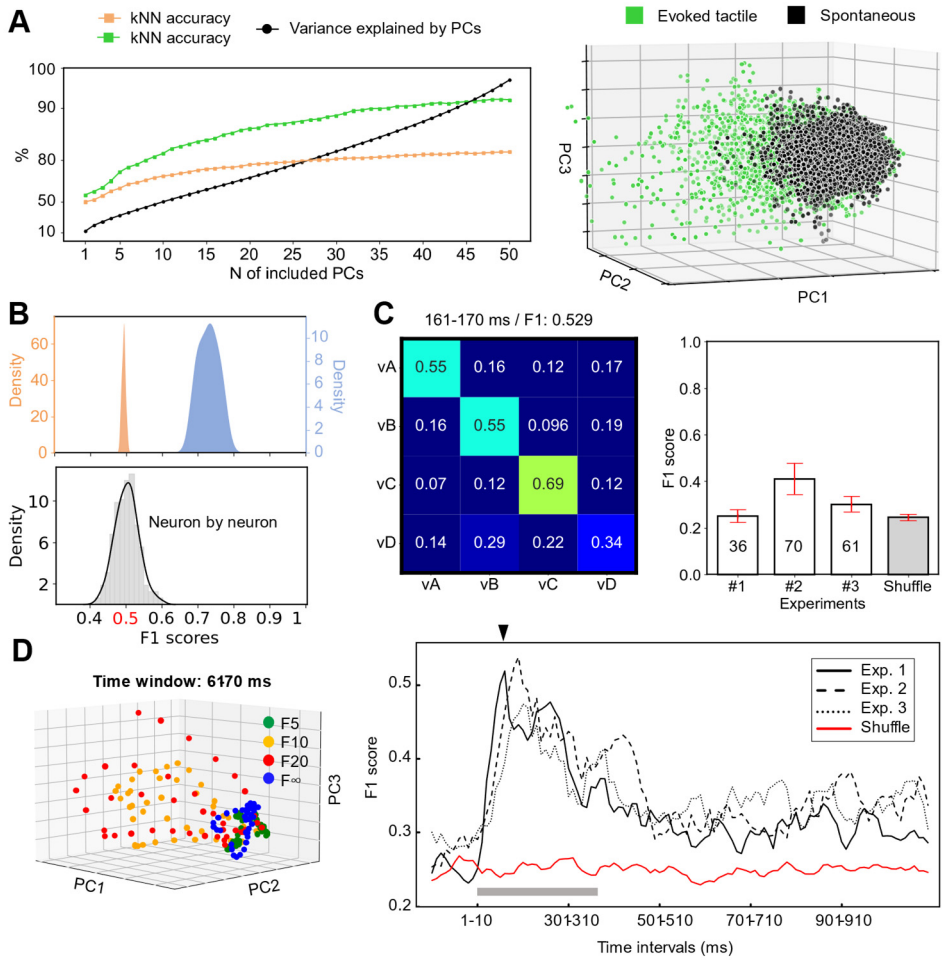

Figure 6. Summary of results from paper III
A) Evoked decoding analysis: Left: kNN decoding accuracy as a function of the number of PCs included in the analysis for separation of spontaneous data from visual (orange) and tactile (green) data, respectively. The black line indicates the cumulative variance explained for each PC. Right: The first 3 PCs of the spontaneous space shown with tactile (green) covariance patterns compared to spontaneous (black) covariance patterns. B) Visuo-tactile decoding analysis: The top figure shows the distribution of F1 scores for the separation of covariance patterns evoked in response to tactile and visuo-tactile input (blue) compared to the shuffled control (orange). The bottom shows the distribution of F1 scores for the separation of the same input in the same population but with responses of each neuron analyzed separately. C) Visual patterns decoding analysis: To the left is an example confusion matrix of the decoding performance of the visual input patterns quantified for a population of S1 neurons in a single time window. To the right is the average decoding performance across all time windows for the full population, shown for each of the three experiments separately and for shuffled labels. D) Tactile patterns decoding analysis: Evoked covariance data for all patterns in one 10 ms time window to the left. To the right, the F1 scores for all time window analyses shown separately for each experiment.

