UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Coding cognition

Representing and communicating information in perceptual and memory systems

Dorman, R.

Publication date
2025

Link to publication

Citation for published version (APA):
Dorman, R. (2025). *Coding cognition: Representing and communicating information in perceptual and memory systems*. [Thesis, fully internal, Universiteit van Amsterdam].

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

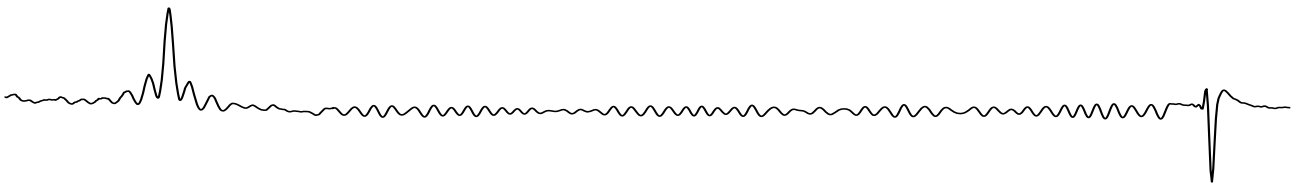
Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)

Download date:08 11月 2026

Chapter 1

General Introduction



The brain remains one of the most elusive scientific topics of the twenty-first century. Within this opaque gray mass, we find our memories, our emotions, our sense of self, our sense of the world around us: arguably, our entire personified existence. To find out how these feats are achieved, neuroscience has investigated the brain on a variety of levels. Students of the brain have moved from the concept of the brain as a vessel for the soul (Hippocrates, Plato; Crivellato & Ribatti, 2007), to the contemporary view of an inconceivably complex biological system able to parallel process a vast array of internal and external inputs to generate the most suitable behavioural output for survival (Gebicke-Haerter, 2023; Kriegeskorte & Douglas, 2018; Parker, 2022; Pennartz, 2015, 2017, 2022, 2024).

In this thesis I will defend the notion that the most important concept in understanding how the brain achieves such cognitive functions is to be found at the level of neural coding within a network of neurons. Many of the important cognitive processes in the brain cannot be fully understood from activity of isolated neurons or large-scale anatomical regions, but from dynamics within larger networks of neurons. Specifically, neurons communicating with one another in larger networks enables the complex computations necessary for perception, memory, decision making, and adaptive behaviour; all the while dealing with uncertain and variable sensory information, changing goals and rules, and while continuing to learn and adapt to the world. While neuroscience has made tremendous progress in reading the signals from such biological networks, the totality of the neural code will remain an enigma for some time. In this thesis, I aim to further the understanding of neural coding in neural networks during cognitive processing, by investigating the activity and communication patterns of neurons, larger populations of neurons, and the oscillatory Local Field Potentials (LFP) in the mammalian brain.

1.1 The Neural Doctrine and Networks of Cognition

A crucial step in understanding neuronal processing came with the formulation of the *neural doctrine* from the work of Camillo Golgi and Ramón y Cajal in the 19th century (De Carlos & Borrell, 2007; Jones, 1999), establishing that the brain is composed of neurons as the fundamental units built up from molecular and sub-cellular building blocks, situated in larger networks, maps, systems, and eventually, humans and human populations (figure 1). Subsequently, the description of membrane currents and the action potential - the neuron's primary signal of communication (Hille, 2025; Hodgkin & Huxley, 1952; Zupanc, 2022) - and the discovery of the synapse and inter-neuronal communication (Südhof & Malenka, 2008; Todman, 2008) provided science with the important concepts to describe the brain as a neural network model (McCulloch & Pitts, 1943).

Following the perspective of the neuron and it's place inside a biological neural network, numerous experts have added neurobiological and computational details to this model such as plasticity (e.g. *Hebbian* learning, spike-time dependent plasticity;

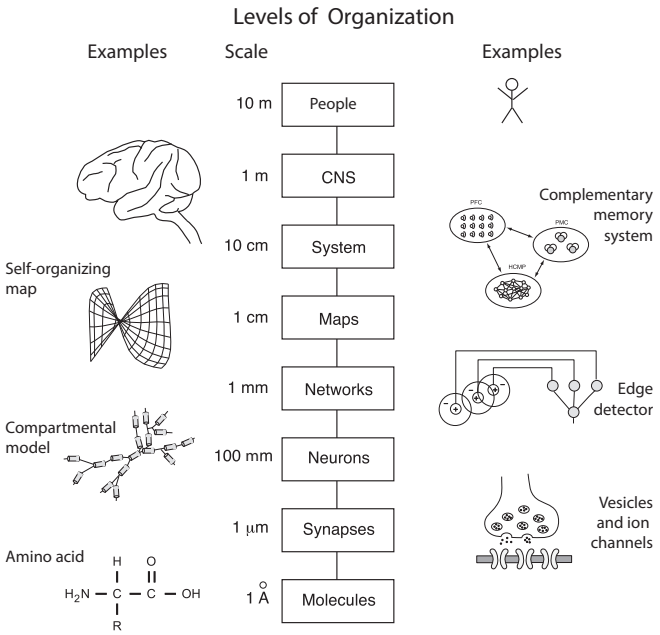


Figure 1: Levels of organization in the central nervous system across spatial scales, illustrating how various structures are built upon smaller, less complex structures. The emergence of the necessary computations for complex behavior and cognition is ascribed to a single brain. Although the brain is made up of macro-scale systems of interacting brain areas, the significant method of interaction on this scale is to be found on the level of interacting neurons and their networks. From Trappenberg (2023), adapted from Churchland and Sejnowski, The Computational Brain, MIT press (1992).

