THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Advancing the Understanding of Phantom Limb Pain through Mathematical Models

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Cover:
A silhouette of a person stretching out a hand. The hand and the head of the person are covered in mathematical equations, and the hand is opaque, intended to illustrate how mathematics can be used to described a sensation such as phantom limb pain. Colorful splashes have been added to the background for artistic flair.

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Everything is vague to a degree you do not realize
till you have tried to make it precise.
– Bertrand Russell

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Abstract

Phantom limb pain is a condition where pain is perceived as arising from a missing limb. Despite being one of the most prevalent and distressing consequences of limb amputation, theories regarding its underlying mechanisms remain disputed. Research on phantom limb pain faces several challenges: pain is a subjective experience that is difficult to measure and quantify, the array of available experimental methods is limited by ethical constraints, and the heterogeneity within the amputee population further complicates efforts to empirically disentangle the factors driving pain.

Mathematical modeling offers a way to shed light on complex topics such as phantom limb pain. This approach is particularly valuable when direct empirical observations are difficult to obtain, since mathematical models can provide insight to how systems behave, enable predictions of scenarios that have not yet occurred and forecast possible consequences of perturbations to a system. While mathematical models alone cannot definitively determine the mechanisms underlying phantom limb pain, they can reveal patterns in complex data, generate testable hypotheses, and guide future research directions.

This thesis aims to apply mathematical models to bridge gaps in the current understanding of phantom limb pain. The included models span neurophysiological mechanisms, cognitive processes, quantification of pain perception, and statistical modeling of neural activity. Together, these models offer insights that can support future research and inform the development and use of interventions aimed at relieving phantom limb pain.

Keywords: Phantom limb pain, pain, neuropathic pain, chronic pain, mathematical modeling, Bayesian inference, active inference, pain maps, computational neuroscience, electroencephalography, EEG, resting state EEG

List of Publications

This thesis is based on the following publications:

[A] **Malin Ramne**, "A Computational Model of Dorsal Horn Circuits' Contribution to Neuropathic Pain". EMBC 2025.

[B] **Malin Ramne**, Jon Sensinger, "A Computational Framework for Understanding the Impact of Prior Experiences on Pain Perception and Neuropathic Pain". PLoS Computational Biology 2024.

[C] **Malin Ramne**, Torbjörn Lundh, Jon Sensinger, "Modeling the Action-Perception Loop and its role in Phantom Limb Pain using Active Inference". Preprint at bioRxiv 2025.

[D] Eric J. Earley, **Malin Ramne**, Johan Wessberg, "Unified Measures Quantifying Intensity and Similarity of Pain and Somatosensory Percepts". Journal of Neurophysiology 2025.

[E] **Malin Ramne**, Eva Lendaro, "Resting-State Theta and Alpha Oscillations in Amputation and Phantom Limb Pain: A Pre-Registered High-Density EEG Study". Preprint at ResearchSquare 2026.

Other publications by the author, not included in this thesis, are:

[F] S. Damercheli, **M. Ramne**, M. Ortiz-Catalan, "transcranial Direct Current Stimulation (tDCS) for the treatment and investigation of Phantom Limb Pain (PLP)". *Psychoradiology*, 2(1), 2022, 23–31, DOI: 10.1093/psyrad/kkac004.

[G] **M. Ramne**, M. Elam, L.S. Löken, M. Ortiz-Catalan, "Neurophysiology of Pain for Non-Neurophysiologists: A Systematic Review". Preprint at ResearchSquare, 2023, DOI: 10.21203/rs.3.rs-2942949/v1.

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Acronyms

ACC:	Anterior Cingulate Cortex
AMI:	Agonist-antagonist Myoneural Interface
CBPT:	Cluster Based Permutation Testing
DRG:	Dorsal Root Ganglion
EEG:	Electroencephalography
fMRI:	Functional Magnetic Resonance Imaging
GMI:	Graded Motor Imagery
IASP:	International Association for the Study of Pain
MEG:	Magnetoencephalography
MI/M1:	Primary motor cortex
MT:	Mirror Therapy
NRM:	Nucleus Raphe Magnus
NRS:	Numeric Rating Scale
PAF:	Peak Alpha Frequency
PAG:	Periaqueductal Gray
PFC:	Prefrontal Cortex
PMI:	Phantom Motor Imagery
PLP:	Phantom Limb Pain
RPNI:	Regenerative Peripheral Nerve Interface
RVM:	Rostroventral Medulla
SI/S1:	Primary somatosensory cortex
SII:	Secondary somatosensory cortex
TMR:	Targeted Muscle Reinnervation
TSR:	Targeted Sensory Reinnervation
VAS:	Visual Analogue Scale

Part I

Overview

Preface

How do you mathematically model pain? That is one of the most common questions I get when I tell people what my research is about. And rightfully so – how does one put numbers and equations on something as abstract as a subjective sensory experience? With this preface, I would like to take you, the reader, along on the mental journey that eventually led me to an answer, and introduce some of the core concepts that the resulting models build upon – concepts that, in fact, influence your life every single day.

When I first started this PhD position, armed with the "there's-no-problem-I-can't-solve" hubris and naivety of a newly graduated engineer, I figured if I just learned what the "hardware" of the pain system is, I could approach it the same way I had approached problems in my mathematics and physics courses: set up a model of the physical and functional properties of each piece, plug them all together, press play on the simulation, and out would come some output corresponding to pain. Easy, right?

However, once I started reading about pain I was quickly humbled by the immense complexity of the human body (more on that in Chapter 2.1). I also realized that my original idea had two major problems. First, it is not particularly well known what "hardware" is actually involved in pain processing. Unlike other sensory modalities – such as vision and hearing, which rely on specialized regions of the brain like the visual and auditory cortex – there is no "pain cortex". Studies of brain activity during pain perception show that

regions across the entire brain are active, highlighting the distributed and highly complex processes involved in the pain experience.

Second, even if it were possible to pinpoint with greater detail which neural circuits are involved in pain processing, too little is known about how the individual components (neurons and other supporting cells) of those circuits work to create large-scale simulations that generate meaningful insights to pain perception and experience (as exemplified by the failure of the billion-euro Human Brain Project, that had set the explicit goal of mapping the entire human brain in computer models). Don't get me wrong – mathematical models can still be immensely useful to model processes at the cellular level. It just didn't seem like that was an approach that would give me satisfactory answers pertaining to the mysteries of phantom limb pain.

With these insights, I started glancing around at other possible approaches at modeling pain. I recalled some papers I had come across which dealt with modeling cognitive processes involved in pain perception. At first, I had dismissed these papers as irrelevant, due to dealing with comparatively "soft" concepts like expectations and emotions (scary to engineers) rather than "hard" concepts like neurons. But the more I read about the complexities of the pain experience, the more appealing this cognitive computational approach seemed for the purpose of modeling pain. In particular, one concept stood out as especially promising: *Bayesian inference*.

So what actually is Bayesian inference? Let's take it word-by-word, starting from the back with *inference*: a conclusion that is formed from (potentially uncertain) evidence. Humans engage in inference all day, every day, at many different levels, from the seemingly mundane task of recognizing sound waves reaching our ears as spoken words, to the sophisticated process of inferring the existence of dark matter based on its gravitational effects. Many forms of sensory perception can be understood as a kind of inference, where the "evidence" is the sensory information arriving from our ears, eyes, skin, and other sensory organs. The *Bayesian* part of Bayesian inference comes from the mathematical formalization of this process, where *Bayes' rule* plays a central role.

For those who (intentionally or not) have suppressed their memories of high-school mathematics, Bayes' rule is a mathematical relation for inverting conditional probabilities:

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)},$$

where A and B are events, $P(A|B)$ is the probability of event A occurring given that B is true (also called the *posterior* probability of A given B), $P(B|A)$ is the probability of event B occurring given that A is true (also called the *likelihood* of A given B), and $P(A)$ and $P(B)$ are the probabilities of events A and B respectively without any conditions. This relation allows you to, for instance, calculate the probability that there is a fire in your local neighborhood given that you see smoke. If you know the overall probability of fires occurring in the area (P(fire), hopefully low), the probability of smoke (P(smoke), which could be high if your neighbors like to barbecue), and the probability that a fire gives off smoke (P(smoke|fire)), you can use Bayes' rule to infer the posterior probability of fire, P(fire|smoke). In Bayesian inference terminology, the smoke is the evidence (or observation) on which the inference is based. Two other key ingredients in the inference process are the *prior probability* of fire, P(fire), and the likelihood of observing smoke when there is fire, P(smoke|fire). These probabilities give us the quintessential Bayesian inference formula for estimating the probability that an explanation is true given some observation:

$$P(\text{explanation}|\text{observation}) \propto P(\text{observation}|\text{explanation}) \times P(\text{explanation})$$

or

$$\text{Posterior} \propto \text{Likelihood} \times \text{Prior}$$

Okay, so we have a formula for calculating one number from a bunch of others numbers – what's the big deal? Well, the thing that is particularly neat about Bayesian inference is that it gives us the ability to make the *optimal* conclusion when the evidence is uncertain. This matters for perception because sensory information arriving to the brain can be noisy, low quality, partially informative and can even be open to multiple interpretations. If we were to only operate based on such ambiguous information it would be very difficult to function well in the world. But when that noisy sensory input is combined with *prior information* – our expectations about how things usually work – we can make better estimates of what is going on, allowing us to interact more effectively with our environment.

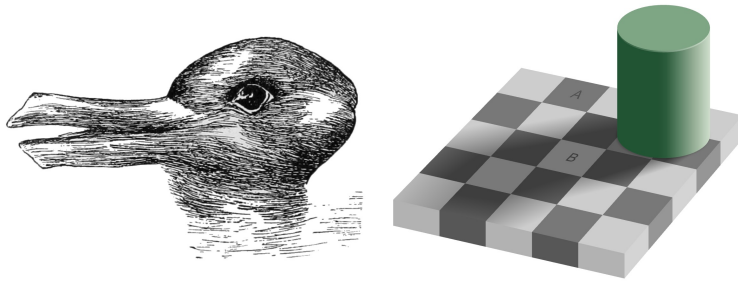

Figure 1: Optical illusions exemplify how expectations can influence perception such that identical sensory input result in vastly different experiences. Some readers will see a duck in the left image, others will see a rabbit. In the right image, the squares marked A and B have the exact same shade of gray, yet it might not look like it to you? This effect is can described mathematically by Bayesian inference.

While Bayesian inference in perception allows us to operate more efficiently in the world, it also comes with a quirk: the same sensory input can produce different experiences depending on the expectations of the observer. For example, when you see a person at a distance your conclusion on who it might be depends on how well you can discern the features of the person, but also on whether or not you are expecting to meet someone in particular at that time and place (see [1] for an elaboration of this example and more on Bayesian models). Sometimes the effect is even subtler, as exemplified by the optical illusions in Figure 1. Do you see a duck or a rabbit in the left image? And in the right image, are squares A and B the same or different shades of gray?

The influence of Bayesian inference is well documented also in the context of pain perception. You might be familiar with the *placebo effect*, where a sugar pill or even a band-aid can result in genuine pain relief – not because of any active ingredient, but because of the expectations they generate. Or perhaps you've experienced a paper cut you didn't notice until you saw the blood, at which point the pain suddenly "appeared". These everyday examples

highlight why Bayesian inference is a compelling framework for modeling pain. What makes it particularly relevant to phantom limb pain is that following amputation the available observations relating to the missing limb become profoundly uncertain. Bayesian inference offers a potential explanation for how that uncertainty might lead to something as undesirable as phantom limb pain.

I hope this preface has given a sense of how pain can, in fact, be modeled mathematically – and that doing so does not necessarily require highly advanced computing methods. Instead, it can often build on rather simple concepts that also apply to a wide range of situations we encounter in everyday life. In the chapters that follow, I will show in more detail how these ideas fit into the broader framework of this thesis: advancing the understanding of phantom limb pain. With that, it is time to move on from this informal introduction and dive into the details. I hope you enjoy reading the rest of this thesis as much as I enjoyed writing it...

CHAPTER 1

Introduction

Mathematics is one of the tools we as humans use to make sense of the world around us, from the fundamental laws of physics to the complex market dynamics of financial trading. Mathematical models allow us to understand how systems operate and how their components interact [2]. They also enable predictions in scenarios we have not yet encountered and help us anticipate the consequences of potential actions. This is especially valuable in the context of complex systems, where dynamics may be difficult to predict and small changes in input can lead to disproportionately large effects on output. One example of such a complex system is the human body – a high-dimensional system with interacting processes across multiple scales. This complexity necessitates abstraction and simplification through modeling in order to understand its biological processes.

One of the most fundamental functions of the human body is protection from harm. Pain serves this purpose: it acts as a warning signal of actual or potential tissue damage [3]. While pain has evolved as a protective mechanism essential for survival, it can at times become maladaptive and persist even after injury has healed. One of the most striking examples where pain is clearly disproportionate to any ongoing tissue damage is phantom limb pain, in which

pain is perceived in a limb that is no longer present.

Despite being one of the most prevalent and distressing consequences of limb amputation, the mechanisms underlying phantom limb pain remain disputed [4, 5]. Research in this area faces several challenges. Pain is inherently subjective, making it difficult to measure and quantify. Experimental methods for studying pain mechanisms are constrained by ethical considerations. Animal research, while allowing for more invasive investigation, presents additional difficulties, such as assessing the presence, intensity, and location of pain. Moreover, the heterogeneity within the population of those with amputation further complicates efforts to empirically disentangle the factors driving phantom limb pain. These challenges are compounded by the fact that prior studies often involve small sample sizes and heterogeneous experimental designs, limiting the strength of conclusions drawn from existing literature [5].

Returning to the tools we use to make sense of the world, mathematical modeling provides a promising avenue for deepening our understanding of phantom limb pain. Although mathematical models alone cannot definitively determine its underlying mechanisms, they can reveal patterns in complex data, generate testable hypotheses, and guide future empirical work [2]. This approach is particularly valuable when direct observation is difficult or impossible, as is the case for phantom limb pain. Mathematical models can be applied in multiple ways to elucidate different aspects of the phenomenon: mechanistic models can explore candidate biological and cognitive mechanisms, while empirical models can enable quantification pain percepts and uncover empirical relationships between neural data and pain reports. For a multifaceted phenomenon like phantom limb pain, a combination of different modeling approaches is necessary to capture its different dimensions.

Together, these perspectives motivate the central theme of this thesis: mathematical modeling offers a powerful set of tools for exploring the mechanisms, perception, and neural signatures of phantom limb pain. By combining mechanistic and empirical approaches, the thesis aims to contribute to an improved understanding understanding of phantom limb pain at multiple levels.

1.1 Research objectives

The overarching aim of this thesis is **to use mathematical models to advance the understanding of phantom limb pain**. Under this umbrella, the thesis pursues the following two research objectives:

R1. Develop mathematical models that propose possible mechanisms of phantom limb pain.

R2. Apply mathematical modeling approaches to quantify and characterize perceptual and neural aspects of phantom limb pain.

1.2 Thesis outline

Part I of this thesis provides the background and context needed to support the papers presented in Part II. Because the work spans two distinct fields – mathematical modeling and pain research – the background chapters are designed to help readers from either discipline bridge the conceptual gap. To this end, Part I includes two introductory chapters: Introduction to the study of pain in Chapter 2, which offers an overview of pain mechanisms and pain science, and Introduction to mathematical models in Chapter 3, which introduces key modeling concepts relevant to the thesis. These are followed by a chapter that focuses specifically on phantom limb pain and summarizes the current state of the field. Chapter 5 provides a summary of the appended publications and their contribution to the field, followed by concluding remarks in Chapter 6.

CHAPTER 2

Introduction to the study of pain

The aim of this chapter is to provide an overview of pain – what it is, how it can be measured, and how the human "hardware" and "software" shape pain perception – for readers with limited clinical or scientific experience of pain. To this end, I'll begin with a deceptively simple question: "What is pain?". While the task of defining pain may seem simple – it is after all something that almost everyone[1] has experienced – formulating a concise yet accurate definition is not trivial. Putting a physical sensation into words is something of a philosophical conundrum, analogous to describing the color red or the basic taste of sweetness. One might be tempted to resort to the definition "you know it when you feel/see/taste it", but in the context of scientific research this type of definition is not very informative or helpful. Instead, we often turn to describing these sensations in terms of the context in which they may be experienced. For example, describing the color red as the color of a strawberry and the taste sweetness as the strawberry's taste. A similar approach is taken by the International Association for the Study of Pain (IASP), who define pain with the following words [3]:

[1] There exist rare genetic conditions that impair the ability to perceive pain, so called congenital insensitivity to pain.

"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."

In other words, pain is a form of warning signal to motivate the organism to withdraw from harmful situations. It may also function as a learning signal, to teach the organism to avoid such harmful situations in the future. As a consequence, pain should typically only arise when there is actual or potential tissue damage present. However, as the "resembling that of" in the definition alludes to, this relationship between tissue damage and pain does not always hold. Pain that arises from actual or threatened tissue damage is often referred to as nociceptive pain, but sometimes pain persists also after tissue damage has healed and all noxious stimuli have been removed. In cases where pain persists or recurs for longer than 3 months, it is classified as chronic pain [6]. Chronic pain is one of the leading global burdens of health [7] as well as an enormous personal and economic burden, affecting more than 30% of people worldwide [8].

The problem of chronic pain is made even more challenging by the fact that pain can arise even in absence of apparent tissue damage. Neuropathic pain is a particular category of pain that is caused by damage or disease of the somatosensory nervous system [6], for example due to nerve compression, as in carpal tunnel syndrome, or viral infection affecting neural tissue, as in shingles. In contrast, nociceptive pain arises from damage to somatic tissue – such as skin, muscles and bone – or visceral organs. A third category of pain, nociplastic pain, arises due to dysfunction of the sensory nervous system, but without damage to somatic, visceral or nervous system tissue [9]. Examples include certain forms of fibromyalgia and complex regional pain syndrome. Since neuropathic and nociplastic pain are caused by damage or dysfunction of the nervous system itself, these types of pain usually do not accurately reflect the level of harm to which the organism is exposed. Furthermore, since damage or dysfunction of the nervous system can occur in many forms and at multiple levels, these pain conditions are often very difficult to treat.

Although these three categories are defined by distinct underlying mechanisms, they are not mutually exclusive and may coexist, as illustrated in Figure 2.1. Both nociceptive and neuropathic pain can present as acute or chronic conditions, whereas nociplastic pain is typically chronic, since the un-

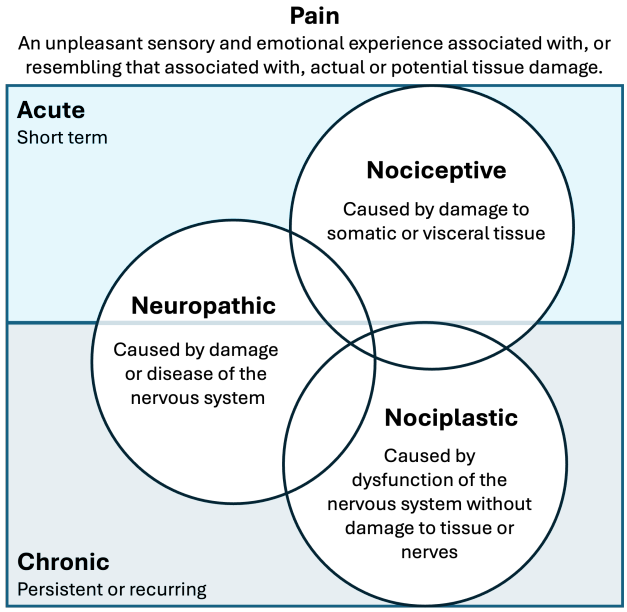

Figure 2.1: Pain can be classified by duration (acute vs. chronic) and by mechanism, including nociceptive pain caused by damage to somatic or visceral tissue, neuropathic pain caused by damage or disease of the nervous system, and nociplastic pain caused by dysfunction of the nervous system without apparent damage. While these categories relate to distinct pain mechanisms, they can also coexist in mixed pain conditions.

derlying neural changes often take time to develop. Consequently, an injury that initially causes nociceptive or neuropathic pain may, through adaptive or maladaptive changes in the nervous system, develop over time to include nociplastic mechanisms. As we will see in Chapter 4, phantom limb pain is a particularly striking example of neuropathic pain that can include nociplastic mechanisms.