Discussion

In this part of the thesis, the results presented in the previous part will be discussed one by one by comparing them with findings in other studies. This is followed by a reflection on the experimental choices in the papers and a discussion of methodological trends in the research field. The findings are then interpreted within the global and local functional organization frameworks, and finally, studies suggesting a relationship between cognitive top-down influence and brain state dependence on cortical sensory integration are put into perspective.

Brain state dependence

Dynamic visual processing

In paper I, we investigated the computations performed by V1 neurons across all cortical layers on different combinations of inputs composed of four basic colors. The study revealed that essentially all color-responsive neurons could decode spatio-temporal patterns of multicolor input and that even neighboring neurons displayed highly diverse response strategies. According to a hierarchical processing framework, closely located neurons should receive similar afferent input, which should be expected to be represented in a similar way. Our data suggests something different, namely a highly complex and varied local circuit organization within the V1 cortex. Furthermore, the finding that there was a rich heterogeneity in how neurons encoded identical inputs across all cortical layers challenges the idea of columnar organization, which posits that neurons in the same vertical column are functionally similar.

We also found that V1 neocortical neurons had a diversified and rich color opponency across the four colors. This was somewhat surprising as rats are dichromatic; however, as described in the introduction, color vision has multiple other mechanisms at hand. For example, individual neurons in the retina network have been shown to combine individual photoreceptor inputs and thereby increase the information about color in the retinal output (Yoshimatsu et al., 2021). Also presented in the introduction are

findings that the thalamocortical network can further recombine afferent signals suggesting that this stage of visual processing also takes part in color interpretation. Finally, the findings that individual cones have different percentages of M-opsins and S-opsins and that rods also have a degree of color tuning (Wang et al., 2011) could also explain why we observe this diverse color tuning.

In conclusion, the study shows that V1 neurons respond to a sequence of color inputs in a way that suggests a dynamic alteration of the state of the local cortical circuitry. This dynamic response indicates a highly adaptable and nuanced processing system within the V1 cortex, capable of responding to the temporal evolution of sensory inputs. Horizontally aligned electrode tracks could have further elucidated the full diversity of neuronal responses, however, we would expect this to display heterogeneity in response profiles as well. Additionally, our stimulation was designed for broad activation of the retina, which may limit our understanding of the spatial aspects of color processing.

Field potentials as biomarkers

In paper II we aimed to control for the current internal cortical state by defining field potentials as biomarkers for such internally generated state changes. We found that spontaneous LFP-SPWs impacted the immediate response to haptic input in the majority of the recorded neurons, suggesting that the current state of the S1 circuitry, reflected by the summed activity of local S1 neurons, affects the evoked responses in individual neurons. As described in the introduction, LFPs have been found to reflect different types of synchronous activity such as excitatory postsynaptic potentials and inhibitory synaptic input (Buzsaki & Kandel, 1998; Hasenstaub et al., 2005). The fact that the evoked response in some neurons was inhibited by preceding LFP-SPWs while it in others was excited, shows how each neuron has its own unique combination of synaptic connections in the S1 circuitry network. This was also indicated by the finding that while LFP-SPWs mostly triggered a massive spike response, they also sometimes occurred subsequent to a build-up of spike activity.

Exactly what the individual LFP-SPWs reflect is impossible to conclude with certainty, but the ones coinciding with an ECoG-SPW could very well reflect some interaction with the hippocampus (because the ECoG-SPW share many similarities with the Hipp-SPW, see *Introduction*). The hippocampus projects to the neocortex via the subiculum, which has widespread connections with the anterior thalamus, the hypothalamus, regions of the temporal/entorhinal cortices surrounding the hippocampus, and the ventral striatum (Matsumoto et al., 2019; Winnubst et al., 2019). This suggests that the hippocampus and the neocortex are highly interconnected, supported by the

finding that brief stimulation in the hippocampus has profound and diversified effects on S1 neuron responses to tactile input (Etemadi et al., 2023). While we cannot say with certainty that the ECoG-SPWs we recorded originated in the hippocampus, this finding supports the idea that events in the hippocampus can impact how S1 neurons respond to haptic input.