Citri & Malenka, 2008; Dan & Poo, 2006; Hebb, 1949), micro- and meso-scale effectors, (neurotransmitters, hormones, both excitatory and inhibitory; Isaacson & Scanziani, 2011), and sensory and motor representations and processing along different levels of abstraction (Hubel & Wiesel, 1962; Kandel et al., 2021; O'Keefe & Dostrovsky, 1971; Woolsey & Van der Loos, 1970; Wurtz, 2009). The neural network model has in part inspired numerous theoretical concepts on functional processing by the brain (Cohen et al., 2022; Pulvermüller et al., 2021) such as *Predictive Coding* (Friston, 2018; Keller & Mrsic-Flogel, 2018; Pennartz, 2015, 2022; Rao & Ballard, 1999), *Attractor Networks* (Barak & Tsodyks, 2007; Pennartz, 2009; Wu & Amari, 2005), Population coding (Averbeck, Latham, & Pouget, 2006; Lukashin & Georgopoulos, 1994), Analysis of the high-dimensional neural signals from large sets of neurons (Cunningham & Yu, 2014), Recurrent Dynamics (Barak, 2017; Güçlü & van Gerven, 2017), to name just a few.

Interestingly, the advancement of computational neuroscience has paradigmatically displayed the model of the brain as a neural network being a versatile tool with which numerous processes ascribed to the brain could be replicated. With relatively simple neural network models (i.e. simple compared to the mammalian brain), a wide array of functions can be simulated (Gurney, 2007; Kriegeskorte & Douglas, 2018), such as sensory processing (Brucklacher et al., 2023; Krizhevsky, Sutskever, & Hinton, 2017;

Yamins & DiCarlo, 2016), working memory (Mejias & Wang, 2022), decision making (Wong & Wang, 2006), attention (Lee, Whittington, & Kopell, 2013), executive control (Ardid & Wang, 2013) and spatial representation (Hasselmo, 2009). Such models are now also showing dynamics that replicate physiological measures we encounter within the brain based on measures of network properties such as neuron types and ratios of inter-laminar connectivity (Moreni et al., 2025). Note, however, that such networks need not always be biologically plausible. A factor diverging from biology is the amount of cells (But, this is quickly increasing, see Igarashi, 2025). Furthermore, such networks drastically simplify the biological mechanisms in question, such as working with rate models instead of discretely spiking models; foregoing neurobiological learning for the computationally efficient algorithm of backpropagation (Rumelhart et al., 2013); or foregoing meso- and/or macro-scale effectors in the brain. As the diverging complexity in computational models shows, there is a considerable spectrum of parameters with which neural models operate. In an established biological neural network, neuroscience still lacks a complete picture of what the precisely entails *neural code*. The following section will aim to unpack what is meant by neural coding as we investigate in cognitive neuroscience.

Signals of the neural system

A *code* is generally viewed as a system of signals or symbols for communication. Although more ambiguous, in neuroscience, *neural code* is generally accepted as "the signals of the [neural] systems" (Cariani & Baker, 2022), meaning the signals measurable in the brain that are encoding information – which can be decoded by a neural systems which would need access to this information (or, the scientist). More concrete and relevant for this thesis, a neural code can be used to encode representations of sensory information, which in turn can be decoded by systems involved in decision making, motor behaviour, spatial organisation, and other cognitive functions not directly addressed in this thesis, such as memory, attention or emotion (Pennartz, 2015; Quiroga & Panzeri, 2013). From the perspective of neural networks, there are several established concepts for neural coding (figure 2): 1) the central 'vehicle' for coding: action potentials, or s*pikes,* generated by a neuron after receiving sufficient input to reach threshold; 2) which specific upstream neurons send spikes (i.e. *From where* are the spikes sent?); 3) to which specific downstream neurons are spikes sent (i.e. *To which target* does the a neuron send a spike?); 4) how downstream neurons integrate the activity of numerous upstream neurons to reach threshold for spiking; and 5) the exact time during which spikes are sent and received. The last two point are crucial given that a given neuron generally requires multiple inputs to reach the threshold for spiking (as mentioned under 1). The timing of both the Excitatory Postsynaptic Potentials (EPSP) and Inhibitory Postsynaptic Potentials (IPSP) from multiple upstream neurons becomes important in controlling the activity of a downstream neurons. (It should be added that the required inputs to reach threshold is not static, as synaptic weights vary in strength, the spiking threshold of neurons has been found to be dynamic and inhibitory interactions can effectively cancel signal propagation, (Currier & Clandinin, 2025; Platkiewicz & Brette, 2010; Wu et al., 2015; Yi et al., 2015).

One might notice these concepts can be found in computational neural network models, often as simplified parameters (e.g. rate-based models, threshold function of a neuron, connectivity profile of the various neurons in layers). Although this list is not exhaustive and misses a great deal of subcellular complexity, the successes of these computational models indicate this is a significant avenue for understanding the fundamental properties of the brain.

Electrophysiology is currently the methodology that provides one of the best spatiotemporal windows into living neural networks and the neural code. Although the recording of neurons in vivo remains difficult and provides a yield representing only a fraction of the actual number of neurons in the mammalian brain, we have learned a tremendous amount about neural processing from merely looking at neuronal spikes (For a historical overview, but also critical thoughts see Drukarch & Wilhelmus, 2023).