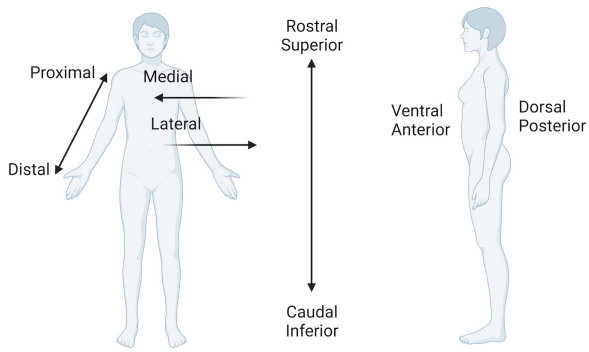

Figure 2.2: Description of anatomical directions. Created with BioRender.com.

2.1 The neurophysiology of pain

The aim of this section is to provide a concise, yet comprehensive overview of the neurophysiology of pain (the "hardware"). A more extensive version of this literature review has been published as a preprint [10]. Although most of the material in this section is not necessary for understanding the papers on which this thesis builds, it is included to offer additional context for the curious reader. Throughout this section, anatomical references are made regarding the location or direction of neural structures and signals. Figure 2.2 may be helpful to readers unfamiliar with this terminology.

The process leading from tissue damage to the experience of pain can coarsely be divided into four phases: transduction, transmission, perception, and modulation [11], as illustrated in Figure 2.3. Important to note is that pain becomes a conscious experience only when the neural signals reach the level of perception, where they are integrated with other sensory stimuli and cognitive processes. The processes leading up to this point are often denoted collectively as *nociception*. The following sections will deal with these four phases one by one.

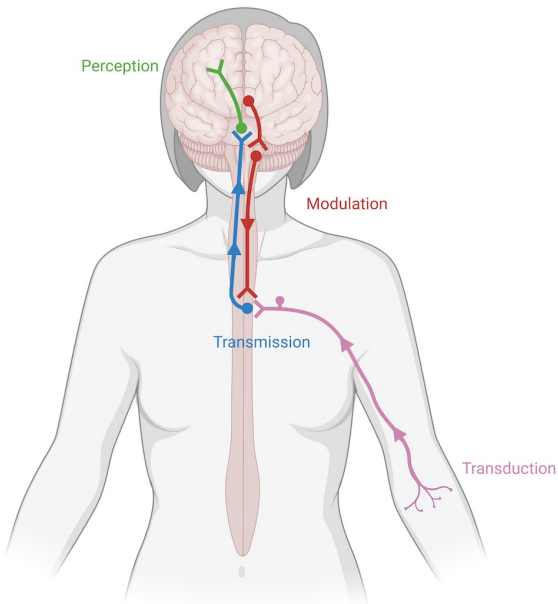

Figure 2.3: The neurophysiologal processes leading up to the experience of pain can be divided into four phases: transduction, transmission, perception, and modulation [11]. Created with BioRender.com.

Transduction

Transduction of pain refers to the process by which a noxious (potentially harmful) stimulus results in electrical activity in nociceptive sensory neurons. These so called nociceptors, are specialized to detect chemical, mechanical, and thermal stimuli that can potentially damage the tissue [11, 12]. The nociceptors innervate different types of tissue such as skin, bones, muscles, joints and certain visceral tissue. Worthy of notice is that nociceptor terminals respond more vigorously to successive stimuli (sensitization), as opposed to reduced responsiveness or adaptation in all other sensory transduction systems [12–15].

Although nociceptive fibers have no specific receptors in the nerve endings (as there are for different modalities of touch), they have plenty of receptors designed to recognize products of cell damage and inflammation [16, 17]. Chemical mediators released into tissues upon injury can increase the pain sensitivity by changing the excitability of individual neurons [16–23] and depolarizing nociceptive sensing terminals by direct activation of ion channels [17, 24]. Sensitization may also in part be due to depletion of degrading enzymes upon repetitive release of the chemicals, leading to prolonged depolarization [25]. Many nociceptors are inactive under normal circumstances and become activated/sensitized in a state of inflammation, so called silent or dormant nociceptors [16, 19, 26–29].

Cell bodies of peripheral afferent neurons are located in the dorsal root ganglia (DRG), just lateral of the spinal cord. Axons from the DRG enter the spinal cord via the dorsal root [30, 31], though there are reports of sensory afferents also in the ventral root (otherwise described to exclusively contain efferent fibers) [27, 32, 33].

Transmission

The previous section dealt with first-order neurons conducting information between the periphery to the spinal cord. Next, we will consider second-order neurons which relay information within the spinal cord and between the spinal cord and the brain. Upon entering the spinal cord first-order neurons synapse onto second-order neurons in the spinal cord grey matter. In other words, the spinal cord is the first place in which information from “the sensors of the body” is relayed and processed. The neurons in the spinal cord grey matter

are divided into sections called lamina according to their cellular structure and anatomical location. The dorsal horn is the main pain processing region of the spinal cord grey matter. There are three functional populations of dorsal horn neurons: interneurons that can make excitatory or inhibitory connections within the spinal cord; propriospinal neurons that extend over multiple spinal segments and are involved in reflex activity and interactions among stimuli at separate bodily locations; and projection neurons that extend beyond the spinal cord to connect to supraspinal cites (i.e., the brain) [19]. The projection neurons can be further divided into two main types: nociceptive specific (NS) neurons that are excited solely by nociceptive afferents, and wide dynamic range (WDR) neurons that are excited by both innocuous and nociceptive stimuli [19, 20, 27, 34–36].

Several mechanisms can alter the responsiveness of spinal cord neurons to innocuous and nociceptive stimuli, giving rise to what is commonly referred to as central sensitization. These include a lowered discharge threshold, such that neurons respond to stimuli that would not normally evoke pain [19, 21, 37]; spontaneous discharge of nociceptors and other neurons involved in nociceptive processing at abnormally high frequencies [27, 37]; and exaggerated firing responses to repeated stimulation, known as wind-up [20, 35, 37]. Central sensitization may also involve an expansion of neuronal receptive fields [19–21, 29, 37, 38] and persistent post-stimulus neuronal firing [37]. Finally, a reduction in central inhibitory control may further contribute to heightened spinal excitability [35, 37].

Perception

There is no single region of the brain that is solely responsible for pain perception, in fact, pain involves a wide range of different cortical and subcortical structures. Figure 2.4 indicates some of the most commonly mentioned brain regions in connection to pain perception.

The thalamus is a major relay point for sensory information [39, 40]. Third-order neurons project from the thalamus to primary somatosensory cortex (SI) [20, 33, 41] in a somatotopically organized manner (meaning that stimuli from different parts of the body map to specific neural regions), and to secondary somatosensory cortex (SII) [41]. There are also projections from the thalamus to the insular cortex which are thought to be involved in dull or deep pain and the longer lasting emotional features of pain [30]. Projections to the prefrontal

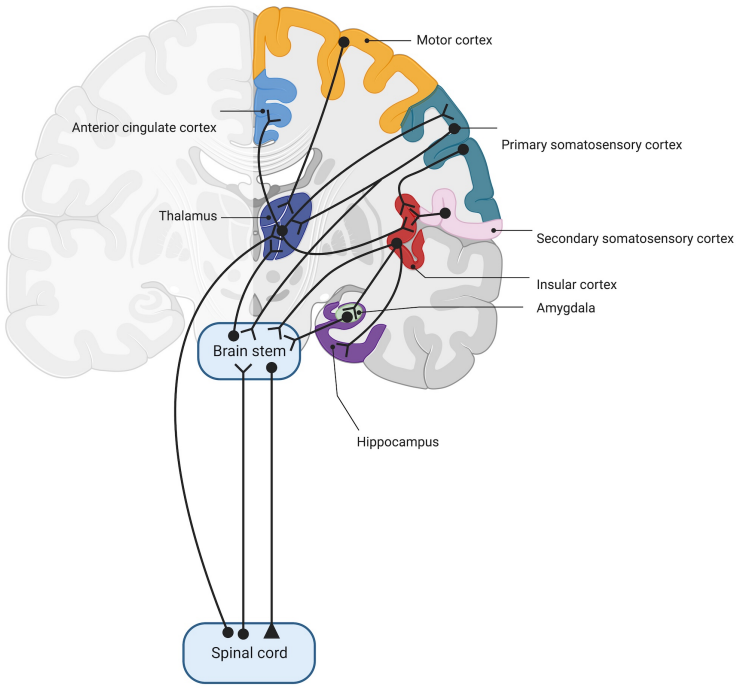

Figure 2.4: Pain perception involves many different cortical and subcortical brain regions. Some of the most prominently mentioned regions are the thalamus, the primary and secondary somatosensory cortices (SI and SII), the anterior cingulate cortex (ACC), the insula, the motor cortex, the limbic system including the amygdala and the hippocampus and several nuclei in the midbrain and brainstem such as the periaqueductal gray (PAG), the nucleus raphe magnus (NRM) and the parabrachial nuclei. Created with BioRender.com.

cortex (PFC) and the limbic system are thought to be related to the arousal mechanism of pain [33].

All cutaneous sensations (sensations of the skin), such as temperature, touch, and pain are equally relayed to SI [42]. Brain imaging studies indicate that SI activation correlates with intensity of pain sensation, but not pain unpleasantness [15, 34, 43, 44]. It has also been observed that SI plays a role in sensory-discriminative functions such as spatial discrimination and intensity encoding [15, 34, 44]. This observation is consistent with hypotheses that parietal cortex (the region in which SI is located) is essential for finer discrimination, localization, and determination of intensity [39, 40, 44]. Worthy of notice is evidence suggesting that SI is not essential for pain perception [25]. Findings supporting this idea are reports that electrical stimulation of somatosensory cortex can produce sensations of tingling, numbness or electricity, but rarely pain, and that lesions to these areas are not always sufficient to entirely alleviate pain [27, 44, 45].

SII may play a role in tactile object recognition and also recognition of the nature of noxious stimuli [44]. SII projects via insular cortex to limbic structures. These cortico-limbic structures are proposed to subserve tactile learning and memory.

The anterior cingulate cortex (ACC) is thought to be involved in unpleasantness and possibly also to attention to pain to some extent. Lesions of ACC have been shown to reduce emotional value and motivation to avoid painful stimuli [15, 44]. Activity in ACC has been noted in response to pain in imaging studies [43, 46–48], and increased activity has been noted in chronic pain [15, 49]. Brain imaging has also shown activity in ACC in response to witnessing others experience pain [48]. ACC may be involved in modulating affective aspects of sensory perception via pain expectation and in mediating attention and anticipation of noxious stimuli. Hypnotic suggestion has been reported to selectively alter the unpleasantness of pain along with reduced pain-evoked activity in ACC [15]. Distracting subjects during noxious stimulation has also been noted to alter ACC activation [31, 47].

The insular cortex is proposed to mediate interoceptive information, i.e., information on the physiological condition of the body across a variety of domains as they relate to motivation, including sensations of pain and temperature, and how different threats affect homeostasis [44, 47, 50]. Brain-imaging studies have shown activity in the insular cortex in response to experiencing

pain, as well as witnessing others experiencing pain [43, 47, 48]. Lesions to the insular cortex have shown apparent reduction in pain affect and appropriate reactions to painful and threatening visual or auditory stimuli, but not pain threshold [44].

The limbic system mediates aversive drive and thus influences motivational components and determines purposeful behavior [19]. The amygdala in one region of the limbic system which receives both noxious and innocuous signals and is an important hub for processing the threatening aspect of pain. Projections from the amygdala are widespread to several brain areas, such as hypothalamus and various regions of the brainstem [51]. The connections to these brain regions are thought to contribute to activation of species specific defense responses, i.e., hormonal, cardiovascular and behavioral reactions. Research suggests inhibition of the amygdala may help reduce experience of, and emotional responses to, chronic pain [51], whereas stimulation of limbic structures can induce behavior which is otherwise associated with pain [52].

Modulation

The body has several mechanisms for modulating pain signals at different levels along the nervous system. Modulation can result in both inhibition and facilitation of transmission and processing of pain. Descending modulation is exerted by three main neurochemical systems: noradrenergic, serotonergic, and opioidergic [53]. Figure 2.5 shows some of the supraspinal regions most prominently involved in pain modulation and their associated neurochemicals and afferent and efferent projections.

The periaqueductal gray (PAG) in the brainstem plays an important role in descending modulation of pain [19, 33, 54]. PAG receives input from cerebral cortex, limbic structures, and the spinal cord [16, 31, 33]. Electrical stimulation of PAG inhibits response to wide spectrum of noxious stimuli [28, 49, 52, 54–57]. Stimulation of PAG also induces a behavioral state suggestive of fear, indicating that PAG likely is involved in complex behavioral responses to stressful or life-threatening situations [28, 58].

The reticular formation is another important region of the brainstem as it relates to nociceptive transmission, arousal and consciousness [13, 39, 41, 59, 60]. Perhaps the most prominent reticular formation nuclei in pain modulation are in the rostroventral medulla (RVM), including nucleus gigantocellu-

laris, nucleus paragigantocellularis, and nucleus raphe magnus (NRM) [25, 28, 32, 41, 49]. The NRM has diffuse projections to the dorsal horn and is the major source of serotonin in the spinal cord [31, 61], and the catecholamine cell groups A5, A6 (the locus ceruleus) and A7, are the primary sources of noradrenergic projections to the spinal cord [28].

Opioid receptors are present on peripheral nociceptive fibers and when endogenous or exogenous opioids bind to these receptors the neurons become hyperpolarized and signal transmission becomes inhibited [22, 62, 63]. However, opioids are less effective once sensitization has been elicited [64]. Thus, preemptive analgesia is often better at reducing pain. Furthermore, damage of a peripheral nerves can lead to loss of opioid receptors, thereby reducing the responsiveness to opioids [65]. There are several additional factors that can impact opioid responsiveness, such as accumulation of opioid antagonists and changes in non-opioid peptides.

Endogenous opioids act also on opioid receptors in the dorsal horn, where inhibitory interneurons synapse onto primary afferent terminals and inhibit incoming nociceptive signals [17, 35, 63]. In addition, descending pathways from the brainstem release serotonin and norepinephrine into the dorsal horn, where these neurotransmitters activate inhibitory interneurons and suppress pain transmission at the spinal level [35, 56, 66]. These inhibitory mechanisms play an important role in endogenous analgesia and are thought to underlie, at least in part, the effectiveness of certain antidepressant medications in treating chronic and neuropathic pain conditions [53, 56].

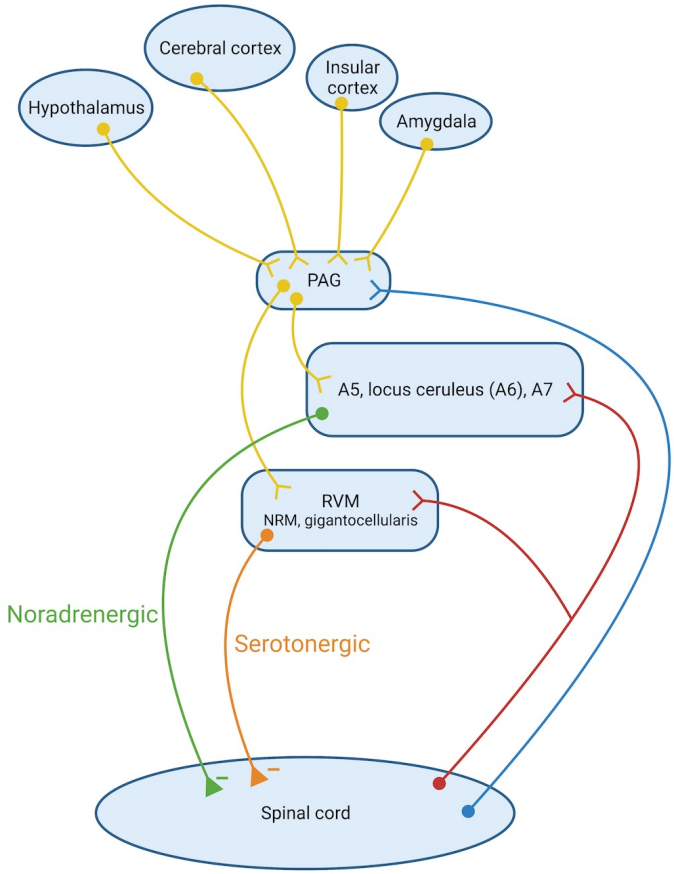

Figure 2.5: Pain modulation involves several cortical and subcortical regions. Certain regions are more strongly associated with certain neurochemicals. RVM of the reticular formation has serotonergic projections to the spinal cord, whilst cell groups A5, A6 (locus ceruleus) and A7 have noradrenergic projections. These regions receive input from other supraspinal regions as well as direct ascending input from the spinal cord. Created with BioRender.com.

2.2 Beyond the neurophysiology

Recall the first words of the IASP definition of pain: "An unpleasant sensory and emotional experience..." (see the start of this chapter for the full definition). While emphasis often is placed on the sensory aspects of pain, the inclusion of words like *unpleasant* and *emotion* in the definition clearly indicates that pain is a complex and multidimensional experience. Or, as Stewart Wolf expressed in a 1967 paper [67]:

"... pain is no more a simple perception of a sensory experience than insult is a simple perception of a sound."

The conscious experience of pain is not an objective reflection of noxious stimuli, but a complex subjective experience influenced by factors such as other sensory stimuli, context, attention, and broader cognitive processes. As a result, identical noxious stimuli can produce vastly different levels of perceived pain depending on the context in which they are occur. An extreme illustration is the well-documented phenomenon of soldiers who remain largely unfazed by severe injuries in combat. In such situations, physiological and psychological responses to threat, stress, and shock can suppress what would normally be overwhelming pain [68]. While this example sits at one end of the spectrum, similar but subtler, effects occur in everyday life. One might fail to notice the sting of a papercut until seeing the blood, or a child's scraped knee may seem to feel better immediately after a band-aid is applied. In both cases, expectations shape the perceived intensity of pain – a phenomenon often referred to as the *placebo effect*. Its "evil twin", the *nocebo effect*, captures the opposite: negative expectations that exacerbate the experience of pain.

Expectations are only one of many cognitive influences on pain. Mood and emotion can also shape pain perception in nuanced ways [69]. A stubbed toe is likely to feel far more bothersome on a cold, rainy Monday morning at the start of a stressful workday than on a Friday afternoon while preparing for an enjoyable evening with friends. Speaking of friends, social context can also have a profound influence on pain: the presence, reactions, or support of others can meaningfully alter how pain is experienced. In 1977 Dr. George Engel condensed these phenomena into the biopsychosocial model of pain, proposing that pain doesn't solely stem from biological factors but is also influenced by psychological and social elements [70]. This framework has been

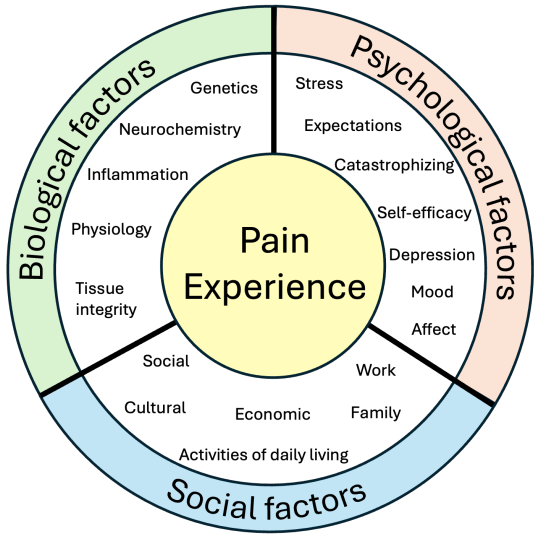

Figure 2.6: Illustration of how various biological, psychological and social factors may contribute to the pain experience, collectively referred to as the biopsychosocial model of pain. Figure adapted from [71].

widely influential in the following decades, shaping many aspects surrounding pain – from assessment and management, to education and research on pain. Figure 2.6 illustrates some of the different factors suggested to influence pain perception within the biopsychosocial model of pain.