Interestingly, we also found that while ECoG-SPWs mostly triggered a massive spike response they were sometimes also preceded by a spike build-up. This could be an indication that sometimes, cortical activity initiates SPWs in the hippocampus rather than the other way around. This is perfectly possible since the hippocampus receives information from many different neocortical regions via the entorhinal cortex (Schultz & Engelhardt, 2014). The Hipp-SPW has also in previous studies also been associated with intense activity in the neocortex, including the S1 (Sirota et al., 2003), and it has been shown that hippocampal neurons carry precise information about tactile stimuli (Pereira et al., 2007). This raises the question if the hippocampus and the neocortex both contribute to the processing of sensory information, potentially through a type of memory consolidation. Indeed, neuronal recordings from the cortex have shown that sensory input is repeatedly followed by internal replay (Nguyen et al., 2023) and the hippocampus has long been argued to be responsible for high-level brain functions, such as replay and recall (Buzsáki, 2015; Kanamori, 1985; Leonard & Hoffman, 2017; Liu et al., 2022). However, to really explore how neocortical and hippocampal field potential events are connected, how they impact the processing of haptic input, and if they both contribute to memory consolidation, one would have to record simultaneously in those regions.

Cortical circuitry complexity

Hypotheses in paper III were based on the assumption that cortical signals are highly complex. This was motivated by observations that natural behavior intrinsically has a high complexity (Cavanaugh et al., 2017; Jordão et al., 2023; Z. Li et al., 2022; Nagamori et al., 2021; Stergiou & Decker, 2011; Tang et al., 2022; Wu et al., 2014) indicating that also brain circuitry operations are characterized by high complexity, i.e. they are high-dimensional. We showed that the spontaneous activity distribution across S1 neuron populations indeed was characterized by high dimensionality and that both tactile and visual input could perturb the spontaneous state space.

Many recent studies use recording methods of lower temporal resolution (i.e. calcium imaging, or spike binning of 100's of ms) to address population representations of real-world parameters (Chaudhuri et al., 2019; Gardner et al., 2022; Marks & Goard, 2021; Stringer et al., 2019, 2021; Xia et al., 2021). These methods are at risk of averaging out

much of the activity that occurs at faster time scales which may result in an elimination of the underlying complexity of brain circuitry signals. Our use of highly repeatable resolvable visual, tactile, and visuo-tactile inputs in combination with neuronal activity recordings at high temporal resolution maximized our chances of capturing population-level signal complexity. This enabled us to analyze rapid, subtle shifts in the S1 activity distribution such as 10 ms time bin comparisons of responses to different tactile activation patterns. This revealed input-specific activity perturbations long after termination of the given stimulation, indicating an internal replay of the signal. Indeed, previous studies have shown that sensory input is repeatedly followed by internal replay, which gradually alters the cortical population responses to the given sensory inputs (Nguyen et al., 2023). The long duration of these poststimulus perturbations could reflect a substrate of working memory-like functions.

Our methodological approach for analyzing the activity distribution patterns in neuron populations enabled us to further capture some subtle changes in the evoked neuronal activity. The approach assumes that the most relevant signals of the neural system reside in the time-varying activity dependencies between the neurons rather than the independent responses of any individual neuron. Indeed, when we performed a traditional correlation-based investigation on individual neurons' responses to tactile and visuo-tactile input patterns, we did not find a difference in responses. But by analyzing covariance patterns in the full recorded population and using the high-dimensional spontaneous state space as an analysis frame, we were able to detect very subtle nuances in the cortical representation of tactile input patterns when they were presented with or without simultaneous visual input.

Some recent multi-neuron studies use dimensionality-reduction techniques to fit highly complex, dynamic neural activity with certain tasks (Jazayeri & Ostojic, 2021; Khona & Fiete, 2022). Our study suggests that the finer nuanced activity representing rich internal processing is better represented in higher-dimensional spaces because this can more accurately capture the brain's capacity for rapid and adaptable responses in multifaceted environments. By using electrophysiological recordings with high temporal resolution and stimulations with high spatiotemporal resolution we found that not only tactile but also visual and visuo-tactile input is encoded by S1 neuron populations, suggesting that the cortex is a global, interconnected network.