However, when relating the neural code to cognition, there are still numerous questions that have not been addressed satisfactorily given the biological complexity found: For instance, which neurons are functionally connected to which other neurons, and how does this connectivity relate to cognitive function and brain state (chapter 2)? Is a neural code based on spiking activity sufficient for appropriately processing and identifying multiple distinct sensory modalities in the brain, or do we need to append the code, e.g. with a signal based on specific temporal correlations of spiking activity with the Local Field Potentials (LFP, chapter 3); Lastly, is the seemingly sensory activity of neurons in a primary sensory cortical areas (V1) actually sensory, or can this be ascribed to other factors such as overt behaviour (chapter 4)?

A final point on neural coding as described in this thesis is the following: the brain, a neural network, and its code as described here are by no means exhaustive concepts in understanding the entire brain. Beneath the level of the neural network lies an important sub-cellular dimension of neuroscience crucial for a functioning brain, such as mechanisms for plasticity and homeostasis. Although the present work focusses extensively on the level of neurons and how they interact, one should not dismiss the different avenues of neuroscience and biology in general. For all incredible things the brain can do, there have been millions of years of evolution, and dozens of processes on the various scales of life, that eventually constructed a biological machine to achieve computations at levels that would have been unimaginable with the molecular tools with which live began. Although I would defend the premise that neural networks are invaluable for cognition and complex thought, their existence would not be possible without all the tools life has offered evolution to work with.

1.2 Coding Cognition

Above, the basic properties of the neural code in networks have been briefly explained. Each of these concepts can be investigated with a multitude of different methods, with various measurements relating to parts of the neural code. Below, the concepts that we will relate to cognition in the awake behaving animal will be explained in more detail.

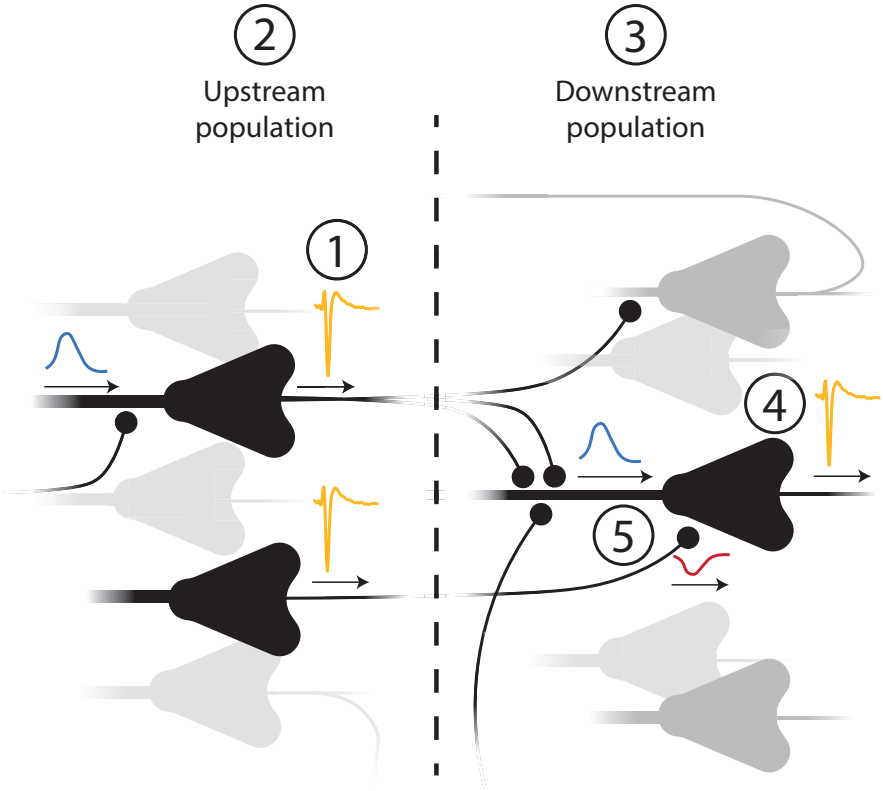


Figure 2: basic concepts of neural coding. See also table 1 for explanations of the numbers. Illustrating basic communication of neurons in an upstream area, connected to a downstream area. Neurons send spikes through their axons to a downstream population, and downstream neurons receive input from upstream neurons on their dendrite or on the soma. Note that in biological conditions the dendrites and axons would be much larger than depicted here and connecting to a wide array of populations (downstream, lateral, and recurrent connections back to the upstream population). Yellow spike exemplifies an action potential, blue lines Excitatory Postsynaptic Potentials (EPSP), and red lines Inhibitory Postsynaptic Potentials (IPSP).

Spike-spike correlations: Population coupling

The action potential, or spike, is by far the most widely used metric of brain activity in invasive *in vivo* neurophysiology. As mentioned, neurons are connected with thousands of other neurons (Binzegger, Douglas, & Martin, 2004; Kandel et al., 2021), and given the need for near-synchronized synaptic input to reach the spiking threshold, the correlations between spikes become an interesting parameter to assess how networks of neurons communicate.