Although the examples above pertain primarily to acute pain, a growing body of evidence suggests that similar factors could contribute to the development and maintenance of chronic pain conditions [72–75]. Expectations may become self-reinforcing, resulting in pain persisting even when the tissue damage has healed. Such expectation effects might be particularly relevant in neuropathic pain where sensory input is unreliable and the brain relies heavily on prediction. Furthermore, cognitive patterns like pain catastrophizing and

fear-avoidance are linked to worse outcomes [72] and chronic pain commonly co-occurs with psychological conditions such as depression and post-traumatic stress disorder [51, 76, 77], although the exact linking mechanism between these conditions remains unclear. Finally, and on a more encouraging note, addressing these factors through targeted interventions has shown promise in improving treatment outcomes for chronic pain [78]. These results provide evidence for likely role of negative affective processes in pathological pain conditions, while also offering hope for more effective treatment opportunities.

2.3 Measuring, assessing and quantifying pain

The study of pain necessitates reliable methods for measuring, assessing, and quantifying an individual's pain experience. One of the primary challenges in measuring pain is its inherently subjective nature. As discussed in previous sections, pain is a highly complex and multifaceted experience, influenced by a wide range of psychological, social, and physiological factors. In an era characterized by advanced biosensors, big data, and high-tech solutions, one might assume that this challenge has been largely overcome. Yet, the most widely used tools for pain assessment remain the Visual Analogue Scale (VAS), the Numeric Rating Scale (NRS) and Likert-scales [79, 80] – all of which rely on self-reported scores along a one-dimensional scale (e.g., 0-10). Unlike physiological parameters such as heart rate or physical activity, which can be passively tracked using mobile devices (e.g., smartphones and smartwatches), pain cannot be directly measured by any sensor. Instead, assessing pain requires individuals to actively report their experience, which often means collapsing the aforementioned complex and multifaceted experience into a single number. This approach not only oversimplifies a rich and dynamic experience, but also makes it difficult for patients to express their pain accurately. Important contextual details are lost, and the subjective, variable nature of pain can introduce significant variability in reported ratings.

Some assessment tools attempt to address these limitation by evaluating multiple dimensions of pain, such as the intensity of different pain sensations, the distinction between pain intensity and unpleasantness, or even the impact of pain on daily activities and quality of life [79]. While these multidimensional assessments provide a more comprehensive understanding of pain, they also yield high-dimensional data that can be challenging to interpret. Addition-

ally, more detailed pain assessments can be burdensome for respondents [81]. Given that chronic pain is often associated with impaired cognitive function and attention [82, 83], this response burden poses a significant challenge in longitudinal pain studies, where participants are required to provide repeated pain ratings over time [84]. Additionally, the process of rating pain itself may alter the perception of pain, further complicating its assessment [85, 86].

Beyond enabling individuals to more accurately express and communicate their pain, multidimensional assessment tools are crucial for identifying potential pain etiologies. Different causes of pain tend to manifest with distinct characteristics, and capturing these nuances can guide diagnosis and treatment. For instance, specific screening questionnaires have been developed to identify neuropathic pain [87], which is clinically important because neuropathic pain often requires different interventions than other pain types.

Some pain experiences are not well captured by standard questionnaires, highlighting the need for alternative or complementary tools for pain assessment. For pain conditions with complex bodily manifestations, tools such as pain drawings have proven valuable for describing and assessing the location, spatial distribution, and variability of pain sensations [88–92]. In more recent time, these approaches have been extended to three-dimensional representations and animations to better capture distorted perceptions of limb position or telescoping, which can occur in conditions such as phantom limb pain [93]. Figure 2.7 shows examples of some different pain measures, from simple rating scales to pain drawings and advanced computer animations. Free-text descriptions can also provide patients with a way to convey their pain experience in a more detailed and nuanced manner, free from the constraints imposed by predefined questionnaire descriptors and scales. However, both pain drawings and free-form descriptions share a common limitation in contexts such as research and longitudinal monitoring: they are difficult to quantify. Mathematical modeling offers a potential avenue for overcoming this challenge by enabling systematic and reproducible quantification of subjective pain reports – which leads us directly to the focus of the next chapter.

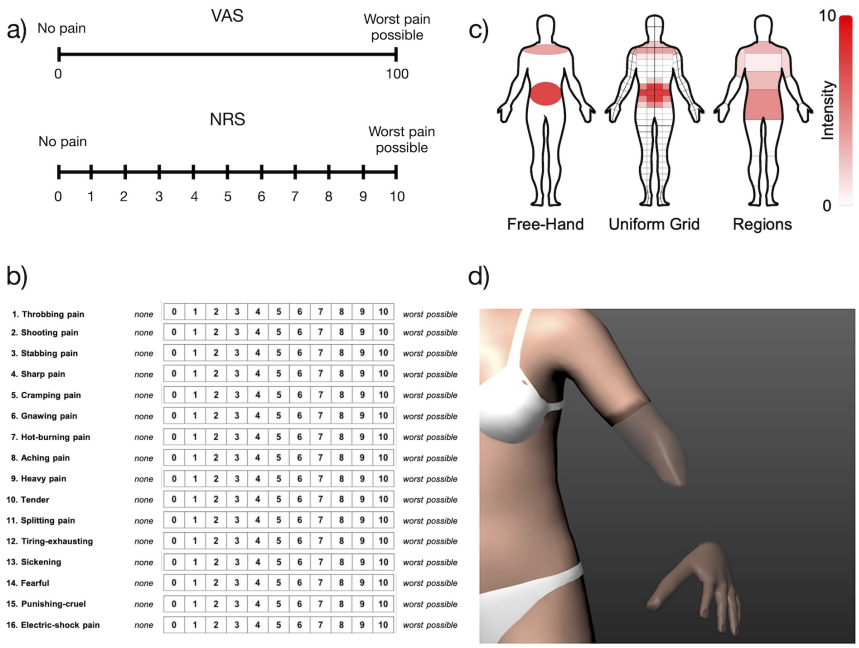

Figure 2.7: Examples of different tools used to measure pain. a) Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS). b) Excerpt from the McGill Short Form Pain Questionnaires version 2 (SF-MPQ-2) [94]. c) Different types of pain drawings, image reproduced from Paper D. d) C.A.L.A, a novel tool for illustrating and documenting phantom limb sensations [93].

CHAPTER 3

Introduction to mathematical models

One possible approach for gaining a better understanding of complex phenomena is through mathematical models. They can provide insight into how a system works and how different components of the system interact. Mathematical models can also enable us to make predictions about scenarios we have not yet encountered and foresee possible consequences of events within the system. For example, even something as simple as the familiar formula speed = distance traveled / time elapsed ($v = d/t$) is a mathematical model: it captures how three quantities relate and allows us to predict how fast we have traveled or how long time a journey of a certain distance will take. Somewhat more elaborate models can be used to describe how the amount of money in a bank account with interest rate, r, accumulates over time ($P(t) = P_0 e^{rt}$, for initial amount of money P_0 at time $t = 0$), helping people plan their finances. And at a much larger scale, highly complex meteorological models combine physics, chemistry, and statistical methods to generate the weather forecasts we rely on every day.

Mathematical models are particularly valuable in areas where direct empirical observations are difficult or limited by ethical concerns. Pain research is one such area. Experimental methods and clinical interventions must be de-

signed with great care, as untested procedures or invasive measurements may inadvertently increase pain or suffering. Attempts to investigate the mechanisms of pain sometimes require inducing pain in human or animal participants, which naturally raises ethical concerns. These constraints often limit the amount and type of data that can be collected. Although mathematical models cannot replace experimental research in uncovering the mechanisms of pain, they can complement it by generating new hypotheses, helping to interpret sparse or noisy data, and providing insights that guide the design of future studies. Thoughtful use of mathematical models may also reduce the number of experiments needed in both humans and animals.

Computational neuroscience – a field dedicated to using mathematical and computational tools to study brain function – illustrates how powerful such approaches can be. For an accessible introduction to how mathematics, physics, and engineering have shaped our understanding of the brain, readers are referred to *Models of the Mind* by Grace Lindsay [95]. Today, mathematical models are used to investigate neural processes at every scale, from the electrical activity of single neurons to theories that attempt to unify perception, action, and cognition. The remainder of this chapter first provides a brief overview of different types of mathematical models and then describes how they can and have been used to gain a better understanding of pain.

3.1 Different types of mathematical models

Mathematical modeling is a vast topic, too large to cover in full in this thesis. For an accessible overview of how models in science improve our understanding of the world, readers are referred to the book *Scientific Models — Red Atoms, White Lies and Black Boxes in a Yellow Book* [2].

There are many different ways to sort mathematical models into different categories, for example based on the type of mathematics they employ or the kinds of questions they are intended to address. For the purpose of this thesis, I will distinguish between two broad categories of mathematical models: *mechanistic models*, which attempt to describe how observed phenomena could be generated by underlying processes of the system, and *empirical models*, which quantify data without explicitly modeling the causal mechanisms that generate them. The two model categories and the interaction between them is illustrated in Figure 3.1. Note that the distinction between mechanistic and

empirical models used here reflects one possible way of categorizing mathematical models, rather than a universally accepted taxonomy. This framework is introduced as a practical guide for the reader, intended to highlight the different contributions of the work included in this thesis rather than to impose a strict or exhaustive classification. Other distinctions and terminologies are used elsewhere and vary depending on disciplinary context and research focus.

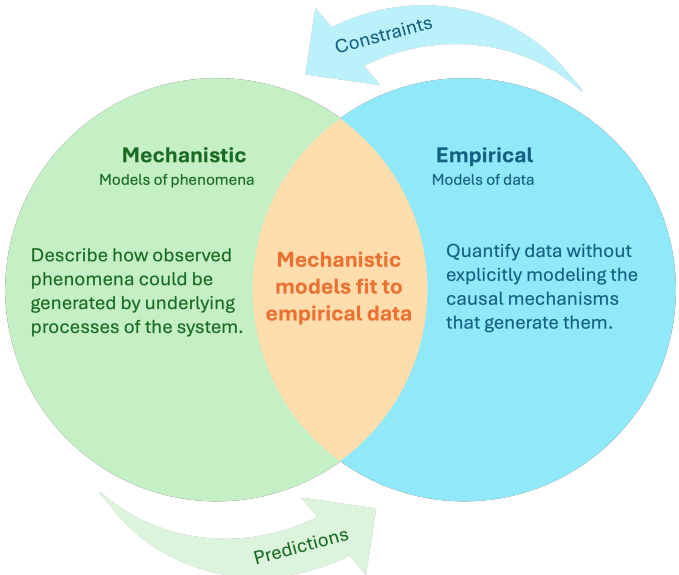

Figure 3.1: Mathematical models can broadly be sorted into two categories with complementary roles: *mechanistic models* explaining how phenomena may arise, and *empirical models* quantifying the patterns they produce. Models from the two categories can interact and influence each other through constraints and predictions, and some models may incorporate elements from both categories.

For many readers – at least this has been my own experience – mechanistic models may be the type of models that are first associated with mathematical modeling. This category includes historically prominent models describing a wide range of phenomena, from Newton's laws of motion to Black-Scholes Model of financial markets. By contrast, empirical models include tools such as rating scales, regression models, and other statistical or geometric representations of data. These models are widely used across scientific disciplines to quantify empirical observations and evaluate experimental hypotheses, yet they may go relatively unnoticed as mathematical models in their own right.

Together, these two categories highlight complementary roles of mathematical modeling: explaining how phenomena may arise and characterizing the empirical patterns they produce. Importantly, mechanistic and empirical models do not exist in isolation but, can interact and influence each other. Mechanistic models can generate predictions about observable quantities, which can then be evaluated using empirical models applied to empirical data. Conversely, empirical models can provide constraints on mechanistic theories by characterizing patterns or statistical relationships that the mechanistic model must account for.

In the following sections I will dive deeper into the possible use cases of models within these categories. However, in practice, the boundary between the categories is not rigid. There exist models that incorporate elements of both mechanistic and empirical approaches, for example by embedding causal assumptions within statistical inference frameworks or by fitting mechanistic models directly to empirical data. Such hybrid models serve to bridge the two categories, illustrating how explanation and empirical evaluation are often tightly coupled in the process of scientific modeling.

Mechanistic models

Mechanistic models aim to answer questions like "Why does the system behave the way it does?", "How would the system respond if we change component X?" and "What mechanisms are sufficient to produce phenomenon Y?". These models necessarily make assumptions about the underlying components and their interactions, which are often formalized mathematically by equations describing how different parts of the system interact (e.g., with *network models* or *stochastic processes*) and how things change over time (*differential equations*). Examples of mechanistic models are Newton's laws describing how

forces cause motion, models of infectious disease spread and predator-prey models of population growth.

Such equation-based models allow us to use tools from mathematical analysis to study and probe various aspects of the studied system, such as identification of steady states, maximal and minimal values, or state-transitions. Yet, some systems may be too complex to describe in terms of systems of equations. In such scenarios simulations of *agent-based models* can be of use. In agent-based models a simulated agent is assigned properties and rules according to which it acts under certain conditions in a simulated environment. Simulations can then be used to investigate how the agent's state and behavior change for different parameter choices. These types of models are used in a variety of applications, ranging from the field of economics to describe market behavior to tumor growth in biomedical contexts.

Importantly, mechanistic models are not limited to modeling physical systems or – using terminology that may be more familiar to readers in computational neuroscience – to the *implementation* level in Marr's levels of analysis[1]. Mechanistic accounts can also be formulated at the *algorithmic* and *computational* levels. In these contexts, underlying mechanisms are not forces, flows, or reactions, but internal information-processing steps such as perception, memory updating, decision rules, or prediction. One influential framework is the Bayesian brain framework, which treats perception, decision-making, and learning as forms of probabilistic reasoning. In Bayesian models, the brain is assumed to combine prior expectations with incoming sensory evidence to form updated beliefs about the world. This framework provides a mechanistic account in the sense that it proposes how the brain computes perceptual estimates, resolves uncertainty, or chooses between competing interpretations, even if the mechanisms are algorithmic rather than biophysical. The Bayesian brain framework has successfully been applied to describe a range of perceptual and sensorimotor tasks [97–101]. By making the hypothesized computational steps explicit, Bayesian models allow cognitive theories

[1]David Marr proposed that information-processing systems can be understood at three complementary levels of analysis: the computational level, which specifies the problem being solved and the goal of the computation; the algorithmic level, which describes the representations and procedures used to solve the problem; and the implementation level, which concerns the physical realization of those procedures in a biological or physical substrate [96]. This framework is widely used in computational neuroscience and related fields as a way to distinguish complementary levels of explanation.

to be tested, compared, and refined in much the same way that mechanistic models are used in the physical sciences.

While mechanistic models can provide causal explanations and even forecasting of future outcomes, the model predictions generally must be interpreted with some caution as this type of model run the risk of relying on faulty assumptions or oversimplifying important details of the system they are intended to model.

Empirical models

Empirical models focus on what is observed rather than why it happens. These models come in many different forms with a wide variety of complexity. One of the simplest forms of empirical model involves mappings measurable quantities to numerical representations. One such example is temperature scales, which map observable effects of thermal energy onto numerical values, without describing the molecular mechanisms that underlie heat. Empirical models can also take more complex forms, involving equations describing the relation between two or more variables, such as dose–response curves showing how a drug's effect increases with dosage.

These models can also make use of tools from probability theory to understand variability, infer patterns, test hypotheses, or make predictions from data. They are often used to answer questions like "Is this effect real or just random noise?" and "What factors predict outcome X?" and are used in all domains of scientific research. For some questions, simple statistical comparisons like t-tests or correlations are sufficient to evaluate differences between groups or relationships between variables. However, often there are multiple factors that influence the variable of interest, calling for more advanced statistical models.

Statistical data models are an important subset of empirical models. At its core, this type of modeling begins with the assumption that any measurement varies across individual research subjects and situations in ways that can be described by a probability distribution. Choosing an appropriate distribution (for example, a normal distribution for continuous measures, or a binomial distribution for yes/no outcomes) is the first step in constructing a model. Next, researchers specify how different factors of interest – such as experimental conditions, participant characteristics, or time – are expected to influence the data. These assumptions are formalized in a mathematical model

that links predictors to the outcome, often through structures such as *linear models*, *generalized linear models*, or *mixed-effects models*. Once specified, the model is fitted to data to estimate how strongly each factor contributes to the observed variability. The fitted model can then be used to test hypotheses (e.g., whether two groups differ significantly), quantify uncertainty (through confidence intervals or credible intervals), and sometimes make predictions about new data. Throughout this process, assumptions about distributional shape, independence of observations, and linearity of effects play a central role and must be assessed to ensure that the conclusions drawn from the model are valid. In this way, statistical data modeling provides a systematic approach to translating noisy, high-dimensional measurements into interpretable scientific claims.

In recent years, a particular type of model has gained a lot of traction in the empirical space: machine learning models. These models can be trained to classify complex data based on relationships between patterns in the data and the target classes. While machine learning models often can achieve very high accuracy, they generally are "opaque boxes" giving little to no insight on the underlying mechanisms.

3.2 Mathematical models of pain

Using mathematical models to study pain is not an idea that is unique to this thesis. In 2021, a systematic review by Lang et al., identified 31 articles using mathematical approaches to study various aspects of pain [102], the earliest dating back to 1981 [103]. More recently, I had the good fortune of attending the first international conference on computational pain neuroscience at Aarhus University, a meeting that gathered researchers with the common interest of using mathematics to better understand pain. Despite being a well-established approach, many open questions remain in pain research that mathematical models may help to address.

Following the categorization outlined in the previous section, mathematical models of pain can be sorted into the following groups: *mechanistic models* investigating hypothetical causal processes of pain, and *empirical models* formalizing how aspects of pain can be quantified without necessarily explaining the underlying processes.

Mechanistic models of pain

Mechanistic models of pain can take on many different forms, depending on the specific pain mechanism they aim at modeling. Some models aim to emulate pain neurophysiology, or the "hardware" involved in pain processing. Others take an alternative approach to modeling pain processing by considering a higher level of abstraction in the form of cognitive computational models. They describe pain as a result of information processing, or the "software", and attempt to capture how expectations, attention, emotions, and memory shape what we feel. Below, I give some examples of modeling approaches that have been applied to investigate the mechanistic underpinnings of pain. Figure 3.2 lists the mechanistic pain models that I have come across during the work in this thesis.

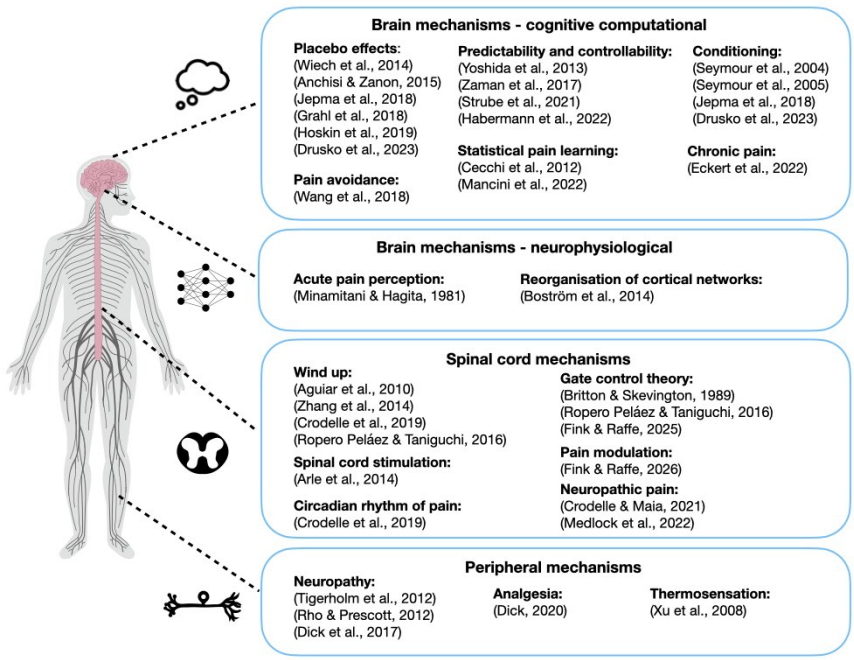

Figure 3.2: Summary of the mechanistic models I have come across during the work with this thesis, sorted according to the pain mechanisms they target. References are listed in Table 6.5 at the end of the bibliography.