Experimental choices

Spatiotemporal input

The rationale for using spatiotemporal stimulation patterns in all papers was that the response to a given input is determined by the physiological structure of the recurrent activity, i.e. the current state of the cortical circuitry. The idea is that the sensory input alters the local cortical state at a very fast time scale, affecting the response to subsequent input, resulting in detailed temporal responses in individual neurons.

By using needle electrodes placed in different parts of the skin different spatiotemporal inputs mimicking different types of haptic skin-object interactions can be generated while still ensuring high repeatability across trials. With this stimulation, our group has shown high decoding capacities in individual neurons at several processing stages such as the cuneate nucleus (Jörntell et al., 2014), the thalamus (Wahlbom et al., 2021), and the primary somatosensory cortex (Oddo et al., 2017). In paper III, we used the same electrotactile stimulation patterns which enabled us to analyze changes, this time in S1 neuronal covariance patterns, at a very fast scale. Because of the high temporal resolution of the stimulation, we were able to perform a systematic test of the separation of the four tactile input patterns across 10 ms time steps. As expected this revealed that the separability of the four tactile input patterns gradually rose and then decayed during the onset of the stimulation patterns but also, unexpectedly, that the separation stayed well above chance long after the tactile input terminated. This could not have been explored without the highly resolvable spatiotemporal input.

In paper I, we aimed to create spatiotemporal visual patterns analog to the tactile patterns. Because the muscles controlling gaze direction, focal plane, and pupil size in the awake state vary at a high pace they are a source of substantial variation in retinal photoreceptor activation across trials. To minimize this variation, we used stimulation composed of temporal sequences of differently colored inputs, which only varied in the order the colors were presented, resulting in different spatiotemporal patterns of retinal photoreceptor activation. As expected, the same color input evoked different responses depending on the preceding input color (illustrated in Figure 4A bottom row), indicating rapid local circuitry state changes among the neuron population in response to color input. In conclusion, the high temporal resolution of the stimulation used in paper III and paper I have made it possible to analyze how local circuitry changes give rise to rapid, dynamic temporal responses among S1 and V1 neuron populations. And crucially, it has allowed us to interpret any variability in neuron responses as internal brain state dependence.

Anesthesia

Ultimately, we want to say something about sensory processing as it occurs naturally. So why not perform experiments in awake animals? The neural activity generated as a result of exploration of one's surroundings and the internal thinking unrelated to the experimental task both generate unnecessarily complex internal signals and brain state changes. Optical imaging studies have shown that fluctuations in internal brain states are as large as the activity evoked by a visual stimulus (Arieli et al., 1996; Petersen et al., 2003). These task-unrelated internal signals will be superimposed on whatever response we generate in our experiment, but anesthesia has the advantage of minimizing such systematic variations in brain state (Wallach et al., 2016). Furthermore, although it can be argued that the awake state is the 'natural' or default mode of the brain if a rat does not care about a stimulation or an experimental task, it can be argued that this is not natural either. Finally, it is hard to deliver the exact same sensory input in the awake state which in our studies was crucial in order to analyze rapidly occurring brain state changes, i.e. the temporal dynamics of neuronal response to sensory input.

So can we transfer what we observed in experiments with anesthetized animals to the awake state? Many studies indicate that this is possible; for example, Luczak & Barthó (2012) investigated the order of neuron recruitment among layer V cortical neurons in both awake and ketamine-anesthetized rodents for spontaneous and evoked activity. The authors found the order to be the same even at short time spans (in the order of 100s of ms), which is crucial when we want to study processing of information that is dependent on the state of the circuitry at fast time scales. In a different study, Zhao et al. (2013) found that the orientation selectivity of dLGN neurons was unchanged in anesthetized mice compared to awake mice. This was later supported by Durand et al. (2016), who compared LGN neuronal spatial and temporal response properties to visual stimuli and found that most qualitative parameters were unchanged between the two states.