Okun et al. (2015) developed a specific method to investigate spike-based correlations between single neurons and entire populations of neurons. Their study showed that

1	*Activated neurons send spikes*	*The central communication mechanism in the neural code is the spike generated by neurons which have received enough input from other neurons or sensory receptors (see also point 4 on integrating input to reach spiking threshold), i.e. the black neurons in figure 1, upstream condition, with spikes indicated.*
2	*Which specific neurons send the spikes*	*Neurons send out spikes over axons that reach multiple other neurons, with estimates of 1,000 to 10,000 target neurons, dependent on animal species, neuron types, and potentially more factors (Kandel et al., 2021). Which specific neurons are activated and send the spikes downstream is crucial for the information flow and processing of the signal in question.*
3	*Which downstream neurons receives the spikes.*	*The target neurons being activated in a network constitutes the next important factor. Neurons can receive input from ~1,000 to several thousands of upstream neurons, with an estimate for cortical neurons to have between 7,000 to 10,000 synapses per cell, of which roughly 90% are excitatory synapses and 10% inhibitory (Kandel et al., 2021). Due to converging information from multiple sources, it is crucial in view of cognitive functions for neural signals to reach appropriate downstream neurons.*
4	*Neurons integrate input to reach spiking threshold.*	*Related to point 2 and 3, multiple spikes from upstream neurons will affect dendrites or somata of downstream neurons through EPSPs or IPSPs. Sufficient excitatory input is required for a neuron to be depolarized significantly for it to reach the spiking threshold.*
5	*Timing of spikes emitted and received*	For a downstream neuron to effectively reach spiking threshold, simultaneous activation by upstream neurons is necessary. For example, synchronous activity of multiple neurons is effective in driving information transmission downstream, and inhibitory input on just the right time could effectively cancel signal propagation (S. Wu et al., 2021).

Table 1: Basic concepts of neural coding. See also figure 2.

spikes of neurons in the mouse visual cortex are correlated with the spikes in local population across a broad spectrum: some neurons are strongly coupled with the activity of nearby neurons, while other seem to lack any correlation with the local population (figure 3A). However, this metric of neuron-population-coupling has

not been applied to inter-areal cortical connections. In Chapter 2 we investigate the single neuron-to-population coupling levels between visual cortex, somatosensory cortex, perirhinal cortex and the hippocampus. Besides quantifying this metric, we investigated how coupling would vary in relation to cognitive phenomena such as spatial representation in the brain and behavioural states such as sleep, active wakefulness and quiet wakefulness.

Local Field Potential – spike correlations: Phase-coding

A second type of signal often recorded *in vivo* (and even outside of brains in the case of EEG) is the Local Field Potential (LFP). LFPs are prominent signals primarily built from the coalescent dendritic activity of neurons arranged in parallel, sometimes including contributions from action potential generation or other membrane currents (Buzsáki, Anastassiou, & Koch, 2012). Compared to the fast and short pulses of the action potential, LFPs are visible as oscillations or event-related deflections of voltages. As with spiking activity, the LFP is a consequence of synchronized activity of larger groups of neurons, and is often interpreted as a proxy of mass synaptic input activity (Burns, Xing, & Shapley, 2010; Gallego-Carracedo et al., 2022).

Sustained oscillations in the LFP in the cortex have been reported and related to computational and cognitive processes. For instance, the *theta* oscillations (4-12 Hz) originating from the rodent hippocampus have been suggested to be relevant for the coordination of neural activity in the context of memory formation (Buzsáki, 2002; Mizuseki et al., 2009), with recent work suggesting cortex-wide coordination (Sattler & Wehr, 2024). Note that these theta oscillations are not necessarily all originating in the hippocampus, but could have neocortical origins (Zimmerman et al., 2025).

Combining the measures of the oscillating LFP and spikes provides us with the combinatory metric known as phase-coding (figure 3B). Sustained oscillations in the LFP have a certain phase associated with each timepoint during the oscillation. Spikes, being a transient phenomenon, can be associated with a specific timepoint and thus a specific phase of an oscillation. This metric provides us with potentially new insights into parts of the neural code. For instance, phase-locking to hippocampal oscillations has been implicated as a metronome for coordinated information transfer from the neocortex to the hippocampus (Battaglia et al., 2011), whereas the phase-of-firing has been shown to code sensory information (Kayser et al., 2009; Montemurro et al., 2008; Panzeri et al., 2015).

In chapter 3, we investigate the relevance of phase-coding for a longstanding question on the process of multisensory integration (Pennartz, 2009). When multiple sensory systems engage with the outside world, they do so in variable formats: 2D images on the retina of the eye, 1D spectral signals in the cochlea of the inner-ear, etc… Nevertheless, visual and auditory information are combined in the cortex for effective behaviour (Buchholz et al., 2012; Meijer et al., 2017; Pennartz, 2009), and studies have shown that primary sensory areas, originally thought to be purely unimodal, can show a host of multisensory responses (Ghazanfar & Schroeder, 2006; Meijer et al., 2020; Meijer et