Biophysical neuron models are detailed models of individual neurons, describing the physical and chemical processes inside and around the cell. These models are particularly well suited to study how electrical signals are generated and how they change over time, allowing researchers to investigate nociceptive transduction and transmission under different conditions. For example, such models have been used to model peripheral afferent neurons [104, 105], wind-up in spinal cord circuits [106, 107], effects of spinal cord stimulation [108] and possible changes in spinal cord circuits in chronic pain [109].

Neuronal population (rate-based) models track how the activity of groups of neurons evolve over time, often using concepts from dynamical systems theory. Compared to simulating individual neurons, these models make it easier to study large-scale interactions of neuronal populations and identification of the patterns the system can fall into, such as steady state activity, bursts, or oscillations. Example applications of this modeling approach are models of spinal cord circuits involved in pain processing [110–112].

Artificial neural networks attempt to mimic networks of interconnected neurons using computer simulations. By incorporating plasticity rules, describing how connections strengthen or weaken based on the activity of individuals neurons, these models allow researchers to explore how connections in the brain might change with learning, injury, or persistent pain. Such models have been used to investigate how somatosensory cortex reorganizes following amputation [113, 114].

Bayesian inference is a framework that has garnered significant attention in the field of pain modeling in recent years [72, 73, 115–117] as it offers a compelling account for how expectations and sensory input are combined in pain perception. The framework is described in more detail in Section 3.1. For pain, Bayesian models have been used to describe how expectations influence pain perception in several different situations, such as experimentally induced placebo hypoalgesia and nocebo hyperalgesia [75, 118], learning of statistical pain patterns [119] and even in chronic pain [74].

Active inference models extend Bayesian inference by combining perception and action. This framework describes how the brain not only interprets sensory signals but also acts to reduce uncertainty or undesirable outcomes. One of the key challenges in modeling the action-perception loop is simultaneously optimizing exploration, exploitation, perception and learning. The active inference framework proposes a simple yet elegant solution to this chal-

lenge: that all living organisms follow the single objective of minimizing the surprise of their sensory observations [120]. Importantly, in the active inference framework surprise has a technical meaning – it measures how much an agent's current sensory observations differ from its preferred sensory observations. This formulation allows outcomes of actions to be quantified in the same units as perception, enabling the optimization of action, perception and learning to all be cast as the minimization of a single quantity.

While active inference has been proposed as a promising framework for describing both how an agent might act when faced with pain and how such actions, in turn, shape pain perception [73, 116, 121], I have encountered only a single concrete implementation of this approach. That model was applied not to pain directly, but to visual foraging for threat assessment and to patient–clinician interactions [122].

In addition to these Bayesian frameworks, *reinforcement learning* has been suggested as a computational theory of learning and adaptive behavior in pain [117, 123]. Reinforcement learning encompasses many different models, with the common goal of learning optimal behavior to maximize some reward (or minimize loss). Such models have been used to describe how predictions of pain are learned in conditioning paradigms [75, 124, 125] and pain-avoidance behavior [126].

Empirical models of pain

In pain research, empirical models are used to describe and quantify characteristics of pain, and for characterizing relationships between variables without explicitly modeling the causal mechanisms that generate them. Some of the simplest – but most widely used – empirical models in pain research are *pain rating scales*, described in 2.3. Rating scales such as the visual analogue scale (VAS) and the numeric rating scale (NRS) are simple models that treat pain intensity as a measurable quantity. While these models are useful for tracking changes, they do not explain why pain fluctuates, and are therefore not mechanistic models. *Composite questionnaire-based scores* are slightly more complex models that combine responses to multiple questions, to quantify different aspects of pain – such as intensity, unpleasantness, or emotional consequences – into numerical scores. Some questionnaire-based scores can be used to identify the etiology of the subjects' pain, such as PainDETECT [127], ID Pain [128] and DN4 [129].

Psychophysical models describe how physical events in the body or environment are transformed into subjective sensations. In the context of pain research, these models help quantify the relationship between a stimulus (such as heat, pressure, or electrical stimulation) and the pain experience it evokes. They are especially valuable because they bridge the gap between objective measurements and subjective reports. In the study of pain, psychophysics are used to measure various characteristics of pain such as threshold, tolerance, modulation, sensitization and habituation [130]. Quantitative sensory testing encompasses a battery of such psychophysical tests that can quantify responses to standardized stimuli and provide information about pain mechanisms. *Pain drawings* are another type of psychophysical model that can be used to describe the spatial spread and variation of pain sensations [88].

Just as in most scientific disciplines, statistical data modeling is an essential tool in pain research. As an example, let's consider the evaluation of a new pain intervention. At first glance, the problem may seem simple: measure pain before and after treatment, compute the difference, and conclude whether the intervention worked. However, this approach overlooks several alternative explanations for changes in pain such as spontaneous remission, natural fluctuations over time, or placebo effects arising simply from participating in a study.

To address these issues, researchers typically compare outcomes between two groups: an intervention group and a control group. The control group may receive no treatment (helping control for spontaneous remission and spontaneous fluctuations) or a sham version of the treatment (controlling for placebo effects by mimicking the intervention without its active component, such as giving a sugar pill instead of a drug). Pain can then be measured before and after treatment in both groups, and statistical tests – among the simplest forms of statistical data models – are used to determine whether the improvement in the intervention group is significantly greater than in the control group.

Even with this more rigorous design, additional factors may influence the results. For example, the intervention and control groups might differ in age, sex, baseline pain levels, or other characteristics. Such differences can sometimes be reduced through careful matching of participants, but matching is not always feasible due to constraints in the study population. In these cases, models such as linear regression provide a way to estimate how much each factor contributes to an outcome measure like pain relief, allowing researchers

to account for confounding variables.

Statistical data modeling also plays a central role in neuroimaging studies of pain, where researchers must interpret large, high-dimensional datasets [131]. As in the previous examples, linear models are useful for some types of questions, such as identifying brain regions whose activity correlates with pain intensity. Other research questions require more advanced techniques. For example, source-reconstruction models estimate which brain areas give rise to recorded neural signals, while network or graph-theoretic models allow researchers to examine whether patterns of connectivity between brain regions differ between individuals with and without chronic pain.

Machine-learning classifiers are another type of empirical models that can be trained to categorize pain states or patient groups based on complex patterns in data, such as questionnaire responses or sensory measurements. They can be useful for identifying subtypes of pain [132]. In recent years, natural language processing and large language models have seen exceptional development, opening up potential for new ways of assessing and quantifying pain from unstructured data such as free-form text and speech [133].

In sum, there are many different ways by which mathematical models can be employed to advance the understanding of pain. In the next chapter, we will first outline the state-of-the art of the main topic of this thesis – phantom limb pain – and then examine how mathematical models can be applied to move the frontier on the collective understanding of this intriguing pain condition.

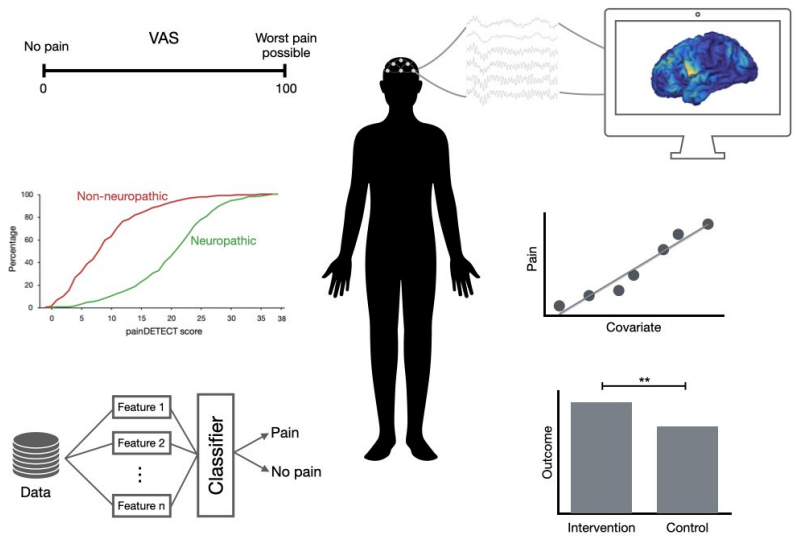

Figure 3.3: Examples of empirical models in pain research include pain rating scales, composite questionnaire scores, machine learning classifiers, source-reconstruction models of neural data, linear regressions and various statistical tests.

CHAPTER 4

Phantom limb pain

From the previous chapters it is clear that the pain experience is influenced by a wide range of neurophysiological, psychological, and social factors, and that pain can be subdivided into different categories depending on the specific cause and characteristics. In this chapter I will narrow in on the particular flavor from the multidimensional pain spectrum that is the main topic of this thesis: phantom limb pain.

4.1 Prevalence

According to a recent meta-analysis the prevalence of phantom limb pain is approximately 64% among individuals with limb amputations [4], with lifetime prevalence reported to be even higher [134]. In comparison, the transition rate to chronic pain for various types of injuries typically falls in the range of 10-30% [135–137], which suggests that the prevalence of phantom limb pain is relatively high compared to other forms of chronic pain.

While most literature focuses on phantom pain in limbs, phantom pain and sensations can also arise in non-limbs. Table 4.1 list the average reported prevalence of phantom pain in breasts, eyes, testes, rectum, and teeth, post

excision or removal, as identified by a systematic literature search. Overall, the reported prevalence of phantom pain seems to be lower in these non-limbs, than in limbs following limb amputations. More detailed reports on the prevalence of phantom pain and phantom sensations for specific body parts and information about the literature search can be found at [138].

Table 4.1: Summary of reported prevalence of phantom pain (PP) in non-limbs based on a systematic literature search [138].

Body part	Nr reports	Total n	% PP: mean (range)
Breast	32	2547	15 (0–53)
Eyes	10	617	24 (4–47)
Testes	3	448	23 (11–32)
Rectum	7	1073	26 (8–63)
Teeth	3	1162	8 (3–15)

4.2 Hypotheses, findings and misconceptions

There are several hypotheses for the possible underlying mechanism of phantom limb pain, some of which are illustrated in Figure 4.1. While some of these hypotheses are sprung out of experimental findings, others have limited empirical support. In fact, strong empirical evidence remains relatively rare in phantom limb pain research. Studies often suffer from limited statistical power due to small sample sizes, high heterogeneity within samples (e.g., relating to level, cause or time of amputation), and inconsistent methodologies [5]. These challenges are further compounded by the historical lack of validated assessment tools. Only recently has the short-form McGill Pain Questionnaire Version 2 – one of the most widely used instruments for assessing neuropathic pain – been validated for use in individuals with phantom limb pain [139]. Furthermore, findings have at times been misinterpreted or taken out of context, leading to potentially faulty conclusions. The following section outlines some of the most commonly cited hypotheses, findings and misconceptions relating to phantom limb pain.

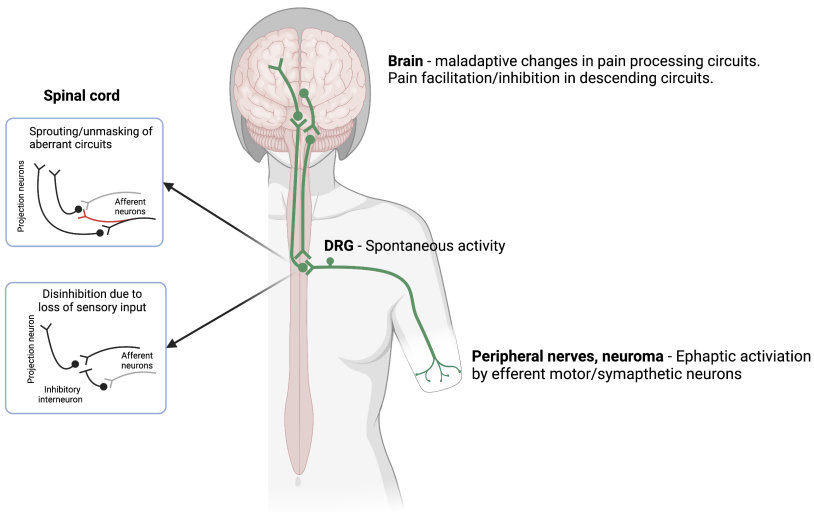

Figure 4.1: A visual overview of some factors that are likely to contribute to phantom limb pain. The relative contribution of each factor likely varies across individuals. Figure created with BioRender.com.

Peripheral Nerve Changes

Although nerves that used to innervate a limb are severed at amputation, this process does not necessarily mean that they are forever silent. As the site of amputation heals the severed nerves will innervate new tissue or form neuromas, which are disorganized bundles of nervous tissue. Stimulation of the tissue or neuroma can then elicit activity in the afferent nerves, resulting in sensations in the missing limb. It is also hypothesized that neuromas can become spontaneously active in absence of external stimulation. If this activity occurs in neurons that used to transmit nociceptive signals it could of course contribute to phantom limb pain. Tentative results indicate that surgical interventions that prevent neuroma formation can reduce post-amputation pain, including phantom limb pain to some extent [140–142]. However, if activity in peripheral neurons were the sole contributor to phantom limb pain, regional anesthesia of the residual limb would consistently relieve phantom pain. While it does provide relief in some cases, it is not universally effective [143–145]. Thus, activity in peripheral afferent nerves may be a contributing factor of phantom limb pain, but cannot account for all cases.

The cell bodies of peripheral afferent neurons are gathered in structures called the dorsal root ganglia (DRG), located just outside of the spinal cord entry point (see Section 2.1 for more details). While anesthesia of the residual limb has limited efficacy at reducing phantom limb pain, several studies have reported complete or near complete reduction of phantom limb pain when anesthesia is applied at the level of the DRG [144, 146]. Similarly, a recent study on an animal model of neuropathic pain following deafferentation showed that clustered firing of neurons in the DRG correlates with pain behavior [147]. In-vivo imaging revealed that sympathetic neurons had sprouted in the DRG following deafferentation, likely resulting in activation of afferent sensory neurons. Inhibition of ectopic activity in sympathetic nerves attenuated cluster firing and pain behavior [147]. While these studies have some limitations that affect their generalizability (lack of blinding, limited sample sizes, heterogeneity in study participants, and species differences in neurophysiology and pain processing), the results still suggest that spontaneous activity that arises in the DRG may contribute to phantom limb pain.

Cortical reorganization

Since the hallmark study by Flor *et al.,* in 1995, the concept of *cortical reorganization* has been closely linked to phantom limb pain in literature. The study encompassing 13 individuals with upper limb amputation (eight with phantom limb pain, five without) demonstrated using magnetoencephalography (MEG) that the cortical representation of the lower face/lips was shifted medially on the side contralateral to the amputation, as compared to the ipsilateral side [148]. Furthermore, the shift was larger in the individuals who had phantom limb pain. The study became the starting point of the cortical reorganization hypothesis of phantom limb pain – that the area in sensorimotor cortex that corresponds to the missing limb becomes "invaded" by neighbouring areas following amputation, resulting in pain in the missing limb. Several subsequent studies have shown similar results as reported the original -95 paper [143, 149–154], but evidence of a causal relationship to phantom limb pain is yet lacking. Analogously, some studies have reported that movement of the lips resulted in neural activation *in* the phantom hand region of somatosensory and motor cortex and that imagined or executed movement of the phantom hand resulted in neural activation in the lip area [150, 155], with association to the presence of phantom limb pain. Meanwhile, others have failed to show a relationship between phantom limb pain and shift of the lip/face representation [156–158], however the inconsistent methodology across studies makes it difficult to directly compare results.

Also within studies that have a similar results, there are methodological discrepancies. Studies differ regarding the modality of stimulation (touch [143, 148, 149, 151, 152] vs. imagined, observed or executed movements [150, 153, 154]), neuroimaging techniques (MEG [148, 151], electroencephalography (EEG) [143, 149, 152], fMRI [150, 153–155]), and even how the level of phantom limb pain is evaluated.

Most studies of cortical reorganization have focused on upper limb amputations, and in particular shift of the face-representation. If there is a causal relationship between cortical reorganization and phantom limb pain, it seems reasonable that similar shifts should occur also for other neighboring cortical areas. Based on the somatotopic mapping in somatosensory and motor cortex, a lateral shift of the residual limb in individuals experiencing phantom limb pain following upper limb amputation could be expected. To my knowledge, only one study has demonstrated such a relationship [154]. Another study did

observe a shift of the residual limb representation, but found no correlation with phantom limb pain intensity [159], and a third study found a shift in the opposite direction [149]. Furthermore, under this hypothesis similar reorganization would be expected to occur following lower limb amputation, yet there are only a few studies investigating this phenomenon. One study states that they "detect" reorganization of the large toe (the paper says "thumb" but I suspect that is an error of translation) representation in lower limb amputees, but do not describe how the reorganization is defined or quantified [160]. Another study found a lateral shift of the *intact* limb following lower limb amputation, but this shift did not correlate with phantom limb pain intensity [161].

At this point it is fairly well established that reorganization of sensory and motor cortex occurs following amputation (such findings were demonstrated in non-human primates over 40 years ago [162]). However, there is a lack of evidence for a causal role of cortical reorganization on phantom limb pain. Further evidence speaking against this theory is the fact that stimulation of somatosensory or motor cortex typically do not elicit pain [45]. Furthermore, studies of acute pain have found similar reorganization [163], as have studies where parts of the body have been anesthetized [164].

Preservation of cortical representation

Following the wave of cortical reorganization-findings came a string of studies showing a relationship between phantom limb pain and *preservation* of the cortical representation of the missing limb during phantom movement. The first study to show this relationship was conducted by Tamar Makin in 2013 [156]. Makin's group subsequently followed up with two additional studies with similar results [158, 165], but others have failed to show the same relationship [150, 166, 167]. Just as in the case of cortical reorganization, the discrepancy in results likely comes down to methodological differences. Two factors that likely contribute are differing mode of stimulation (phantom movement [156, 158, 165] vs. imagined, mirrored or observed movements [166, 167]) and how phantom limb pain is measured. All of the studies showing a positive correlation use a unique measure of phantom limb pain, so called "pain magnitude". This measure is intended to capture the chronicity of the pain by dividing the pain intensity (0: 'no pain' – 10: 'worst pain imaginable') by frequency (1 – 'all the time', 2 – 'daily', 3 – 'weekly', 4 – 'several times

per month' and 5 – 'once or less per month'). However, dividing two *ordinal* variables is mathematically ill defined. Since the distance between two values on each of the ordinal scales is not known, and might vary on different parts of the scale (e.g., is the difference between 'daily' and 'weekly' the same as the difference between 'weekly' and 'monthly'?), performing mathematical operations with this type of variable has poorly defined results. Thus, any statistical calculations performed on this measure of pain are at risk of leading to faulty conclusions. Therefore, it is yet uncertain if and how phantom limb pain relates to activation strength in sensorimotor cortex during phantom movements.

A recent first-of-its-kind longitudinal study followed subjects before and after planned amputations [168]. This study observed stable cortical representations of both hand and lips in primary sensorimotor regions following upper limb amputation, with no particular associations to phantom limb pain. While this study is uniquely positioned to investigate possible changes in cortical representations following amputation, it does have a few limitations. First, there are only three subjects in the group that is followed before and after amputation. Second, all of these subjects had some level of pain and disability of the limb prior to amputation, possibly influencing the results.

While *cortical reorganization* and *preservation of cortical representations* initially were pitted against each other as two mutually exclusive mechanisms of phantom limb pain, it has later been recognized that both phenomena can occur simultaneously [164, 169]. Taken together, there is little doubt that some form of reorganization may occur in sensorimotor regions of cortex following amputation, without complete erasure of the phantom representation. What still remains unclear is if and how these findings relate to phantom limb pain.