In fact, the only notable difference is that more synchronized neuronal activity is present in deep sleep, which has been found to affect decoding performance. In the awake state, EEG and ECoG recordings are characterized by desynchronized waves (Petersen & Crochet, 2013), whereas deep sleep is characterized by slow waves with irregular occurrences of desynchronized activity (Niedermeyer & da Silva, 2005). Decoding performance, i.e. uniqueness in response profiles to different types of input, is higher during desynchronized activity compared to synchronized activity in S1 neurons according to Enander et al. (2019). This is supported by Bengtsson & Jörntell (2007), who showed that anesthesia affects the efficacy of synaptic transmission, which can impact how accurately different types of input are represented by individual neurons. Therefore, if anything, it seems that what we have observed in our experiments

in terms of decoding capabilities of sensory input reflects the same qualities as in the awake state but possibly with lower accuracy.

Functional organization

Support for a holistic model

In his thesis, Enander (2019) outlines the discussion of functional organization during the 20th century in neuroscience. He explains how, with advances in technology and anatomical knowledge, the era was characterized by a move from broader theories about brain function to more specific ideas about localized brain activities and hierarchical information processing. Researchers like Korbinian Brodmann played a key role in this by creating a brain map divided into distinct regions suggesting that different areas of the brain have specific functions (Enander, 2019). The latter part of the 20th century, however, saw a revival in holistic theories of brain function, emphasizing the intricate connections within the brain and the plasticity of brain networks. The results presented in this thesis are in support of the holistic theories and suggest that simple localization models cannot fully explain how the brain processes sensory information.

In paper III, we found that not only did S1 neuron populations respond to visual input, but subtle nuances of visual information were represented in the population covariance patterns. This has previously also been demonstrated for haptic input in V1 neurons (Enander et al., 2019), and in a review paper, it has even been argued that the whole neocortex might be processing multisensory information (Ghazanfar & Schroeder, 2006). We also found that the S1 cortical state could be manipulated with visual input such that the same tactile input patterns generated different covariance patterns compared to when they were presented alone. This is an indication of integration of multisensory input which according to the functional localization principle is otherwise reserved for later processing stages. While some studies argue that MI is a higher-order mechanism only taking place when attention has been directed to the event (Alsius et al., 2005; Busse et al., 2005; Fairhall & MacAluso, 2009; Talsma & Woldorff, 2005) other studies suggest that it is an automatic process (Bertelson et al., 2000; Spence et al., 2000; Vroomen et al., 2001b, 2001a). The latter could explain why we find integration of visuo-tactile input even though the animal is anesthetized.

The fact that ECoG-SPWs in paper II were found to modulate the effect of LFP-SPWs on neuronal responses to haptic input further supports the notion that primary sensory regions are susceptible to remote cortical events. We think that although the decoding

accuracy of visual and tactile input is higher, and responses more intense, in their corresponding cortical regions, that sensory information processing is not confined to a single, specific area of the brain. In fact, decoding accuracy in primary sensory regions might be high exactly as a result of coordinated activity across multiple, interconnected brain regions. In conclusion, we do not think that the functional localization model can fully explain what we observed in the studies presented in this thesis.

Narrow definitions

Although the support for a more interconnected understanding of the nervous system has accumulated in recent years (Gerfen et al., 2018; Winnubst et al., 2019) many studies still support the idea that specific brain regions are responsible for specific functions. Tools like fMRI and PET scans enable the visualization of active brain areas in living individuals and are often used to correlate activation in specific regions to specific tasks or stimuli. For example, a recent study exposed participants to simple geometric shapes like circles, triangles, and stars, and observed increased activity in the occipital lobe, fusiform gyrus, sub and middle occipital gyrus, and cerebellar V1 (Wei et al., 2023). The authors conclude that these regions are associated with object and face recognition, and early visual processing. One problem with correlation-based approaches like this is that if the signal is sufficiently rich, the chances of finding at least some correlation with almost any external variable can be high. Hence, correlations can be found without necessarily providing any information or any clear idea of how the problem is structured internally in the brain networks. Another problem with fMRI is that only activity exceeding some baseline is considered important and how this baseline is defined is often rather arbitrary (Stark & Squire, 2001).