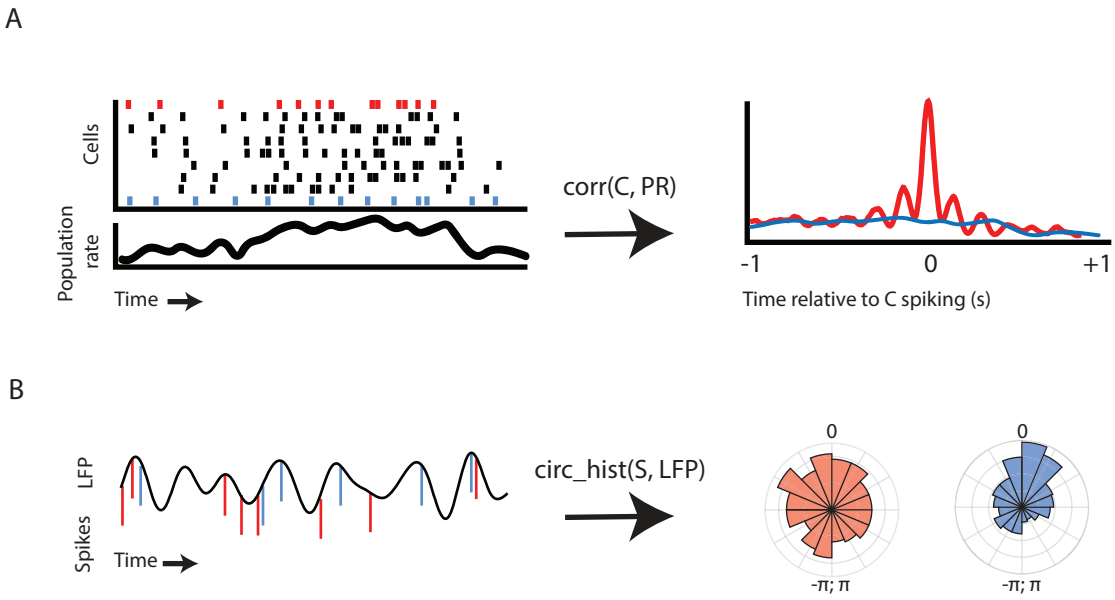


Figure 3: Neural coding concepts studied in this thesis. A) Single-neuron to population coupling (SNPC) measures the correlation between spikes of neurons. The SNPC provides a metric of a neuron's spiking synchrony with a population of neurons. Left: example spikes in a raster plot and the summed population rate, with red, highly coupled, and blue, uncoupled, neurons. X-axis corresponds to Right: by correlating (corr[x,y]) one cell's spiking (C) with the population rate (PR), a level of coupling can be quantified. Red and blue lines correspond to the highly coupled and uncoupled neurons, respectively. T=0 corresponds to the seed cell spiking. B) Phase-coding combines the spiking activity with the local LFP. Information is coded in the phase of spikes relative to oscillations in the LFP. Left: example spikes plotted on an example LFP trace. Red spikes belong to a cell with no phase preference; blue spikes correlate with the upper phase segment of the LFP. Right: circular histograms (circ_hist[X,Y]) represent the spike counts of a neuron (S) relative to the phase of an LFP oscillation. Note how the red cell has no strong preference along the radial axis, and the blue cell has a strong preferred direction, i.e. is strongly phase-locked with a preferred phase-of-firing.

al., 2017). Furthermore, a neuron can not directly interpret a spike as "belonging" to a particular modality. Spikes representing information from different sensory modalities look the same, and a neuron receiving information about multiple modalities does not have access to any ground truth on each spikes' origin. This prompts that the identification and segregation of multisensory information needs to be done on a relational basis: by determining how information represented in the brain relates to each other, and how this can be segregated (note that this would not be possible with single neurons, or in a situation where there is but one input source (Pennartz, 2009, 2015, 2022).

How these multisensory signals interact is still not fully understood, and notably: a purely spike-based code would not be theoretically suitable for relaying modality information while appropriately signalling the unimodal sensory information (Pennartz, 2009, 2015). In chapter 3, we investigate if phase-coding adds a layer to the neural code of multisensory integration.

Spike-behaviour correlations: Motor correlates in sensory cortex
Lastly, a crucial point in the investigation of the neural code is addressed: the potential contamination of the recorded neural signals by activity that is unrelated to the signal of interest. A common method in cognitive neurophysiology is subjecting awake behaving animals to a cognitive task while recording brain activity, such as responding if a certain stimulus is shown. Said neural activity is then related to an element of the task, e.g. a sensory stimulus, or another parameter. In the context of studying multisensory integration, a recent study highlighted a potentially problematic effect of non-relevant behavior correlating with activity recorded in sensory cortices (Bimbard et al., 2023; Oude Lohuis et al., 2024; Stringer et al., 2018), obfuscating any potential cross-modal signals. In chapter 4, we employ a designed forced delay in a behavioral task to ensure a period of sensory stimulation without overt behavior triggered by the proximity of the reward apparatus, in an effort to secure a period of stimulus-related neural activity, that is not contaminated by unrelated motor behavior.

1.3 Experimental framework

Extracellular recordings. As mentioned before, a typical experiment in cognitive neurophysiology as the ones employed in this thesis, requires electrophysiological recordings from within the brain, and an awake animal performing a certain task related to the cognitive process in question. In chapter 2 we make use of chronically implanted tetrodes in multiple brain areas of the freely moving rat (Buzsáki, 2004; Lansink et al., 2009; Vinck et al., 2016). A rat is implanted with a *quad-drive* (figure 4A), from which four bundles with eight tetrodes each can be directed to four different brain areas. This drive allows the animal to freely move around on a maze, without the need for head restriction, providing us with simultaneous electrophysiological recordings from multiple areas during active locomotor behavior. Each individual tetrode is composed of four intertwined wires, providing the research with more effective methods to sort the spikes recorded from said tetrode.

Next, in chapter 3 and 4 we made use of high-density silicon probes in headfixed mice during a multisensory detection task. Silicon probes consisted of an elongated silicon shaft on which multiple electrodes are situated, in the case of our experiments: 64 electrodes per probe (figure 4B). Such probes are inserted acutely while the mouse is headfixed, and although they do not provide chronic recordings in our experiments, they span all layers of the cortex, and the large amount of electrodes greatly facilitates spike-sorting (Rossant et al., 2016) as well as attribution of single units to specific layers..