Sensorimotor incongruence

Sensorimotor incongruence refers to the mismatch between visual and proprioceptive feedback resulting from motor intention that occurs following amputation. This concept was first proposed by Harris in the late 90s [170]. The idea arose following results of the possible therapeutic effect of mirror therapy on phantom limb pain [171] and suggests that phantom limb pain is analogous to the nausea that arises when visual information is incongruent with vestibular and proprioceptive feedback (i.e., motion sickness). Harris further suggested that providing visual feedback that is congruent with motor intentions, as

in mirror therapy, thus could alleviate the pain. A study by McCabe *et al.*, is often cited as evidence that pain can be elicited from incongruent movement and visual feedback [172], but closer inspection of the results indicate otherwise. While some participants did experience pain during incongruent movement, the pain was never described as exceeding 2 out of 10 on verbal rating scale or distinguished from "discomfort", and more importantly pain was reported also in the case of congruent movement and visual feedback (6 of 40 participants reported "pain or discomfort" for incongruent movement, the corresponding number for congruent movement was 5 out of 40). Additionally, it is not possible to exclude that this pain may have arisen from muscle fatigue or any other cause.

While many case studies report positive outcomes of mirror therapy, trials have failed to show strong evidence of clinically meaningful reduction in pain [173]. Furthermore, this hypothesis seemingly predicts that better ability to move the phantom limb would result in more incongruence and ultimately more phantom limb pain. However, there is at least tentative evidence of the opposite, that the ability to move the phantom is associated with lower phantom limb pain [154, 165, 174], and leveraging phantom movements has shown promising results for relieving phantom limb pain [175].

In more recent time, sensorimotor incongruence has been re-framed in the context of predictive coding. In this framework, phantom limb pain is suggested to arise as a consequence of mismatches between interoceptive predictions and sensory input [176]. Similar ideas have been proposed for pain processing in general [73, 115].

Other hypotheses

The hypotheses listed above are the ones that have gained the most traction in academic literature in recent years. I will also briefly summarize some of the other ideas I have come across during the past years immersed in the study of phantom limb pain:

Pain memory. One idea is that phantom limb pain is a re-experiencing of pre-amputation pain in the form of pain memory. While prolonged pre-amputation has been reported as a risk factor for developing phantom limb pain [4], it is not a necessary requirement. phantom limb pain can arise even in absence of pre-amputation pain.

Spinal cord disinhibition and hyperexcitability. Relatively little emphasis has been placed on spinal cord circuits' possible contribution to phantom limb pain. However, there are some ideas on how mechanisms in the spinal cord may contribute to phantom limb pain. It has been suggested that disinhibition at the spinal cord level, either by disrupted descending modulation or loss of peripheral afferent input, could be a contributing factor in some neuropathic pain conditions . Similarly, structural and functional changes in the spinal cord circuits may lead to hyperexcitability in response to input that normally would not generate pain [177].

Stochastic entanglement. This hypothesis proposes that the stochastic activity following an amputation could result in the pain system becoming pathologically "entangled" with other networks in the brain, such as the sensorimotor system [178]. As a consequence of this entanglement, the pain system may become sporadically activated by activity in networks that are otherwise unrelated to pain. However, the assumptions underlying this hypothesis are not specified in sufficient detail, and the notion of "entanglement" remains conceptually broad, making it difficult to derive concrete, empirically testable predictions.

Electromagnetic force fields and quantum tunneling. Suggestions have been made that phantom limb pain may be triggered by "environmental electromagnetic fields" [179] or by quantum tunneling of potassium ions through cell membranes [180]. Empirical evidence supporting the existence of interactions of the environmental force fields and the human nervous system, or a meaningful effect of quantum phenomena such as tunneling, is lacking.

4.3 Mathematical models of phantom limb pain

Just as in most other fields of research, mathematical models play an important role in the study of phantom limb. Empirical models such as statistical data models are used in a wide range of settings, such as quantifying differences between study cohorts or determining the efficacy of some treatment across time. In neuroimaging studies of phantom limb pain, statistical data modeling techniques such as general linear models, functional connectivity analysis,

and network-based approaches have been used to relate neural activity to pain measures, see the previous section for references to such studies.

Rating scales and composite questionnaire scores are another type of empirical model that are commonly used in pain research to attempt to quantify the pain experience into numerical representations. These tools attempt to quantify the pain experience by mapping subjective reports onto numerical scales, typically reflecting overall pain intensity or weighted combinations of different pain characteristics. For phantom limb pain, the Short-Form McGill Pain Questionnaire was recently validated to have acceptable test-retest reliability [139]. Responses to this questionnaire can be converted into a total or several subscale scores, allowing for comparison across individuals, cohorts, or time points. However, such scales fail to capture the spatial distribution and variability of pain sensations, factor that is especially relevant to phantom limb pain as phantom sensations do not always conform to typical bodily representations – for example, due to telescoping or distorted perceptions of limb position. To better capture these complex experiences, a novel three-dimensional animation tool has been developed that allows individuals to illustrate and document phantom sensations in greater detail [93]. This tool provides possibility for richer description and quantification of phantom limb pain.

As for mechanistic models, I have only come across a few mathematical models of this sort that deal with phantom limb pain, and a few more that deal with related phantom limb topics. One of the earliest examples is a model where self-organizing maps are used to demonstrate how reorganization of somatosensory cortex might be driven by spontaneous activity in peripheral neurons following amputation, although this model makes no mention of phantom limb pain [113]. Using a similar approach Boström at al., showed how both cortical reorganization and preservation of the cortical representation can co-occur following amputation [114]. While this model does unify two apparently contradictory findings related to phantom limb pain, it makes no claims of providing a unique explanatory account for the mechanism underlying the pain itself. Rather, the model relies on the the assumption that the causal driver of phantom pain is the abnormally enhanced spontaneous activity of deafferented peripheral afferent neurons.

When it comes to mechanistic models explicitly dealing with phantom limb pain, I have found two examples, each with quite different approaches. The

first model goes down the path of neurophysiology, using a neuron population rate-based approach to model spinal cord circuits involved in pain processing [112]. The relatively simple model demonstrates characteristics of a number of different pain conditions. For simulations of phantom limb pain, the model relies on a negative firing threshold in the projection neurons, giving a possible explanatory mechanism. However, it is not quite clear what a negative firing threshold corresponds to in neurophysiology.

The second mechanistic model of phantom limb pain takes a cognitive computational approach, proposing predictive coding as a possible mechanism of phantom limb pain [176]. The model is "conceptual" in the sense that is does not perform any numerical calculations. Nevertheless, the model offers predictions of how phantom limb pain might arise as a consequence of mismatches between interoceptive predictions and sensory input in a three step process: 1) the functional reorganization in somatosensory cortex leads to a prediction error triggered by peripheral input from neighboring areas and by intentional movements of the amputated limb, which 2) evokes an aversive sensation such as pain, and 3) leads to activation of the salience network and to peripheral and central disinhibition. Together, these mechanisms are suggested to increase the probability of phantom limb pain.

While this model presents an intriguing explanation of phantom limb pain based on prediction errors, it relies on assumptions that are currently not well supported by empirical evidence. For instance, step 2) of the process relies on the assumption that a mismatch between motor intention and sensory input, or between different sensory modalities, can elicit pain and other aversive sensations. Motion sickness is cited as one such example, along with studies that have used mirrors to experimentally induce sensorimotor incongruence in healthy individuals. However, the link between motion sickness and pain remains unclear, as does the evidence that any of the pain reported in the experimental condition was causally related to incongruence of movements and sensory feedback (see the discussion on Sensorimotor Incongruence in the previous section). The model additionally assumes that "in healthy individuals, the stimulation of a body part results exclusively in activation of the corresponding cortical representation". Brain imaging studies have shown that there exist significant overlap of cortical representations also in non-amputees [164]. It is possible that the change or absence of sensory input from the missing limb does lead to unexpected patterns of activations in somatosensory

cortex. However, the causal relationship between this mismatch and phantom limb pain in this framework is based on assumptions with limited empirical evidence.

4.4 Current consensus – or the lack thereof

To round out this section on phantom limb pain, I will attempt to summarize the current consensus as I understand it. For a comprehensive review on the challenges in the field of phantom limb pain research, readers are referred to [5]. The review underscores that the overall low incidence of amputation, heterogeneity within the study population and methodological limitations in earlier studies have made it difficult to accumulate robust and reliable data. The authors also list a number of recommendations for future studies to reduce the impact of these challenges, including larger and more homogeneous study samples (e.g., by amputation type), use of prospective longitudinal designs, pre-registering outcome measures for more hypothesis driven research, and development of standardized, comprehensive assessment tools that cover multiple pain characteristics.

To summarize my observations related to phantom limb pain during my years in the field, I have prepared tables for some of the commonly cited phenomena and findings. The tables list supporting and detracting papers and an estimate of the confidence in each phenomenon's validity given the current literature. The tables each deal with one of four categories: Phenomenology in Table 4.2, Risk factors and predictors in Table 4.3, Interventions for preventing and relieving phantom limb pain in Table 4.3, and Neuroimaging findings in Table 4.5.

Table 4.2: Some of the most commonly cited phenomena in relation to phantom limb pain, along with supporting and detracting papers and an estimate of the confidence in each phenomenon's validity. References are listed in Table 6.1 at the end of the bibliography.

		Key publications			
	Phenomenon	**Supporting**	**Detracting**	**Strength of evidence**	**Comments**
Phenomenology	Not all amputees develop PLP	(Nikolajsen, 2012)**, (Limakatso et al., 2020)*, (Stankevicious et al., 2021)*		++	While PLP is one of the most common problems reported by amputees, there is also a significant portion of this population who do not develop pain in their phantom limb.
	Onset of PLP typically occurs within the first days or weeks following amputation	(Nikolajsen, 2012)*		+	While PLP onset typically occurs in the subacute phase of limb-loss, there exist reports of both earlier and later PLP onset (acute ≈ during anaesthesia, late ≈ months to years later)
	Phantom pain is less prevalent in non-limbs	(Ramne et al., 2025)		+	Phantom pain occurs also in non-limbs, but the prevalence is generally observed to be lower than in limbs.
	Phantom pain is usually intermittent	(Nikolajsen, 2012)**		++	While most amputees who experience phantom pain do so in intermittent episodes lasting seconds, minutes or hours, some amputees do experience constant pain from their missing limb.
	Ability to move the phantom limb is associated with less PLP	(Gagne et al., 2009), (Raffin et al., 2012), (Raffin et al., 2016), (Kikkert et al., 2017)	(Richardson et al., 2006)	+	Most studies report that impaired ability to voluntarily move the phantom limb is associated with more PLP

Notation: * Systematic review; ** Literature review; ++/— Strong evidence for/against; +/– Tentative evidence for/against; ? Inconclusive evidence

		Key publications			
	Risk factor/predictor	**Supporting**	**Detracting**	**Strength of evidence**	**Comments**
Risk factors and predictors	Persistent pre-amputation pain increases risk of PLP	(Nikolajsen, 2012)**, (Limakatso et al., 2020)*		++	While pre-amputation pain increases the risk of PLP, the characteristics of the pain pre- and post-amputation are not necessarily similar.
	Pain in the residual limb is positively associated with presence of PLP	(Richardson et al., 2006), (Nikolajsen, 2012)**, (Limakatso et al., 2020)*		++	While PLP is considered to be distinct from residual limb pain, the two tend to co-occurr, suggesting possible shared mechanisms.
	Proximal site of amputation is positively associated with prevalence of PLP	(Limakatso et al., 2020)*		+	There is tentative evidence that more proximal amputation is associated with higher presence of PLP.
	Lower limb amputation is associated with higher risk of PLP than upper limb amputation	(Dijkstra et al., 2002), (Poor Zamany Nejat Kermany et al., 2016)	(Shukla et al., 1982), (Ephraim et al., 2005), (Davidson et al., 2010)	?	A recent meta-analysis by (Limakatso et al., 2020) concluded that PLP is more prevalent following lower limb amputation. However, upon closer inspection, one of the included sources had errors in their reported data. Other sources cite PLP as more prevalent following upper limb amputation.
	Upper limb amputation is associated with higher risk of PLP than lower limb amputation	(Shukla et al., 1982), (Ephraim et al., 2005), (Davidson et al., 2010)	(Dijkstra et al., 2002), (Poor Zamany Nejat Kermany et al., 2016)	?	

Notation: * Systematic review; ** Literature review; ++/— Strong evidence for/against; +/– Tentative evidence for/against; ? Inconclusive evidence

Table 4.3: Some of the most commonly cited risk factors and predictors of phantom limb pain, along with supporting and detracting papers and an estimate of the confidence in each risk factor's validity. References are listed in Table 6.2 at the end of the bibliography.

Table 4.4: Some of the most commonly cited interventions for preventing or relieving phantom limb pain, along with supporting and detracting papers and an estimate of the confidence in each intervention's validity. References are listed in Table 6.3 at the end of the bibliography.

		Key publications			
	Intervention	**Supporting**	**Detracting**	**Strength of evidence**	**Comments**
Prevention and pain relief	Surgical reconstruction of peripheral nerves (TMR/RPNI/TSR/AMI) reduces the presence of PLP	(Gardetto et al., 2021), (Srinivasan et al., 2021), (Mauch & Kao, 2023)*, (Hagiga et al., 2023)*, (Bishay et al., 2024)*, (Carter et al, 2024)*		+	While there are several case and cohort studies reporting reductions of post amputation pain following various surgical reconstruction techniques, high-quality evidence in the form of randomized control trials are largely lacking.
	Local/regional anesthesia of the limb reduces PLP	(Birbaumer et al., 1997)	(Birbaumer et al., 1997), (Vaso et al., 2014), (Zheng et al., 2022)	–	(Zheng et al., 2022) is a study in rodent model of neuropathic pain
	DRG nerve block reduces PLP	(Vaso et al., 2014), (Zheng et al., 2022), (Grant et al., 2023), (Goyal et al., 2024)		++	While these studies show promising results för DRG nerve block relieving PLP, there are methodological limitations in terms of sample size, randomization and blinding. (Zheng et al., 2022) is a study in rodent model of neuropathic pain
	Phantom movement interventions reduce PLP	(Ortiz-Catalan et al., 2016), (Perry et al., 2018), (Lendaro et al., 2025)	(Chan et al., 2007)	++	There are a variety of interventions that use some form of imagined or executed movements of the phantom limb and/or augmented visual input relating to the missing limb. Some interventions combine the two by matching the visual feedback to imagined or executed phantom movements. Here, I have attempted to divide the interventions based on whether they 1) include executed phantom movements, 2) include imagined imagery of the phantom limb, and 3) if they include visual imagery of the phantom limb.
	Mental imagery phantom interventions (PMI, GMI) reduce PLP	(Beaumont et al., 2011), (Foell et al, 2014), (Herrador Colmenaro et al, 2017)	(Chan et al., 2007)	+	
	Visual imagery interventions (MT, AR/VR) reduce PLP	(Chan et al., 2007), (Beaumont et al., 2011), (Herrador Colmenaro et al., 2017), (Lendaro et al., 2025)		++	

Notation: * Systematic review; ** Literature review; ++/— Strong evidence for/against; +/– Tentative evidence for/against; ? Inconclusive evidence

Table 4.5: Some of the most commonly cited neuroimaging findings in relation to phantom limb pain, along with supporting and detracting papers and an estimate of the confidence in each finding's validity. References are listed in Table 6.4 at the end of the bibliography.

		Key publications			
	Finding	**Supporting**	**Detracting**	**Strength of evidence**	**Comments**
Neuroimaging findings	(Cortical reorganisation) Medial shift of lip/face representation is associated with PLP in upper limb amputees	(Flor et al., 1995), (Birbaumer et al., 1997), (Lotze et al., 2001), (Karl et al., 2001), (Grusser et al., 2001), (Foell et al., 2014), (Raffin et al., 2016)	(Makin et al., 2015)	++	(Makin et al., 2015) found a significant medial shift of the lip representation in amputees but the shift did not correlate with any of the pain measures.
	(Cortical reorganisation) Activation in phantom hand region during lip movement is associated with PLP in upper limb amputees	(MacIver et al., 2008)	(Makin et al., 2013), (Kikkert et al., 2018)	?	This finding is analogous to the one in the row above, since the lip and hand areas are adjacent to each other. The distinction is in the method used to measure reorganisation (difference in distance of center of gravity vs amount of activation within defined ROIs)
	(Cortical reorganisation) Activation in lip/face region during phantom hand movement is associated with PLP in upper limb amputees	(Lotze et al., 2001), (MacIver et al., 2008)		+	While most studies on cortical reorganisation focus on changes in representations adjacent to the phantom cortex, this finding suggests that there may occur shift or spread also of the phantom representation.
	(Cortical reorganisation) Lateral shift of residual limb is associated with PLP in upper limb amputees	(Raffin et al., 2016)	(Karl et al., 2001), (Schwenkreis et al., 2001)	?	Based on the somatotopic mapping and findings of medial shift of lip/face representation, a similar lateral shift of the residual limb could be expected. While one study did demonstrate this finding, others found no association to PLP (Schwenkreis et al., 2001) or even shift in the opposite direction (Karl et al., 2001).
	(Cortical reorganisation) Medial shift of residual limb is associated with PLP in lower limb amputees	(Zheng et al., 2021)	(Schwenkreis et al., 2003)	?	Similar reorganisation would be expected to occur following lower limb amputation as in upper limb amputation, yet such studies are few and inconclusive.
	(Preservation of cortical representation) Level of activation in phantom SI/M1 during phantom movement correlates with PLP	(Makin et al., 2013), (Kikkert et al., 2017), (Kikkert et al., 2018)	(Diers et al., 2010), (Andoh et al., 2020)	?	There is strong evidence that there is preserved cortical representation of the phantom limb, however the association to PLP remains unclear.

Notation: * Systematic review; ** Literature review; ++/— Strong evidence for/against; +/– Tentative evidence for/against; ? Inconclusive evidence

As can be surmised from the tables, there are few points where there is strong consensus on topics related to phantom limb pain. As has previously been mentioned, heterogeneous methodology and low statistical power make it challenging to draw strong conclusions from existing literature. The lack of strong evidence in empirical studies also makes it difficult to discern the contributions of possible pain mechanisms, which has downstream implications for difficulties in applying appropriate interventions.

To assess the potential completeness of the existing hypotheses on phantom limb pain mechanisms in Section 4.2 and the mechanistic mathematical models in Section 4.3, the hypotheses and models are cross-checked against the phenomena from the Tables 4.2-4.5. Phenomena with inconclusive evidence are omitted. The results are presented in Table 4.6.

In evaluating hypotheses and models against observed phenomena, I have tried to distinguish between different levels of alignment. First, a hypothesis or model may clearly account for a phenomenon – that is, the mechanism explicitly predicts, explains, or reproduces the phenomenon in a way that is consistent with existing observations. Second, a hypothesis or model may be in contradiction with a phenomenon, meaning that its assumptions or predicted outcomes are at odds with empirical evidence or established characteristics of the phenomenon. Third, a hypothesis or model may not account for a phenomenon at all – that is, the phenomenon falls entirely outside the scope of the proposed mechanism, and the hypothesis provides no means by which it could be explained. Finally, a hypothesis or model may potentially relate to a phenomenon, but the effect is unclear or under-specified in existing descriptions of the hypothesis or implementations of the model. In this case, the mechanism could plausibly influence the phenomenon, but the available formulations or interpretations do not provide sufficient information to determine the effect with confidence. Each of these four classifications are indicated in the table as follows:

Y: The hypothesis/model does account for this phenomenon,

X: The hypothesis/model is in contradiction with this phenomenon,

–: The hypothesis/model does not speak to this phenomenon,

?: The hypothesis/model might account for this phenomenon.

Table 4.6: A summary of how different hypotheses and mechanistic models of phantom limb pain account for various phantom limb pain phenomena.