Arbitrary or narrow definitions of what is considered relevant neuronal activity also seem to have guided theories about blob/interblob structures. Also here, it is peaks in metabolism that is analyzed (Wong-Riley & Carroll, 1984) resulting in a 'tip of the iceberg' effect as in fMRI. These approaches can lead to oversimplification and may show highly separated preferences in neurons that in fact have highly overlapping response profiles. The same is true for many neurophysiology studies. As described in the introduction, to evaluate whether or not a neuron has a preference for a certain parameter, response preference must first be defined. This definition not only varies from one study to another but is also often rather narrow, for example, the number of action potentials fired within a very short, predefined time window, or the definition is sometimes even absent in the methods section. As described in the introduction, this has been especially notable for studies of the V1 where decades of research have been dedicated to exploring the idea of functional columnar organization since it was first

reported by David H. Hubel and Torsten Wiesel in the fifties. In paper I, we attempted to break from convention by introducing a novel stimulus different from the commonly used orientation lines and drifting gratings. Our stimulus was high-resolution and spatiotemporally dynamic, which enabled us to analyze the temporal aspect of neuronal responses to input patterns rather than categorizing them into 'preferred' input based on spike counts. As a result, our findings offer a different perspective on functional organization compared to previous studies emphasizing a columnar functional structure.

The broader perspective

The result of our brain's ability to process and interpret incoming sensory information is perception. As stated repeatedly throughout this thesis, perception is determined both by the characteristics of the sensory input and by the state of the neural circuit when and where the input arrives. Blinking, adjusting body position, planning movement, etc., is reflected as internal activity and can in principle affect the context within which sensory information is interpreted. Different cognitive mechanisms are also known to influence how cortical neurons respond to sensory stimuli; attentional mechanisms in particular have been demonstrated to have a significant effect.

In a review paper titled *Brain states: Top-Down Influences on Sensory Processing* Gilbert & Sigman (2007) point towards attention as the primary top-down modulator of sensory input but challenge the metaphor of attention as a spotlight for perception. They argue that attention is more than a passive filter merely selecting sensory inputs and highlight the diverse ways in which it has been shown to influence perception and sensory processing. For example, a behavioral study has shown that focusing on one feature of an object improves discrimination of its other features (Blaser et al., 2000), suggesting that spatial attention to an object enhances the processing of all its features, not just the spatial location. This is supported by single-cell recordings in primate V1, where neuronal responses have been found to not only change during attention to the task but to be modulated by the context in which the stimuli are presented, suggesting that attention not only enhances sensory input but actively reshapes the representation of it (Christ et al., 2001; W. Li et al., 2004).

Direct estimates for attentional states were first observed with EEG as slow, large-amplitude oscillations during so-called 'quiet wakefulness' in humans (Berger, 1929). Later, extracellular recordings revealed correlations between synchronous activity at different frequencies with behavioral and attentional state changes (Buzsáki & Draguhn, 2004; Engel et al., 2001; Riehle et al., 1997; Steinmetz et al., 2000; Steriade

et al., 1993). These distinct patterns of cortical synchrony have later been demonstrated in whole-cell recordings to have significant and dynamic effects on the intracellular membrane potential in primary somatosensory barrel cortex (Poulet & Petersen, 2008), reflecting the direct impact of widespread cortical activity on individual neurons. The fact that these modifications by attention also occur in primary sensory regions further suggests that top-down influence happens in parallel with sensory information processing rather than in a hierarchical order. This view is also put forward in a review paper on MI where it is argued that integration of multimodal input takes place at multiple processing stages and that in between these stages, there is dynamic modulation due to the interference of top-down mechanisms such as attention (Calvert & Thesen, 2004).