Behavioural techniques. Next to the neural signals, an equally important factor in our experiments is the behavioral task. After all, we aim to correlate behavior witnessed from the animal with neural signals. In chapter 2, the task was designed to study processing of visual and tactile cues on a figure-eight shaped maze. An implanted rat was positioned on the middle arm of the figure-eight maze, after which visual cues were presented to indicate on which arm a reward was to be found. In addition, a tactile cue was presented along the arms of the maze correlating with the size of the reward. Such a freely moving task design provided us with data we could correlate to the animals movement, location on the maze, reward and sensory cues. Additionally, the rats in question were allowed to have periods of quiet wakefulness during the recording, and enjoyed sleep before and after the task, providing us with valuable data on the various brain states.

In chapter 3 and 4, mice were subjected to a headfixed multisensory detection task. This task was designed to study multisensory processing in the context of stimulus detection and was set up according to a two-alternative forced choice design. The headfixed mouse was placed in front a monitor and two speakers, and was presented with visual, auditory, audiovisual (i.e. multisensory) cues of varying intensity. A two-pronged lick-spout was positioned in front of the animal on which it had to indicate whether it had seen or heard a stimulus (i.e. lick to the right); or if it did not perceive a stimulus (i.e. lick to the left). For a certain delay period following stimulus onset, the reward apparatus was out of reach of the animal, until it moved in position for the animal to provide a response. The benefit of this headfixed task is that it offers more control of the sensory stimulation the animal receives and allows researchers to use high-density silicon probes. The two-alterative forced choice design implemented here offers the advantage that the no-detection response was not confounded by motivational lapses. Since the animal was required to response on each trial, the data indicates for each trial if there was a perceived or a not-perceived response.

Advanced analytical techniques. Besides experimental techniques, contemporary neuroscience makes use of computational and analytical developments. Before the raw data of spiking neurons can even be used, they are subjected to spike-sorting: a process whereby individually detected spikes are analysed and clustered as belonging to a single unit. This processing steps allows us to analyse signals from single neurons and is crucial in making judgements of the behavior of individual neurons. For example, in chapter 3 it would not be possible to make any statements on an individual neuron's behavior in terms of phase-coding without single unit resolution.

On matters of oscillations and phase-coding as relevant for chapter 3, the Fieldtrip toolbox (Oostenveld et al., 2011) was of great value. LFP analysis typically involves frequency-based analysis (such as wavelet convolution) to determine LFP power of frequencies of interest, and in the context of phase-coding, identifying the phases of LFP oscillations at frequencies of interest to match these with the spiking activity of individual neurons. Furthermore, we made use of the Pairwise Phase Consistency (Vinck et al., 2012; Vinck et al., 2010), an unbiased, trial and spike-rate independent

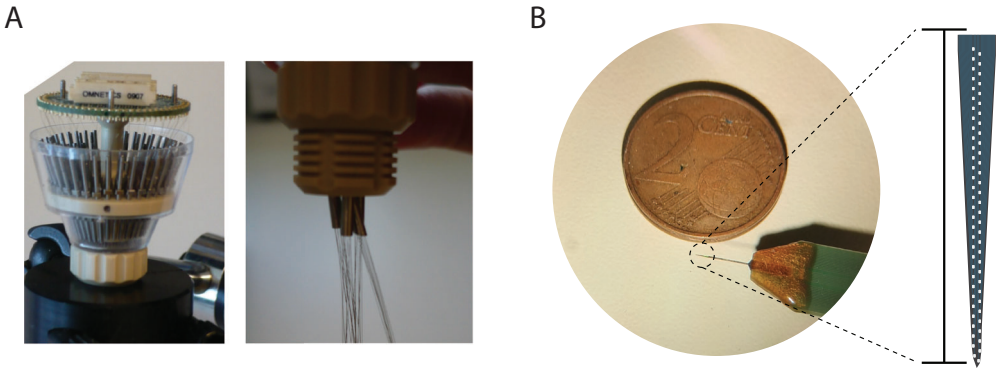


Figure 4: A) left: Upper part of the Quad-drive used to record in the freely moving animals. Right: Four different areas are targeted with four bundles of eight tetrodes each. B) Photograph of a silicon probe with a 2 eurocent coin for scale. Inset shows the number and density of electrodes on the bottom section of the probe, which was inserted into the visual cortex.

measure of the strength of phase-locking. Lastly, in Chapter 4, a Random Forest algorithm was crucial in determining how much a neurons activity could be related to a sensory or behavioral component.

Brain areas of interest.
The current consensus in neuroscience states that the brain, and especially the neocortex, processes information roughly in a hierarchy of sensory signals to a higher level of abstraction, in relation to time and space and efficient, spatiotemporal encoding of episodic memories. This is referred to as the cortico-hippocampal hierarchy (Buzsáki & Chrobak, 1995; Van Strien, Cappaert, & Witter, 2009). Furthermore, the sensory-frontal hierarchy is thought to subserve effective categorization and rule-based learning (Alexander & Brown, 2018; Fuster, 2001; Miller & Cohen, 2001). In this thesis, we investigated neural coding various areas: in Chapter 2, we recorded along the cortico-hippocampal hierarchy, to investigate neuron-population interactions in relation to of visual and tactile information travel towards the hippocampus and back. To this end, we performed simultaneous tetrode recordings in the rat hippocampus, perirhinal cortex, somatosensory barrel cortex, and visual cortex (Figure 5A). In chapter 3 and 4, we exclusively recorded from the mouse visual cortex using high-density silicon probes.