Legend: Yes (Y) — Does account for this phenomenon; Maybe (?) — Might account for this phenomenon; No (X) — In contradiction with this phenomenon; N/A (–) — Does not speak to this phenomenon

			Hypothesis						
	Phenomenon and strength of evidence		Evoked activity in periphery	Spontaneous activity in periphery	Spontaneous activity in DRG	Cortical reorganisation	Preserved cortical representation	Sensorimotor incongruence	Pain memory
Phenomenology	Most but not all amputees develop PLP	++	Y	Y	Y	Y	Y	?	Y
	Time to PLP onset: immediate	+	Y	Y	Y	?	Y	Y	Y
	Time to PLP onset: weeks to months	++	Y	Y	Y	Y	?	X	?
	Time to PLP onset: years to decades	+	Y	?	?	?	?	X	?
	Phantom pain is less prevalent in non-limbs	+	Y	X	X	?	?	Y	X
	Temporal pain dynamics: intermittent	++	Y	Y	Y	Y	Y	Y	Y
	Temporal pain dynamics: chronic	+	X	Y	Y	Y	Y	X	Y
	Ability to move the phantom limb is associated with less PLP	+	–	–	–	?	Y	X	–
Risk factors and predictors	Persistent pre-amputation pain	++	?	?	?	–	–	–	Y
	Pain in the residual limb	++	Y	Y	?	–	–	–	?
	Proximal site of amputation	+	?	?	?	Y	?	Y	X
Prevention and pain relief	Surgical reconstruction of peripheral nerves (TMR/RPNI/TSR/AMI)	+	Y	Y	?	?	X	Y	X
	Local/regional anesthesia ***does not*** reduce PLP	+	X	X	Y	Y	Y	Y	Y
	DRG nerve block reduces PLP	++	Y	Y	Y	X	X	X	X
	Phantom movement interventions reduce PLP	++	X	X	X	Y	Y	X	X
	Mental imagery interventions (PMI, GMI) reduce PLP	+	X	X	X	?	?	Y	X
	Visual imagery interventions (MT, AR/VR) reduce PLP	++	X	X	X	?	?	Y	X
Neuroimaging findings	Shift of neighbouring representations toward the phantom region correlates with PLP	++	–	–	–	Y	X	–	–
	Level of activity in phantom SI/MI during phantom movement correlates with PLP	+	?	?	?	X	Y	–	–

		Mathematical models		
Spinal cord disinhibition/ hyperexcitability	Stochastic entanglement	Self organizing maps (Boström ,2014)	Gate theory (Ropero Pelaez, 2016)	Predictive coding (Weiss, 2022)
Y	Y	Y	Y	Y
Y	?	Y	X	?
Y	Y	Y	Y	Y
?	?	?	?	?
X	Y	X	X	?
Y	Y	Y	Y	Y
Y	Y	Y	Y	?
–	Y	?	–	Y
Y	?	–	–	–
Y	?	–	–	–
?	Y	?	?	Y
Y	?	Y	?	Y
?	Y	X	Y	Y
Y	X	Y	X	X
X	Y	?	X	Y
X	X	?	X	?
X	X	?	X	Y
–	–	Y	–	Y
?	–	Y	–	Y

In constructing the table, I have tried to treat the hypotheses as if they were causally related to phantom limb pain and mutually exclusive. For example, when evaluating cortical reorganization as a hypothesis, I have assumed that peripheral interventions (such as regional anesthesia of the residual limb or surgical procedures targeting peripheral nerves) would not influence phantom limb pain if that pain were solely caused by cortical changes. This simplifying assumption is necessary for comparison, but it does not reflect the likely reality: phantom limb pain is almost certainly not explained by a single mechanism, but by multiple interacting processes whose relative contributions vary across individuals. This complexity is reflected in the fact that no hypothesis or model receives a full score across all phenomena. A further implication is that the phenomena themselves are not universal – different individuals exhibit different subsets of the clinical and perceptual features associated with phantom limb pain. Thus, a given hypothesis may account well for the experiences of some individuals but not others. The mathematical models included in the table are somewhat less ambiguous, as they explicitly formalize the assumed contributions of different mechanisms, and in some cases the models integrate several of the listed hypotheses within a single framework.

I acknowledge that the selection of phenomena may be biased toward the topics most relevant to my work. There are additional topics not considered here, for example pharmacological interventions for phantom limb pain (see [181] for a review). I also acknowledge that the hypotheses presented in the literature vary in their level of specificity and that different researchers may interpret them differently, particularly regarding whether a proposed mechanism is framed as causal or correlational.

This chapter has outlined the current state of phantom limb pain research, including prevailing hypotheses, empirical findings, and some commonly held misconceptions. A recurring theme is the persistent lack of consensus on the mechanisms driving phantom limb pain, the effectiveness of proposed treatments, and even several foundational observations in the field – revealing many gaps that are open for further investigation. Some of these gaps can only be addressed by experimental and clinical research, which is beyond the scope of this thesis centered on mathematical modeling. Other issues can, at least in part, be addressed through the use of mathematical models. In the next chapter, I summarize how the work included in this thesis relates to these gaps and contribute to advancing the understanding of phantom limb pain.

CHAPTER 5

Summary of the publications and their contribution to the field

Before turning to the summary of the publications, I will begin by briefly recapping the preceding chapters. Chapter 1 introduced the overarching aim of this thesis: to use mathematical models to advance the understanding of phantom limb pain. The following two chapters set the stage for how the publications in this thesis address this aim by introducing the study of pain and mathematical modeling, respectively. Together, these chapters highlighted the many complexities inherent in both the pain experience and the scientific study of pain, and suggested that mathematical models can provide a means of navigating this complexity in two distinct but overlapping ways: through mechanistic and empirical modeling approaches.

Chapter 4 summarized the current state of phantom limb pain research, and mapped out several of the gaps in the field. Some key challenges that were identified to continue to hinder progress include the lack of precisely formulated and testable hypotheses, the lack of standardized quantifiable outcome measures, and the lack of rigorous, hypothesis-driven empirical studies. These challenges motivated the research objectives of this thesis, which brings us back to Chapter 1:

R1. Develop mathematical models that propose possible mechanisms underlying phantom limb pain.

R2. Apply mathematical modeling approaches to quantify and characterize perceptual and neural aspects of phantom limb pain.

Using the categories of mathematical models introduced in Chapter 3, the first research objective is primarily pursued through mechanistic modeling, as exemplified by Papers A, B, and C. The second objective is addressed through empirical modeling approaches, which are the focus of Papers D and E. Figure 5.1 illustrates how the publications relate to these model categories and how the categories connect to the research objectives.

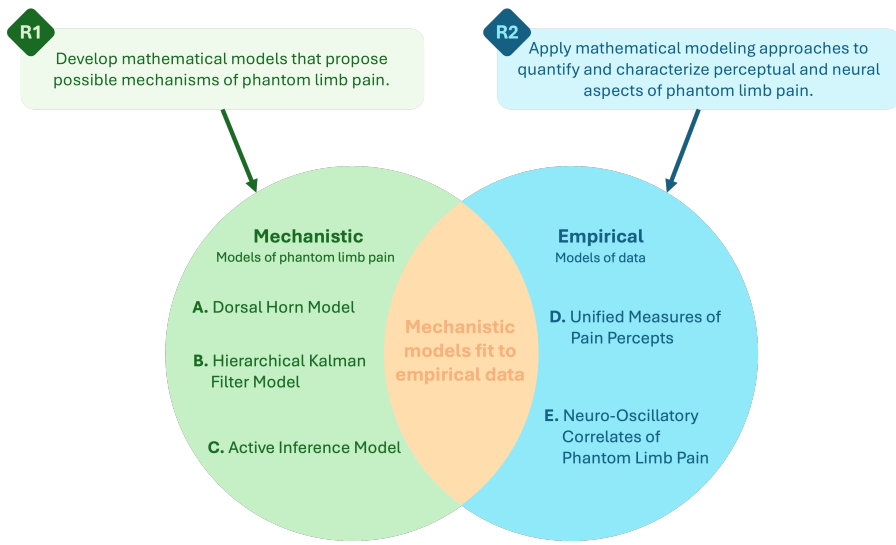

Figure 5.1: Conceptual overview of how the publications included in this thesis relate to the research objectives and the two broad categories of mathematical modeling introduced in Chapter 3. Papers A, B and C employ mechanistic modeling approaches to propose possible mechanisms underlying phantom limb pain, addressing the first research objective (R1). Papers D and E employ empirical modeling approaches to quantify perceptual and neural aspects of phantom limb pain, addressing the second research objective (R2).

The mechanistic models developed in Papers A, B, and C each generate testable hypotheses that can guide the design of future experiments and help disentangle the potential mechanisms underlying phantom limb pain. To evaluate the specific contributions of these mechanistic models, it is useful to consider them in relation to established hypotheses and models about phantom limb pain. For this purpose, I have incorporated the three models into the hypotheses × phenomena table introduced in the previous chapter (Table 4.6), allowing a structured comparison of how well each model accounts for key empirical observations. The table is limited to mechanistic models because it assesses how well different hypotheses explain known phenomena. The remaining two papers serve complementary aims – Paper D introduces quantitative tools for characterizing pain maps, and Paper E examines neural correlates of phantom limb pain – and do not propose mechanistic accounts. They therefore fall outside the scope of this particular comparative framework.

Although none of the three mechanistic models developed in this thesis provide a complete account of all phenomena, each offers a distinct and meaningful contribution to the field. The dorsal horn model in Paper A shares several features with the model proposed by Ropero-Pelaez and Taniguchi [112], but importantly extends it by incorporating spontaneous dorsal root ganglion activity as a potential driver of phantom limb pain. The hierarchical Kalman filter model in Paper B provides a mechanistic explanation for why persistent pre-amputation pain is a strong risk factor for phantom limb pain. Despite being one of the phenomena with the strongest empirical support, few other hypotheses or models address this phenomena, making this contribution particularly valuable. The active inference model in Paper C consolidates how loss of limb control, ambiguity in sensory input pertaining to limb position, residual noxious input, and pre-amputation pain all may contribute to phantom limb pain, thus offering the most complete account of phantom limb pain of the hypotheses and models considered. Nonetheless, some phenomena remain unaccounted for by the model, and for others it is not yet clear how the model fares based on the current implementation.

Table 5.1: A summary of how the mechanistic models included in this thesis fit into the landscape of existing models, hypotheses and phenomena.

Legend:				
Yes (Y)	Does account for this phenomenon	No (X)	In contradiction with this phenomenon
Maybe (?)	Might account for this phenomenon	N/A (–)	Does not speak to this phenomenon

			Hypothesis						
	Phenomenon and strength of evidence		Evoked activity in periphery	Spontaneous activity in periphery	Spontaneous activity in DRG	Cortical reorganisation	Preserved cortical representation	Sensorimotor incongruence	Pain memory
Phenomenology	Most but not all amputees develop PLP	++	Y	Y	Y	Y	Y	?	Y
	Time to PLP onset: immediate	+	Y	Y	Y	?	Y	Y	Y
	Time to PLP onset: weeks to months	++	Y	Y	Y	Y	?	X	?
	Time to PLP onset: years to decades	+	Y	?	?	?	?	X	?
	Phantom pain is less prevalent in non-limbs	+	Y	X	X	?	?	Y	X
	Temporal pain dynamics: intermittent	++	Y	Y	Y	Y	Y	Y	Y
	Temporal pain dynamics: chronic	+	X	Y	Y	Y	Y	X	Y
	Ability to move the phantom limb is associated with less PLP	+	–	–	–	?	Y	X	–
Risk factors and predictors	Persistent pre-amputation pain	++	?	?	?	–	–	–	Y
	Pain in the residual limb	++	Y	Y	?	–	–	–	?
	Proximal site of amputation	+	?	?	?	Y	?	Y	X
Prevention and pain relief	Surgical reconstruction of peripheral nerves (TMR/RPNI/TSR/AMI)	+	Y	Y	?	?	X	Y	X
	Local/regional anesthesia ***does not*** reduce PLP	+	X	X	Y	Y	Y	Y	Y
	DRG nerve block reduces PLP	++	Y	Y	Y	X	X	X	X
	Phantom movement interventions reduce PLP	++	X	X	X	Y	Y	X	X
	Mental imagery interventions (PMI, GMI) reduce PLP	+	X	X	X	?	?	Y	X
	Visual imagery interventions (MT, AR/VR) reduce PLP	++	X	X	X	?	?	Y	X
Neuroimaging findings	Shift of neighbouring representations toward the phantom region correlates with PLP	++	–	–	–	Y	X	–	–
	Level of activity in phantom SI/MI during phantom movement correlates with PLP	+	?	?	?	X	Y	–	–

		Mathematical models			Thesis contributions		
Spinal cord disinhibition/ hyperexcitability	Stochastic entanglement	Self organizing maps (Boström ,2014)	Gate theory (Ropero Pelaez, 2016)	Predictive coding (Weiss, 2022)	**Dorsal horn model (Paper A)**	**Hierarchical Kalman filter (Paper B)**	**Active Inference (Paper C)**
Y	Y	Y	Y	Y	Y	Y	Y
Y	?	Y	X	?	X	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y
?	?	?	?	?	?	Y	Y
X	Y	X	X	?	X	X	?
Y	Y	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	?	Y	Y	Y
–	Y	?	–	Y	–	–	Y
Y	?	–	–	–	–	Y	Y
Y	?	–	–	–	–	–	–
?	Y	?	?	Y	?	?	?
Y	?	Y	?	Y	?	Y	Y
?	Y	X	Y	Y	Y	Y	Y
Y	X	Y	X	X	Y	Y	Y
X	Y	?	X	Y	X	?	Y
X	X	?	X	?	X	?	?
X	X	?	X	Y	X	?	Y
–	–	Y	–	Y	–	–	–
?	–	Y	–	Y	–	–	–

Looking beyond the mechanistic models, Paper D addresses the lack of quantitative methodologies for reliably accumulating data on phantom limb pain by introducing novel, unified measures to quantify the similarity and intensity of pain maps. While tools like C.A.L.A. offer a method for describing and quantifying phantom pain through 3D visualization and surface area calculation [93], the measures proposed in Paper D incorporate additional analytical nuances by accounting for incomplete spatial summation, providing consistent metrics for non-overlapping sensory maps and being map-agnostic, meaning that they can be applied to many different types of pain maps. These measures have potential value both in clinical practice – where they may help track changes in phantom sensations over time – and in research settings, including meta-analyses combining data collected with diverse methods. Finally, Paper E applies a hypothesis-driven analytic approach leveraging empirical models to investigate previously unexplored neural correlates of phantom limb pain. In line with best-practice recommendations, both the hypotheses and the analysis plan were pre-registered, thereby increasing transparency, scientific rigor, and the interpretability of the findings.

Taken together, the five publications in this thesis offer a coherent set of contributions that directly engage with several pressing challenges in phantom limb pain research. The work in this thesis demonstrates how mathematical models can complement experimental and clinical work to advance the field and provide insights that can support both future research efforts and clinical management.

5.1 Summary of Publications

Paper A

Malin Ramne
A Computational Model of Dorsal Horn Circuits' Contribution to Neuropathic Pain
Published in 2025 in the proceedings of the *47th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, DOI: 10.1109/EMBC58623.2025.11253737 .

The dorsal horn of the spinal cord is the first site for a synaptic relay in the somatosensory nervous system, where peripheral afferents synapse onto second order neurons. Projection neurons then transmit the information from the dorsal horn to supraspinal neural circuits for further processing. Despite the crucial role in pain processing, little emphasis has been placed on the dorsal horn circuits' possible contribution to neuropathic pain conditions such as phantom limb pain. This paper presents a mathematical model of the integration of noxious and innocuous somatosensory afferent input in the dorsal horn. The firing rate of distinct neural populations are modeled using differential equations. The model replicates several well-known pain phenomena, including wind-up and pain inhibition by touch. Changes in afferent input and modifications of the synaptic connections, which are hypothesized to occur following nerve injury, reveal possible mechanisms of neuropathic pain conditions such as phantom limb pain and allodynia.

Author contributions: MR contributed with conceptualization and implementation of the model, and writing and editing of the manuscript.

Paper B

Malin Ramne, Jon Sensinger
A Computational Framework for Understanding the Impact of Prior Experiences on Pain Perception and Neuropathic Pain
Published in 2024 in *PLoS Computational Biology*
DOI: 10.1371/journal.pcbi.1012097 .

To efficiently navigate the world and avoid harmful situations, it is beneficial to learn from prior pain experiences. This learning process typically results in certain contexts being associated with an expected level of pain, which subsequently influences pain perception. While this process of pain anticipation has evolved as a mechanism for avoiding harm, recent research indicates that overly precise expectations of pain may in fact contribute to certain chronic pain conditions, especially when sensory input has become unreliable, such as after limb loss. However, it remains an open question how prior experiences contribute to pain expectations. In this paper, we apply a hierarchical Bayesian approach to model how people integrate prior experiences in their future expectations of pain. This hierarchical model structure is able to describe how several counterintuitive but well-documented pain phenomena, such as offset analgesia and placebo hypoalgesia, can arise. In simulations of neuropathic pain, the model corroborates that persistent non-neuropathic pain is a risk factor for developing neuropathic pain following denervation, and additionally offers an interesting prediction that complete absence of informative painful experiences could be a similar risk factor. Taken together, these results provide insight to how prior experiences may contribute to pain perception, in both experimental and neuropathic pain conditions such as phantom limb pain.

Author contributions: MR and JS jointly conceptualized the model. MR implemented the model in code and drafted the manuscript, with support and feedback from JS. MR and JS both edited and approved the final manuscript.

Paper C

Malin Ramne, Torbjörn Lundh, Jon Sensinger
Modeling the Action-Perception Loop and its role in Phantom Limb Pain using Active Inference
Preprint at bioRxiv 2025, DOI: 10.64898/2025.12.05.692511
Submitted to *Journal of Theoretical Biology* .

The heterogeneity within the amputee population makes it challenging to empirically disentangle the possible factors driving phantom limb pain. Consequently, it is often difficult to ensure that interventions are targeting relevant mechanisms, leading to variable efficacy at the individual level and limited efficacy at the group level. Mathematical modeling offers a way to shed light on such complex phenomena, as exemplified by recent applications of the Bayesian inference framework to describe various aspects of pain perception. Yet, pain is not only passively inferred but also actively shaped through interactions with the environment – a dimension that classical Bayesian models typically fail to capture. Because amputation disrupts both sensory inputs related to the limb and the ability to perform actions, a model that incorporates both sensory and active components of pain may provide new insight into the mechanisms underlying phantom limb pain. To this end, we developed a model within the active inference framework, which extends Bayesian inference to include action selection. The model provides a conceptual account of how loss of limb control, ambiguity in sensory input pertaining to limb position, residual noxious input, and pre-amputation pain may contribute to the emergence and persistence of phantom limb pain. Furthermore, the model offers insight into the possible mechanisms underlying common interventions and may help account for their variable efficacy across individuals.

Author contributions: MR and JS jointly conceptualized the model. MR implemented the model in code and drafted the manuscript, with support and feedback from JS and TL. All authors edited and approved the final manuscript.

Paper D

Eric J. Earley, **Malin Ramne**, Johan Wessberg
Unified Measures Quantifying Intensity and Similarity of Pain and Somatosensory Percepts
Published in 2025 in *Journal of Neurophysiology*,
DOI: 10.1152/jn.00031.2025 .

Pain maps are a common measure for characterizing how the quality and intensity of pain may vary across different regions of the body or the affected area. Such characterization are especially valuable in pain conditions with complex bodily manifestations such as phantom limb pain, yet existing methods for quantification of the intensity and similarity of percepts recorded with these measures can give non-unique results. Furthermore, differing methodology of how the data is recorded introduces additional challenges for compounding or comparing data across studies. In this paper, we propose novel and unifying measures to quantify the similarity and intensity of pain maps and somatosensory percepts. These measures are generalizable and can be applied to any application of somatosensory maps, and are usable with both discretized and free-hand drawings in both 2D and 3D representations. The utility of the measures is demonstrated using data from two studies, proving strong agreement with the validation studies. These results illustrate the potential as agnostic measures for quantifying somatosensory percepts in studies and meta-analyses. In the clinical setting, these measures may aid in improved pain characterization, granting a better understanding of the needs and progression of patients experiencing pain.

Author contributions: EE conceptualized the measures, their mathematical derivation and code implementation. MR reviewed the mathematical derivations, contributed with expertise in how the measures could be used in the field of pain research and aided in finding appropriate datasets for validation of the measures. JW contributed with expertise in how the measures could be used in the field of somatosensory research. EE drafted the majority of the manuscript, MR contributed to the sections on pain. All authors edited and approved the final manuscript.