The idea that attentional states shape how the brain interprets sensory input has been suggested as an explanatory model for perceptual disorders such as dissociative somatoform symptoms (DSS), which have medical characteristics but no acknowledged medical cause. DSS can involve changes in sensory perception, pain symptoms, and loss or reduction of motor control (Nijenhuis et al., 1996), and can be severely disabling (Fink, 2017). Barsky (1992) and Rief & Barsky (2005) argue that somatoform symptoms result from an increased tendency to direct attention to somatic sensations and appraise them as pathological. Predictive coding theory has been put forward as an alternative theoretical framework in which DSS is explained as the result of 'prediction errors'. Within this framework, the brain is seen as a constant prediction-maker and false expectations to increase certain bottom-up signals so that they are perceived as painful or suboptimal sensory experiences.

The diversity of frameworks for understanding how suboptimal sensory experiences come about and how functions in the brain are organized reflects the complexity with which the brain interprets sensory information. With each finding our understanding of how top-down processes, expectations, and brain circuitry mechanisms actively shape the brain's interpretive mechanisms evolves. The results presented in this thesis provide insight into these intricate processes and could be instrumental in guiding future studies aiming to uncover the neural correlates of brain state dependence and its influence on sensory integration. This could ultimately lead to a more comprehensive understanding of how perception is constructed in the brain.

Concluding remarks

Not only higher-order cognitive processes but also behaviors unrelated to direct stimuli, like blinking or adjusting body position, reflect internal brain processes and might influence how the brain interprets sensory information. In other words, cortical neurons' internal signals carry more implicit information than just responses to sensory stimuli. This thesis has investigated this phenomenon by asking how neurons in primary cortical regions interpret haptic and visual events under the influence of time-varying brain states.

The results from paper I illustrated a nuanced encoding of spatiotemporal color patterns across V1 neurons recorded along the same vertical axis, challenging the notion of columnar functional organization in this region. In paper II, we found that local and remote field potential sharp waves had a diverse impact on S1 neuronal responses to haptic input, suggesting widespread, state-dependent processing of haptic information. Paper III explored the dimensionality of the spontaneous S1 local state and revealed that both tactile, visual, and visuo-tactile input could shift the high-dimensional state space, sometimes long after termination of the stimulation. Collectively, these findings suggest that cortical processing of visual and haptic input is highly dynamic and complex and that the representation of sensory information is dependent on local as well as more widespread neural activity at the time when the input arrives.

In a discussion, methodological trends in sensory information processing research were presented. It was argued that the trends reflect the popularity of certain theoretical frameworks, in particular the idea of functional localization and hierarchical information processing. The results from the three papers were compared with other research findings, which supported the idea of a more interconnected functional organization in the nervous system. Finally, the impact of higher-order cognitive functions on sensory processing was put into perspective, and studies suggesting that attention can have significant, dynamic effect on cortical sensory processing at various processing stages, were presented.

In conclusion, the research presented in this thesis has shown that neocortical interpretation of haptic and visual input is widespread and dynamic. By stepping away from traditional paradigms and embracing the complexity of the brain's processing

abilities, we have gained a richer understanding of cortical sensory processing. Our findings advocate for a more diverse perspective of how neuronal responses are defined and analyzed and encourage a departure from dimensionality reduction and correlation-based approaches towards a recognition of the brain's inherent internal complexity.

Our result points towards a widespread information processing framework where remote cortical areas influence brain circuitry operations in primary sensory regions. It is our hope that this work not only contributes to the scientific understanding of sensory processing but also paves the way for new approaches to study the architecture of cortical networks.

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About the author

Sofie Skårup Kristensen holds an MA in Psychology and an MSc in Neuropsychology. She has pursued her PhD studies at the lab Neural Basis of Sensorimotor Control at the Department of Experimental Medical Science, Lund University. Here, she has investigated the processing and representation of sensory information in the rat neocortex using different electrophysiological techniques.

Sofie's studies have led to three original research papers which are presented and discussed in this thesis. All analyses and discussions are centered around the hypothesis that the same sensory input can be processed in different ways in the cortex depending on the state of the brain when and where the input arrives. By reading this thesis, you will learn about the basic principles of visual and tactile sensory processing, from the eyes and the skin to the brain, and about opposing theoretical viewpoints of how sensory input becomes holistic and continuous experiences.

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