Visual cortex. Photic information is captured via the retina and reaches the primary visual cortex via the dorsal lateral geniculate nucleus of the thalamus (c.q. mainly reaches the cortex: minor pathways exist from the retina to the superior colliculus, suprachiasmatic nucleus, accessory optic nucleus, and pretectal area). Although primarily processing visual information, the primary visual cortex has by now been recognized as a multisensory area (Ghazanfar & Schroeder, 2006; Pennartz, Oude Lohuis, & Olcese, 2023). For instance, auditory information has been found to shape visual processing (Ibrahim et al., 2016), and direct connection from auditory areas to the visual cortex have been described (Iurilli et al., 2012; Shams, Kamitani, & Shimojo,

2000). Such auditory signals are assumed to support visual processing of multisensory input and help shape vision. Secondary visual areas show higher levels of abstraction dependent on the processing streams (i.e. the ventral *what* pathway, generally involved in object recognition; and the dorsal *where* pathway, generally involved with processing space and action (Mishkin, Ungerleider, & Macko, 1983). In the cortico-hippocampal hierarchy, visual information primarily reaches the hippocampal complex via parietal and/or temporal routes through the perirhinal and postrhinal cortex (Burwell & Amaral, 1998; Kuan et al., 2015; Naber, Witter, & Lopes Da Silva, 2000).

Somatosensory barrel cortex. The barrel cortex is part of the somatosensory cortex in the rodent, appropriately named after the barrel shaped columns found to represent the different vibrissae, or whiskers. Rodents, being small animals generally moving around in enclosed small spaces, foraging for small invertebrates, are highly dependent on the tactile information from their whiskers. Appropriately, tactile information from the whiskers is represented across a large portion of the rodent cortex. Mechanoreceptors in the hair-follicles and whisker muscles provide information about whisker deflections via trigeminal nuclei and three thalamic pathways (lemniscal, paralemniscal and extralemniscal) to the somatosensory cortex (Staiger & Petersen, 2021). As with the visual cortex, somatosensory cortex has now been described as being multisensory in nature (Ghazanfar & Schroeder, 2006). Likewise, tactile information also reaches the hippocampal complex via perirhinal and postrhinal cortex (Burwell & Amaral, 1998; Kuan et al., 2015; Naber, Witter, & Lopes Da Silva, 2000).

Perirhinal cortex. Traveling along the cortico-hippocampal hierarchy, the above mentioned perirhinal cortex has been shown to be an important 'gating' area, filtering highly processed multisensory information before this is relayed towards the hippocampus and other structures for memory formation (Agster & Burwell, 2009; Burwell & Amaral, 1998; Deacon et al., 1983; Naber, Witter, & Lopes Da Silva, 1999). Although the perirhinal cortex is a neocortical area, its cytoarchitecture differs from typical neocortical microcircuits, e.g. with different ratios of neuron types compared to other neocortical areas (Kealy & Commins, 2011; Pelletier, Apergis, & Paré, 2004). The perirhinal cortex has been shown to be strongly multisensory, receiving inputs from all sensory areas (Fiorilli et al., 2021; Jacklin et al., 2016), seems to signal unexpected rewards possibly to facilitate learning and adaptive behavior (Fiorilli et al., 2024), and even shows spatial correlates in rats performing a freely moving task in a maze (Bos et al., 2017).

Hippocampus. The hippocampus is the only non-neocortical area in this thesis, yet it is regarded as part of the archicortex. The organization of the hippocampus follows an intricate organization of sub-areas: Cornu Ammonis 1, 2 and 3, (CA1, CA2 and CA3), the dentate gyrus, and a key output reaches the subicular complex (Amaral & Witter, 1989; Van Strien, Cappaert, & Witter, 2009). The hippocampus receives cortical information via the postrhinal and perirhinal cortex, mostly through the entorhinal cortex. Input from the entorhinal cortex is projected to the various sub-areas in the hippocampus (viz. DG and CA1), and from the dentate gyrus information follows the trisynaptic

pathway to CA3, CA1 and the subiculum, from which information is projected to the entorhinal cortex and other areas (Amaral & Witter, 1989).

The hippocampus has been found to have some extraordinary features. Of relevance for this thesis is the parallel alignment of cell bodies and dendritic trees (Figure 5B) enabling it to act as a powerful oscillator. Specifically, the hippocampus has been shown to generate strong theta oscillations, which even obfuscates if theta activity recorded in neocortical areas is of hippocampal or local origin (Buzsáki, 2002; Ruikes et al., 2024; Zimmerman et al., 2025). Secondly, the hippocampus shows striking correlation of single neuron spiking with the spatial position of an animal, testifying to the existence of 'place cells' (O'Keefe & Dostrovsky, 1971), which are assumed to be a form of relational coding of self-position and objects in spatial dimensions (Behrens et al., 2018; Whittington et al., 2020). This spatial representation is assumed to support spatial navigation and to link spatial information to other elements of episodic memory (Alme et al., 2014; O'keefe & Nadel, 1978).

1.4 Summary of the chapters

In this thesis we aim to investigate three elements of neural coding: single-unit to population coupling based on spiking activity (Chapter 2), phase-coding (Chapter 3), and motor-related spiking activity during sensory processing (Chapter 4).