Paper E

Malin Ramne, Eva Lendaro
Resting-State Theta and Alpha Oscillations in Amputation and Phantom Limb Pain: A Pre-Registered High-Density EEG Study
Preprint at ResearchSquare 2026, DOI: 10.21203/rs.3.rs-8645281/v1
Submitted to *Brain Topography* .

While neuroimaging studies of phantom limb pain have predominantly employed fMRI and MEG, resting-state EEG could offer complementary insight into intrinsic brain oscillations but remains largely unexplored in this specific context. Systematic reviews suggest that chronic pain is associated with increased theta-band power and reduced peak alpha frequency in resting-state EEG, but whether these patterns extend to phantom limb pain is unknown. In this study, we used high-density resting-state EEG to examine theta-band power and peak alpha frequency in amputees with phantom limb pain, amputees without phantom limb pain, and intact controls. We employed mixed-effects models with bootstrap inference, multiple sensitivity analyses, and exploratory cluster-based permutation testing, and to ensure transparency and scientific rigor, the hypotheses and analysis plan were pre-registered. Across all primary and sensitivity analyses we found no evidence that these oscillatory markers generalize to phantom limb pain. We did observe tentative evidence for amputation-related alterations in alpha-band dynamics, and an exploratory analysis within the phantom limb pain group showed a positive association between one measure of peak alpha frequency and pain intensity. However, inconsistent replication across spectral measures and statistical approaches indicates that these amputation and pain intensity-related findings should be interpreted with caution and require confirmation in larger, well-powered studies. Taken together, these results suggest that resting-state EEG markers commonly reported in chronic pain do not straightforwardly generalize to phantom limb pain, and that alterations in alpha-band dynamics may be driven by multiple processes following amputation.

Author contributions: MR and EL jointly conceptualized the study. EL contributed to collection of the dataset that this study uses. MR formatted the data according to the BIDS standard and prepared the open access repositories. MR planned and implemented the statistical analysis, with support and feedback from EL. Both authors edited and approved the final manuscript.

CHAPTER 6

Concluding remarks

This thesis aims to advance the understanding of phantom limb pain through the use of mathematical models. Part I provides foundational context to the research contributions in Part II, where Chapter 2 situates phantom limb pain within the wider landscape of pain research and Chapter 3 illustrates how mathematical models can generate insights by a variety of different approaches. The fourth chapter of Part I reviews prevailing hypotheses and empirical findings on phantom limb pain, but perhaps more importantly, it identifies common misconceptions and points out contradictory or insufficient evidence. This chapter highlights that phantom limb pain is troubling not only because of the immense suffering it causes, but also because of the lack of consensus among researchers and clinicians regarding its underlying mechanisms. In such a landscape, mathematical modeling offers a particularly valuable set of tools. Models allow complex phenomena to be quantified more reliably, help reveal patterns hidden in data, and generate explicit, testable hypotheses that can guide future empirical work. Crucially, mathematical models require that assumptions and relationships be stated unambiguously. This level of precision is often absent in purely conceptual descriptions of hypotheses, where ambiguity can foster misconceptions, misunderstandings, and

incorrect inferences – issues that have long complicated the study of phantom limb pain. The chapter on phantom limb pain is rounded out with a mapping of the proposed mechanisms against the best-supported phenomena. This synthesis helps clarify where explanatory gaps remain and provides a structured framework into which future research can be placed.

The five publications in Part II of the thesis address several key challenges in phantom limb pain research. The mechanistic models in Papers A, B, and C demonstrate how a mathematical approach can generate explicit, testable hypotheses about the mechanisms underlying phantom limb pain, while also revealing gaps and inconsistencies in existing hypotheses. Paper D provides a quantitative method for measuring phantom percepts – both painful and non-painful – and for tracking how these percepts change over time. Finally, Paper E present new empirical evidence on oscillatory neural correlates of phantom limb pain and amputation, based on statistically principled analyses of resting-state neural activity. Taken together, this thesis offers a coherent set of contributions that directly engage with several pressing challenges in phantom limb pain research, and offer insights that can support both future research efforts and clinical management of phantom limb pain.

Future work

While mathematical modeling provides a powerful framework for clarifying mechanisms, refining hypotheses, and quantifying and analyzing data, progress ultimately depends on empirical studies capable of generating data for testing, constraining and validating these models. The work included in this thesis points to several experimental directions that could substantially improve the understanding of phantom limb pain.

Perhaps most prominently – and as suggested across all three mechanistic models – phantom limb pain likely arises from a combination of peripheral and central mechanisms. However, the relative contribution of these mechanisms remains unclear at both the individual and group levels. Although some studies have attempted to disentangle these effects [143, 144, 146], they often share common limitations in the field: small and heterogeneous samples, limited blinding, and a lack of longitudinal follow-up. One particularly valuable next step would be a replication of the 2014 study by Vaso et al. [144], but carried out with stronger methodological rigor, including larger samples, proper blinding (e.g., sham injections), possible cross-over design, and multi-center

collaboration. Such a study could meaningfully clarify the respective roles of peripheral and central mechanisms, leading to more targeted and effective clinical management strategies.

A related priority is the development of clinical tools for determining whether an individual's phantom limb pain is primarily driven by peripheral mechanisms. Papers B and C suggest that interventions targeting central pain-processing mechanisms may prove ineffective in cases where pain is in fact driven by peripheral afferent input – for example from a neuroma or spontaneous activity in the dorsal root ganglion. Differentiating these mechanisms at the individual level is therefore essential for selecting appropriate, mechanism-based interventions. Moreover, investigating individual differences in how sensory modalities, expectations, and cognitive factors shape sensory and pain perception may also shed light on why certain interventions benefit some amputees but not others. Psychophysical experiments probing such differences could offer valuable group-level insights that eventually support more tailored, individualized approaches to clinical management.

More broadly, the field would benefit from explicitly hypothesis-driven research grounded in carefully specified causal models. For example, many intervention studies invoke the notion of "reversing maladaptive plasticity", while providing little clarity on the specific assumptions about causal pain mechanisms. These studies typically build on the neuroimaging findings of cortical reorganisation, and assume that reversal of cortical reorganisation will result in reduction of phantom limb pain. However, this assumption is problematic in several ways. First, there is no clear causal relation between cortical reorganisation and phantom limb pain. Second, the ability for the intervention to reverse cortical reorganization may not be empirically established. Here, a comprehensive neuroimaging study that applies multiple methodologies within the same cohort – mirroring those used across previous, often contradictory studies – could help to resolve longstanding misconceptions about cortical reorganisation or preservation and their relationship to phantom limb pain.

On the topic of neuroimaging, Paper E explores oscillatory neural activity as a potential correlate of phantom limb pain and amputation, an aspect that has received comparatively little attention in prior work. Using statistically principled analyses of resting-state EEG data, the study shows that oscillatory markers commonly reported in chronic pain do not directly generalize to phantom limb pain. However, the findings also suggest the presence of

amputation-related alpha-band alterations and potential modulation of peak alpha frequency by pain intensity. These findings highlight the need for future neuroimaging studies to distinguish pain-specific effects from broader consequences of sensory deafferentation, and to combine measures of neural activity with detailed assessments of both painful and non-painful phantom percepts in larger cohorts.

Once some of these conceptual and methodological uncertainties have been resolved and hypotheses can be formulated with greater precision, longitudinal studies could play a transformative role for the field. For this type of study, tools such as the measures proposed in Paper D can be of use for reliably quantifying and tracking changes in phantom sensations across time. Two longitudinal study designs that could be of particular value are studies following individuals before and after amputation, and studies tracking participants before, during, and after a clearly hypothesis-driven intervention. Although such studies pose logistical challenges and would likely require multi-site collaboration, they have the potential to fundamentally advance the understanding of the causal mechanisms of phantom limb pain.

In parallel with these empirical studies, mathematical modeling should also continue to be used in the investigation of phantom limb pain. A promising direction for future work lies in developing models that integrate mechanistic and empirical perspectives, a gap that remains relatively underexplored in this thesis. Another open and interesting topic that could be investigated with mathematical models is the contribution of affective processes to phantom limb pain. Pain and emotion are closely linked and there are tentative results indicating that addressing fear and negative emotions can have a profound impact on recovery from chronic pain conditions. Limb amputation often involves a significant psychological burden, possibly further exacerbating the contributions of these factors. Therefore, it would be very interesting to investigate possible mechanisms linking affective processes and phantom limb pain.

In conclusion, moving forward mathematical modeling and empirical studies should be conducted in tandem in research on phantom limb pain. The modeling work can help better specify well-defined research questions and hypotheses, and also provide some of the tools needed to conclusively answer those questions. Meanwhile, well designed empirical studies a necessary to constrain the models and to validate or debunk their predictions.

References

[1] W. J. Ma, K. P. Kording, and D. Goldreich, "Bayesian Models of Perception and Action an Introduction," *MIT Press*, vol. 13, no. April, 2021.

[2] P. Gerlee and T. Lundh, *Scientific models: Red atoms, white lies and black boxes in a yellow book*. 2016. DOI: 10.1007/978-3-319-27081-4.

[3] S. N. Raja et al., "The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises," *PAIN*, vol. 161, no. 9, 2020, ISSN: 0304-3959. DOI: 10.1097/j.pain.0000000000001939.

[4] K. Limakatso, G. J. Bedwell, V. J. Madden, and R. Parker, "The prevalence and risk factors for phantom limb pain in people with amputations: A systematic review and meta-analysis," *PLOS ONE*, vol. 15, no. 10, e0240431, Oct. 2020. DOI: 10.1371/journal.pone.0240431.

[5] H. R. Schone et al., "Making sense of phantom limb pain," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 93, no. 8, 833 LP –843, Aug. 2022. DOI: 10.1136/jnnp-2021-328428.

[6] R.-D. Treede et al., "A classification of chronic pain for ICD-11," *PAIN*, vol. 156, no. 6, 2015, ISSN: 0304-3959.

[7] T. Vos et al., "Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019," *The Lancet*, vol. 396, no. 10258, pp. 1204–

1222, Oct. 2020, ISSN: 0140-6736. DOI: 10.1016/S0140-6736(20)30925-9.

[8] S. P. Cohen, L. Vase, and W. M. Hooten, "Chronic pain: an update on burden, best practices, and new advances," *The Lancet*, vol. 397, no. 10289, pp. 2082–2097, May 2021, ISSN: 0140-6736. DOI: 10.1016/S0140-6736(21)00393-7.

[9] M. A. Fitzcharles, S. P. Cohen, D. J. Clauw, G. Littlejohn, C. Usui, and W. Häuser, *Nociplastic pain: towards an understanding of prevalent pain conditions*, 2021. DOI: 10.1016/S0140-6736(21)00392-5.

[10] M. Ramne, M. Elam, L. S. Löken, and M. Ortiz-Catalan, "Neurophysiology of pain for non-neurophysiologists: a systematic review [preprint]," *Research Square*, May 2023. DOI: 10.21203/rs.3.rs-2942949/v1.

[11] D. L. Ellison, "Physiology of Pain," *Critical Care Nursing Clinics of North America*, vol. 29, no. 4, pp. 397–406, 2017, ISSN: 08995885. DOI: 10.1016/j.cnc.2017.08.001.

[12] W. W. Monafo, "Physiology of Pain," *Journal of Burn Care & Rehabilitation*, vol. 16, no. Supplement 1, pp. 345–347, May 1995, ISSN: 0273-8481. DOI: 10.1097/00004630-199505001-00002.

[13] K. R. Greer and J. W. Hoyt, "Pain: Theory, Anatomy, and Physiology," *Critical Care Clinics*, vol. 6, no. 2, pp. 227–234, 1990, ISSN: 0749-0704. DOI: 10.1016/S0749-0704(18)30373-7.

[14] A. J. Meyr and J. S. Steinberg, "The Physiology of the Acute Pain Pathway," *Clinics in Podiatric Medicine and Surgery*, vol. 25, no. 3, pp. 305–326, 2008, ISSN: 0891-8422. DOI: 10.1016/j.cpm.2008.02.012.

[15] K. G. Usunoff, A. Popratiloff, O. Schmitt, and A. Wree, *Functional Neuroanatomy of Pain* (Advances in Anatomy, Embryology and Cell Biology: 184), 1st ed., Simon Rallison, Ed. Berlin: Springer, Heidelberg, 2006, pp. 1–4, ISBN: 978-3-540-28166-5. DOI: 10.1007/3-540-28166-5.

[16] K. Baker, "Recent advances in the neurophysiology of chronic pain," *Emergency Medicine Australasia*, vol. 17, no. 1, pp. 65–72, Feb. 2005, ISSN: 1742-6731. DOI: 10.1111/j.1742-6723.2005.00689.x.

[17] J. Clancy and A. McVicar, "Neurophysiology of pain.," *The British journal of theatre nursing : NATNews : the official journal of the National Association of Theatre Nurses*, vol. 7, no. 10, pp. 19–27, Jan. 1998, ISSN: 1353-0224.

[18] M. Bennett, "The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs," *Pain*, vol. 92, no. 1, pp. 147–157, 2001, ISSN: 0304-3959. DOI: 10.1016/S0304-3959(00)00482-6.

[19] L. A. Lamont, W. J. Tranquilli, and K. A. Grimm, "Physiology of Pain," *Veterinary Clinics of North America: Small Animal Practice*, vol. 30, no. 4, pp. 703–728, 2000, ISSN: 0195-5616. DOI: 10.1016/S0195-5616(08)70003-2.

[20] S. Marchand, "The Physiology of Pain Mechanisms: From the Periphery to the Brain," *Rheumatic Disease Clinics of North America*, vol. 34, no. 2, pp. 285–309, 2008, ISSN: 0889-857X. DOI: https://doi.org/10.1016/j.rdc.2008.04.003.

[21] H. G. Schaible and R. F. Schmidt, "Neurophysiology of chronic inflammatory pain: electrophysiological recordings from spinal cord neurons in rats with prolonged acute and chronic unilateral inflammation at the ankle.," *Progress in brain research*, vol. 110, pp. 167–176, 1996, ISSN: 0079-6123. DOI: 10.1016/s0079-6123(08)62573-x.

[22] L. U. Sneddon, "Comparative physiology of nociception and pain," *Physiology*, vol. 33, no. 1, pp. 63–73, 2018, ISSN: 15489221. DOI: 10.1152/physiol.00022.2017.

[23] A. Swift, "Physiology–how the body detects pain stimuli.," *Nursing times*, vol. 111, no. 39, pp. 20–23, Sep. 2015, ISSN: 0954-7762.

[24] R. A. Meintjes, "An overview of the physiology of pain for the veterinarian," *The Veterinary Journal*, vol. 193, no. 2, pp. 344–348, 2012, ISSN: 1090-0233. DOI: 10.1016/j.tvjl.2012.03.001.

[25] B. Bishop, "Pain: Its Physiology and Rationale for Management: Part I. Neuroanatomical Substrate of Pain," *Physical Therapy*, vol. 60, no. 1, pp. 13–20, Jan. 1980, ISSN: 0031-9023. DOI: 10.1093/ptj/60.1.13.

[26] G. J. Bennett, "Update on the Neurophysiology of Pain Transmission and Modulation: Focus on the NMDA-Receptor," *Journal of Pain and Symptom Management*, vol. 19, no. 1, Supplement 1, pp. 2–6, 2000, ISSN: 0885-3924. DOI: 10.1016/S0885-3924(99)00120-7.

[27] T. Lundeberg, "Pain physiology and principles of treatment.," *Scandinavian journal of rehabilitation medicine. Supplement*, vol. 32, pp. 13–41, 1995, ISSN: 0346-8720.

[28] W. D. Willis and K. N. Westlund, "Neuroanatomy of the pain system and of the pathways that modulate pain," eng, *Journal of Clinical Neurophysiology*, vol. 14, no. 1, pp. 2–31, Jan. 1997, ISSN: 0736-0258. DOI: 10.1097/00004691-199701000-00002.

[29] A. Wright, "Recent concepts in the neurophysiology of pain," *Manual Therapy*, vol. 4, no. 4, pp. 196–202, 1999, ISSN: 1356-689X. DOI: 10.1054/math.1999.0207.

[30] S. Khalid and R. S. Tubbs, "Neuroanatomy and Neuropsychology of Pain," eng, *Cureus*, vol. 9, no. 10, e1754, Oct. 2017, ISSN: 2168-8184. DOI: 10.7759/cureus.1754.

[31] J. M. Rosenow and J. M. Henderson, "Anatomy and physiology of chronic pain," eng, *Neurosurgery clinics of North America*, vol. 14, no. 3, pp. 445–462, 2003, ISSN: 1042-3680. DOI: 10.1016/s1042-3680(03)00009-3.

[32] N. Wentworth Dolphin, "Neuroanatomy and neurophysiology of pain: nursing implications," *International Journal of Nursing Studies*, vol. 20, no. 4, pp. 255–263, 1983, ISSN: 0020-7489. DOI: 10.1016/0020-7489(83)90017-2.

[33] P. A. Young, "The anatomy of the spinal cord pain paths: a review.," *The Journal of the American Paraplegia Society*, vol. 9, no. 3-4, pp. 28–38, 1986, ISSN: 01952307. DOI: 10.1080/01952307.1986.11719621.

[34] H. Godfrey, "Understanding pain, part 1: physiology of pain," *British Journal of Nursing*, vol. 14, no. 16, pp. 846–852, Sep. 2005, ISSN: 0966-0461. DOI: 10.12968/bjon.2005.14.16.19725.

[35] G. I. Lee and M. W. Neumeister, "Pain: Pathways and Physiology," *Clinics in Plastic Surgery*, vol. 47, no. 2, pp. 173–180, 2020, ISSN: 15580504. DOI: 10.1016/j.cps.2019.11.001.

[36] W. D. Willis, "Neurophysiology of nociception and pain in the spinal cord.," *Research publications - Association for Research in Nervous and Mental Disease*, vol. 58, pp. 77–92, 1980, ISSN: 00917443.

[37] M. Aguggia, "Neurophysiology of pain," *Neurological Sciences*, vol. 24, no. 2, s57–s60, 2003, ISSN: 1590-3478. DOI: 10.1007/s100720300042.

[38] T. L. Yaksh, *New horizons in our understanding of the spinal physiology and pharmacology of pain processing*, 1993.

[39] E. Briggs, "Understanding the experience and physiology of pain," *Nursing standard: official newspaper of the Royal College of Nursing*, vol. 25, no. 3, pp. 35–39, Sep. 2010. DOI: 10.7748/ns2010.09.25.3.35.c7989.

[40] A. H. Thomson, "The anatomy, physiology, and psychology of pain.," *Journal of occupational medicine. : official publication of the Industrial Medical Association*, vol. 7, no. 10, pp. 526–534, Oct. 1965, ISSN: 0096-1736.

[41] S. V. Wilkinson, M. T. Neary, R. O. Jones, and K. F. Sunshein, "The neuroanatomy of pain.," *Clinics in podiatric medicine and surgery*, vol. 11, no. 1, pp. 1–13, Jan. 1994, ISSN: 0891-8422.

[42] C. G. Smith, "The anatomy of pain.," *University of Toronto medical journal*, vol. 27, no. 3, pp. 89–97, Dec. 1949, ISSN: 0042-0239.

[43] R.-R. Nir, R. Lev, R. Moont, Y. Granovsky, E. Sprecher, and D. Yarnitsky, "Neurophysiology of the Cortical Pain Network: Revisiting the Role of S1 in Subjective Pain Perception Via Standardized Low-Resolution Brain Electromagnetic Tomography (sLORETA)," *The Journal of Pain*, vol. 9, no. 11, pp. 1058–1069, Nov. 2008, ISSN: 1526-5900. DOI: 10.1016/j.jpain.2008.06.008.

[44] A. Schnitzler and M. Ploner, "Neurophysiology and Functional Neuroanatomy of Pain Perception," *Journal of Clinical Neurophysiology*, vol. 17, no. 6, pp. 592–603, 2000, ISSN: 0736-0258. DOI: 10.1097/00004691-200011000-00005.