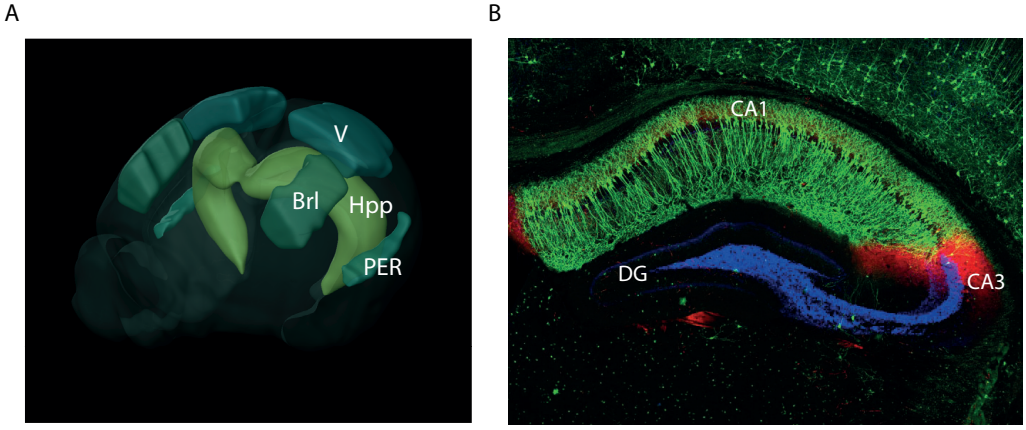


Figure 5: Areas of interest for this thesis. A) 3D projection highlighting the various brain regions investigated. V: Visual cortex, including V1 and secondary visual cortices; Brl: Barrel field of the somatosensory cortex; PER: Perirhinal cortex; Hpp: Hippocampal region, of which the CA1 region was recorded from. Image rendered using the Allen Mouse Brain Atlas (Wang et al., 2020). B) Histological section of the hippocampus illustrating its cellular organization, which, among other features, facilitates the generation of strong oscillatory signals. DG: dentage gyrus. Adapted from NIH Image Gallery, Ranauk Basu, University of Utah.

Spike-based coupling between single neurons and populations across rat sensory cortices, perirhinal cortex and hippocampus.
Chapter 2 aims to investigate the neural code on the level of spike correlations. Although we typically ascribe processing of certain types of information to dedicated cortical areas (i.e. visual information to visual areas), specific as an area may be, it never operates in a vacuum. Indeed, the neocortex is well interconnected (Barthó et al., 2004; Douglas & Martin, 2004; Perich & Rajan, 2020; Tyagi, 2015), but this connectivity is subject to functional rules: neurons are wired together based on functionality (Engel, Schölvinck, & Lewis, 2021). In Chapter 2, we investigate cell to population correlations in the awake behaving rat. It has been known that spatially restricted neuronal populations (within one cortical area, such as V1) are often highly synchronous (i.e. like a choir), yet a subpopulation of cells may exist that diverts from this regime by not firing in sync with the local population (i.e. like a soloist in the choir, Okun et al. 2009). Here, we investigate the phenomenon of S*ingle-Neuron to Population Coupling* (SNPC) between multiple areas. We describe levels of coupling in and between four cortical areas: visual cortex, barrel cortex, perirhinal cortex and the CA1 region of the hippocampus. Next, we question the functional relevance of SNPC. First, we ask if spatial selective cells in the hippocampus exhibit strong or weak coupling with other hippocampal neurons or other areas. Lastly, we investigated levels of population coupling in different brain states (active wakefulness, quite wakefulness and slow-wave sleep).

Feature and modality-specific phase-coding in mouse primary visual cortex during multisensory detection. Chapter 3 investigates the neural code on the level of spike–LFP correlations. During multisensory stimulation, sensory information of various formats (i.e. vision in a 2D retinotopic projection; audition in a tonotopic organization) have to be combined. A purely rate based representation of multisensory inputs would lead to interference of the representation of unisensory features. We propose that phase-coding provides an additional parameter to represent modality specificity without distorting other unisensory features that require stable encoding. We will test the hypothesis that phase-coding by temporally specific spike-LFP correlations may contribute to a neural code which facilitated the integration of information from multiple senses. We record V1 activity while a mouse is performing a multisensory detection task, and assess how neurons' spiking activity locks to the phase of the LFP, and how this locking changes with respect to the stimuli and modalities presented.

Low impact on orofacial motion on selective primary visual cortex responses to visual stimulation with delayed introduction of reward apparatus.
Lastly, in chapter 4, we investigate a recently highlighted neurophysiological confound which might obfuscate the investigation of neural codes. Earlier studies in multimodal integration have shown diverse responses in seemingly specific sensory areas. Recent studies showed an important confound: much of the activity in sensory areas appears correlated with movement, so called *motor confounds (*Bimbard et al., 2023; Stringer et al., 2018). The premise of these results stirred research on sensory processing, as it became unclear what sort of activity was related to actual sensory stimulation, and

what activity is related to the animal walking, licking, grooming, whisking, or other behaviour. We aimed to separate the orofacial motor activity from sensory activity by using a forced delay by means of a moving reward apparatus, so we could present a stimulus and only after a delay give the animal the opportunity to provide a respond by licking the reward spout. We test the hypothesis that this delay period provides us with less orofacial movement, and thus less interference of non-stimulus related activity.