[45] C. A. Carlsson and L. Pellettieri, "A clinical view of pain physiology.," *Acta chirurgica Scandinavica*, vol. 148, no. 4, pp. 305–313, 1982, ISSN: 0001-5482.

[46] J. E. Brown, N. Chatterjee, J. Younger, and S. Mackey, "Towards a Physiology-Based Measure of Pain: Patterns of Human Brain Activity Distinguish Painful from Non-Painful Thermal Stimulation," *PLOS ONE*, vol. 6, no. 9, e24124, Sep. 2011. DOI: 10.1371/journal.pone.0024124.

[47] H. Flor, *Psychological pain interventions and neurophysiology: Implications for a mechanism-based approach.* Flor, Herta: Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Square J5, Mannheim, Germany, D-68159, herta.flor@zi-mannheim.de, 2014. DOI: 10.1037/a0035254.

[48] J. Zaki, T. D. Wager, T. Singer, C. Keysers, and V. Gazzola, "The Anatomy of Suffering: Understanding the Relationship between Nociceptive and Empathic Pain," *Trends in Cognitive Sciences*, vol. 20, no. 4, pp. 249–259, Apr. 2016, ISSN: 1364-6613. DOI: 10.1016/j.tics.2016.02.003.

[49] S. Bourne, A. G. Machado, and S. J. Nagel, "Basic anatomy and physiology of pain pathways," *Neurosurgery Clinics of North America*, vol. 25, no. 4, pp. 629–638, 2014, ISSN: 15581349. DOI: 10.1016/j.nec.2014.06.001.

[50] T. Dillworth, M. E. Mendoza, and M. P. Jensen, "Neurophysiology of pain and hypnosis for chronic pain," *Translational Behavioral Medicine*, vol. 2, no. 1, pp. 65–72, Mar. 2012, ISSN: 1869-6716. DOI: 10.1007/s13142-011-0084-5.

[51] E. R. Scioli-Salter, D. E. Forman, J. D. Otis, K. Gregor, I. Valovski, and A. M. Rasmusson, "The Shared Neuroanatomy and Neurobiology of Comorbid Chronic Pain and PTSD: Therapeutic Implications," *The Clinical Journal of Pain*, vol. 31, no. 4, pp. 363–374, 2015, ISSN: 0749-8047. DOI: 10.1097/AJP.0000000000000115.

[52] A. Hedlin and J. Dostrovsky, "Understanding the physiology of pain.," *The Canadian Nurse*, vol. 75, no. 2, pp. 28–30, Feb. 1979, ISSN: 0008-4581.

[53] I. Tavares and D. Lima, "From neuroanatomy to gene therapy: searching for new ways to manipulate the supraspinal endogenous pain modulatory system," *Journal of Anatomy*, vol. 211, no. 2, pp. 261–268, Aug. 2007, ISSN: 0021-8782. DOI: 10.1111/j.1469-7580.2007.00759.x.

[54] J. Edmeads, "The physiology of pain: A review," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 7, no. 4, pp. 413–419, 1983, ISSN: 0278-5846. DOI: 10.1016/0278-5846(83)90004-0.

[55] B. Bishop, "Pain: Its physiology and rationale for management. Part III. Consequences of current concepts of pain mechanisms related to pain management," *Physical Therapy*, vol. 60, no. 1, 1980, ISSN: 00319023. DOI: 10.1093/ptj/60.1.24.

[56] H. L. Fields, "Neurophysiology of Pain and Pain Modulation," *The American Journal of Medicine*, vol. 77, no. 3, Part 1, pp. 2–8, 1984, ISSN: 0002-9343. DOI: https://doi.org/10.1016/S0002-9343(84)80097-2.

[57] J. L. Willems, "Neurophysiology of pain.," *Acta anaesthesiologica Belgica*, vol. 32, no. 1, pp. 7–12, 1981, ISSN: 0001-5164.

[58] M. J. Hoffert, "The Neurophysiology of Pain," *Neurologic Clinics*, vol. 7, no. 2, pp. 183–203, 1989, ISSN: 0733-8619. DOI: 10.1016/S0733-8619(18)30809-0.

[59] F. P. Haugen, "Recent advances in the neurophysiology of pain," *Anesthesiology.*, vol. 16, no. 4, pp. 490–494, 1955. DOI: 10.1097/00000542-195507000-00003.

[60] M. M. Tekavec, "Anatomy and physiology of the nervous system pain mechanism and pain control.," *Journal of the National Analgesia Society*, vol. 5, no. 4, pp. 19–31, Oct. 1976.

[61] W. D. J. Willis, "Dorsal Horn Neurophysiology of Paina," *Annals of the New York Academy of Sciences*, vol. 531, no. 1, pp. 76–89, Jun. 1988, ISSN: 0077-8923. DOI: https://doi.org/10.1111/j.1749-6632.1988.tb31815.x.

[62] J. M. McHugh and W. B. McHugh, "Pain: neuroanatomy, chemical mediators, and clinical implications.," *AACN Clinical Issues*, vol. 11, no. 2, pp. 168–178, May 2000, ISSN: 1079-0713. DOI: 10.1097/00044067-200005000-00003.

[63] B. Bishop, "Pain: Its Physiology and Rationale for Management: Part II. Analgesic Systems of the CNS," *Physical Therapy*, vol. 60, no. 1, pp. 21–23, Jan. 1980, ISSN: 0031-9023. DOI: 10.1093/ptj/60.1.21.

[64] A. H. Dickenson, "Recent advances in the physiology and pharmacology of pain: Plasticity and its implications for clinical analgesia," *Journal of Psychopharmacology*, vol. 5, no. 4, pp. 342–351, 1991, ISSN: 14617285. DOI: 10.1177/026988119100500424.

[65] A. H. Dickenson, *Neurophysiology of opioid poorly responsive pain*, 1994.

[66] A. I. Basbaum and H. L. Fields, "The origin of descending pathways in the dorsolateral funiculus of the spinal cord of the cat and rat: Further studies on the anatomy of pain modulation," *Journal of Comparative Neurology*, vol. 187, no. 3, pp. 513–531, 1979, ISSN: 10969861. DOI: 10.1002/cne.901870304.

[67] S. Wolf, "The physiology of pain.," *Parodontologie and academy review*, vol. 1, no. 1, pp. 67–78, Mar. 1967, ISSN: 0369-8092.

[68] F. Cervero, *Understanding Pain: Exploring the Perception of Pain*. 2012, p. 188, ISBN: 9780262526067.

[69] K. Wiech and I. Tracey, *Pain, decisions, and actions: A motivational perspective*, 2013. DOI: 10.3389/fnins.2013.00046.

[70] G. L. Engel, "The Need for a New Medical Model: A Challenge for Biomedicine," *Science*, vol. 196, no. 4286, pp. 129–136, Apr. 1977. DOI: 10.1126/science.847460.

[71] L. M. Adams and D. C. Turk, "Central sensitization and the biopsychosocial approach to understanding pain," *Journal of Applied Biobehavioral Research*, vol. 23, no. 2, 2018, ISSN: 17519861. DOI: 10.1111/jabr.12125.

[72] C. Büchel, "The role of expectations, control and reward in the development of pain persistence based on a unified model," *eLife*, vol. 12, A. Meulders and D. M. Harper, Eds., e81795, 2023, ISSN: 2050-084X. DOI: 10.7554/eLife.81795.

[73] A. Tabor and C. Burr, "Bayesian Learning Models of Pain: A Call to Action," *Current Opinion in Behavioral Sciences*, vol. 26, pp. 54–61, 2019, ISSN: 2352-1546. DOI: 10.1016/j.cobeha.2018.10.006.

[74] A.-L. Eckert, K. Pabst, and D. M. Endres, *A Bayesian model for chronic pain*, 2022. DOI: 10.3389/fpain.2022.966034.

[75] M. Jepma, L. Koban, J. van Doorn, M. Jones, and T. D. Wager, "Behavioural and neural evidence for self-reinforcing expectancy effects on pain," *Nature Human Behaviour*, vol. 2, no. 11, pp. 838–855, 2018, ISSN: 2397-3374. DOI: 10.1038/s41562-018-0455-8.

[76] R. J. Gatchel, *Comorbidity of Chronic Pain and Mental Health Disorders: The Biopsychosocial Perspective.* 2004. DOI: 10.1037/0003-066X.59.8.795.

[77] I. Yalcin and M. Barrot, "The anxiodepressive comorbidity in chronic pain," *Current Opinion in Anesthesiology*, vol. 27, no. 5, 2014, ISSN: 0952-7907. DOI: 10.1097/ACO.0000000000000116.

[78] Y. K. Ashar et al., "Effect of Pain Reprocessing Therapy vs Placebo and Usual Care for Patients With Chronic Back Pain: A Randomized Clinical Trial," *JAMA Psychiatry*, vol. 79, no. 1, pp. 13–23, Jan. 2022, ISSN: 2168-622X. DOI: 10.1001/jamapsychiatry.2021.2669.

[79] D. C. Turk and R. Melzack, *Handbook of pain assessment (3rd ed.).* 2011.

[80] O. Karcioglu, H. Topacoglu, O. Dikme, and O. Dikme, *A systematic review of the pain scales in adults: Which to use?* 2018. DOI: 10.1016/j.ajem.2018.01.008.

[81] S. Rolstad, J. Adler, and A. Rydén, "Response burden and questionnaire length: Is shorter better? A review and meta-analysis," *Value in Health*, vol. 14, no. 8, 2011, ISSN: 10983015. DOI: 10.1016/j.jval.2011.06.003.

[82] R. P. Hart, M. F. Martelli, and N. D. Zasler, *Chronic pain and neuropsychological functioning*, 2000. DOI: 10.1023/A:1009020914358.

[83] X. Zhang et al., *Evidence for Cognitive Decline in Chronic Pain: A Systematic Review and Meta-Analysis*, 2021. DOI: 10.3389/fnins.2021.737874.

[84] R. de la Vega, P. Sakulsriprasert, J. Miró, and M. P. Jensen, "Optimizing Pain Intensity Assessment in Clinical Trials: How Many Ratings are Needed to Best Balance the Need for Validity and to Minimize Assessment Burden?" *Journal of Pain*, vol. 25, no. 7, 2024, ISSN: 15288447. DOI: 10.1016/j.jpain.2024.01.339.

[85] J. M. Berthelot, J. Nizard, and Y. Maugars, *The negative Hawthorne effect: Explaining pain overexpression*, 2019. DOI: 10.1016/j.jbspin.2018.10.003.

[86] L. A. Aaron, J. A. Turner, L. Mancl, H. Brister, and C. N. Sawchuk, "Electronic diary assessment of pain-related variables: Is reactivity a problem?" *Journal of Pain*, vol. 6, no. 2, 2005, ISSN: 15265900. DOI: 10.1016/j.jpain.2004.11.003.

[87] N. Attal, D. Bouhassira, and R. Baron, "Diagnosis and assessment of neuropathic pain through questionnaires," *The Lancet Neurology*, vol. 17, no. 5, pp. 456–466, 2018, ISSN: 1474-4422. DOI: https://doi.org/10.1016/S1474-4422(18)30071-1.

[88] N. Shaballout, A. Aloumar, T. A. Neubert, M. Dusch, and F. Beissner, "Digital pain drawings can improve doctors' understanding of acute pain patients: Survey and pain drawing analysis," *JMIR mHealth and uHealth*, vol. 7, no. 1, 2019, ISSN: 22915222. DOI: 10.2196/11412.

[89] J. Rosner et al., "Assessment of neuropathic pain after spinal cord injury using quantitative pain drawings," *Spinal Cord*, vol. 59, no. 5, 2021, ISSN: 14765624. DOI: 10.1038/s41393-021-00616-6.

[90] M. G. Villa, T. S. Palsson, A. C. Royo, C. R. Bjarkam, and S. A. Boudreau, "Digital Pain Mapping and Tracking in Patients with Chronic Pain: Longitudinal Study," *Journal of Medical Internet Research*, vol. 22, no. 10, 2020, ISSN: 14388871. DOI: 10.2196/21475.

[91] C. M. Brummett et al., "Preliminary validation of the Michigan Body Map," *Pain*, vol. 157, no. 6, 2016, ISSN: 18726623. DOI: 10.1097/j.pain.0000000000000506.

[92] S. C. Kirshblum et al., *The 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury*, 2011. DOI: 10.1179/107902611X13186000420242.

[93] M. Bressler et al., "Visualizing the Unseen: Illustrating and Documenting Phantom Limb Sensations and Phantom Limb Pain With C.A.L.A.," *Frontiers in Rehabilitation Sciences*, vol. 3, 2022, ISSN: 26736861. DOI: 10.3389/fresc.2022.806114.

[94] R. H. Dworkin et al., "Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2)," *PAIN*, vol. 144, no. 1, 2009, ISSN: 0304-3959.

[95] G. Lindsay, *Models of the Mind*. 2021. DOI: 10.5040/9781472966445.

[96] D. Marr, T. A. Poggio, and S. Ullman, *Vision : A Computational Investigation into the Human Representation and Processing of Visual Information.* (The MIT Press Ser). MIT Press, 2010, ISBN: 9780262289610.

[97] L. Acerbi, S. Vijayakumar, and D. M. Wolpert, "On the Origins of Suboptimality in Human Probabilistic Inference," *PLOS Computational Biology*, vol. 10, no. 6, e1003661, Jun. 2014. DOI: 10.1371/journal.pcbi.1003661.

[98] M. Berniker and K. Kording, "Estimating the sources of motor errors for adaptation and generalization," *Nature Neuroscience*, vol. 11, no. 12, pp. 1454–1461, 2008, ISSN: 1546-1726. DOI: 10.1038/nn.2229.

[99] R. E. Johnson, K. P. Kording, L. J. Hargrove, and J. W. Sensinger, "Adaptation to random and systematic errors: Comparison of amputee and non-amputee control interfaces with varying levels of process noise," *PLOS ONE*, vol. 12, no. 3, e0170473, Mar. 2017. DOI: 10.1371/journal.pone.0170473.

[100] D. Blustein, A. Shehata, K. Englehart, and J. Sensinger, "Conventional analysis of trial-by-trial adaptation is biased: Empirical and theoretical support using a Bayesian estimator," *PLOS Computational Biology*, vol. 14, no. 12, e1006501, Dec. 2018. DOI: 10.1371/journal.pcbi.1006501.

[101] D. H. Blustein, A. W. Shehata, E. S. Kuylenstierna, K. B. Englehart, and J. W. Sensinger, "An analytical method reduces noise bias in motor adaptation analysis," *Scientific Reports*, vol. 11, no. 1, p. 9245, 2021, ISSN: 2045-2322. DOI: 10.1038/s41598-021-88688-5.

[102] V. A. Lang, T. Lundh, and M. Ortiz-Catalan, "Mathematical and Computational Models for Pain: A Systematic Review," *Pain Medicine*, 2021, ISSN: 1526-2375. DOI: 10.1093/pm/pnab177.

[103] H. Minamitani and N. Hagita, "A Neural Network Model of Pain Mechanisms: Computer Simulation of the Central Neural Activities Essential for the Pain and Touch Sensations," *IEEE Transactions on Systems, Man and Cybernetics*, vol. 11, no. 7, pp. 481–493, 1981, ISSN: 21682909. DOI: 10.1109/TSMC.1981.4308725.

[104] J. Tigerholm et al., "Modeling activity-dependent changes of axonal spike conduction in primary afferent C-nociceptors," *Journal of Neurophysiology*, vol. 111, no. 9, pp. 1721–1735, Dec. 2013, ISSN: 0022-3077. DOI: 10.1152/jn.00777.2012.

[105] Y.-A. Rho and S. A. Prescott, "Identification of Molecular Pathologies Sufficient to Cause Neuropathic Excitability in Primary Somatosensory Afferents Using Dynamical Systems Theory," *PLOS Computational Biology*, vol. 8, no. 5, e1002524, May 2012.

[106] P. Aguiar, M. Sousa, and D. Lima, "NMDA Channels Together With L-Type Calcium Currents and Calcium-Activated Nonspecific Cationic Currents Are Sufficient to Generate Windup in WDR Neurons," *Journal of Neurophysiology*, vol. 104, no. 2, pp. 1155–1166, Jun. 2010, ISSN: 0022-3077. DOI: 10.1152/jn.00834.2009.

[107] T. C. Zhang, J. J. Janik, and W. M. Grill, "Modeling effects of spinal cord stimulation on wide-dynamic range dorsal horn neurons: influence of stimulation frequency and GABAergic inhibition," *Journal of Neurophysiology*, vol. 112, no. 3, pp. 552–567, Apr. 2014, ISSN: 0022-3077. DOI: 10.1152/jn.00254.2014.

[108] J. E. Arle, K. W. Carlson, L. Mei, N. Iftimia, and J. L. Shils, "Mechanism of dorsal column stimulation to treat neuropathic but not nociceptive pain: Analysis with a computational model," *Neuromodulation*, vol. 17, no. 7, 2014, ISSN: 15251403. DOI: 10.1111/ner.12178.

[109] L. Medlock, K. Sekiguchi, S. Hong, S. Dura-Bernal, W. W. Lytton, and S. A. Prescott, "Multiscale Computer Model of the Spinal Dorsal Horn Reveals Changes in Network Processing Associated with Chronic Pain," *The Journal of Neuroscience*, vol. 42, no. 15, 3133 LP –3149, Apr. 2022. DOI: 10.1523/JNEUROSCI.1199-21.2022.

[110] J. Crodelle, S. H. Piltz, M. H. Hagenauer, and V. Booth, "Modeling the daily rhythm of human pain processing in the dorsal horn," *PLOS Computational Biology*, vol. 15, no. 7, e1007106, Jul. 2019. DOI: 10.1371/journal.pcbi.1007106.

[111] J. Crodelle and P. D. Maia, *A Computational Model for Pain Processing in the Dorsal Horn Following Axonal Damage to Receptor Fibers*, 2021. DOI: 10.3390/brainsci11040505.

[112] F. J. Ropero Peláez and S. Taniguchi, "The Gate Theory of Pain Revisited: Modeling Different Pain Conditions with a Parsimonious Neurocomputational Model," eng, *Neural plasticity*, vol. 2016, p. 4 131 395, 2016, ISSN: 1687-5443. DOI: 10.1155/2016/4131395.

[113] M. Spitzer, P. Böhler, M. Weisbrod, and U. Kischka, "A neural network model of phantom limbs," *Biological Cybernetics*, vol. 72, no. 3, pp. 197–206, 1995, ISSN: 03401200. DOI: 10.1007/BF00201484.

[114] K. J. Boström, M. H. De Lussanet, T. Weiss, C. Puta, and H. Wagner, "A computational model unifies apparently contradictory findings concerning phantom pain," *Scientific Reports*, vol. 4, Jun. 2014, ISSN: 20452322. DOI: 10.1038/srep05298.

[115] A. Tabor, M. A. Thacker, G. L. Moseley, and K. P. Körding, "Pain: A Statistical Account," *PLOS Computational Biology*, vol. 13, no. 1, e1005142, Jan. 2017. DOI: 10.1371/journal.pcbi.1005142.

[116] B. Seymour and F. Mancini, "Hierarchical models of pain: Inference, information-seeking, and adaptive control.," *NeuroImage*, vol. 222, p. 117 212, 2020, ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2020.117212.

[117] Z. S. Chen and J. Wang, "Pain, from perception to action: A computational perspective," *iScience*, vol. 26, no. 1, Jan. 2023, ISSN: 2589-0042. DOI: 10.1016/j.isci.2022.105707.

[118] D. Anchisi and M. Zanon, "A Bayesian Perspective on Sensory and Cognitive Integration in Pain Perception and Placebo Analgesia," *PLOS ONE*, vol. 10, no. 2, e0117270, Feb. 2015. DOI: 10.1371/journal.pone.0117270.

[119] F. Mancini, S. Zhang, and B. Seymour, "Learning the statistics of pain: computational and neural mechanisms," *bioRxiv*, p. 2021.10.21.465270, Jan. 2021. DOI: 10.1101/2021.10.21.465270.

[120] T. Parr, G. Pezzulo, and K. J. Friston, *Active Inference: The Free Energy Principle in Mind, Brain, and Behavior*. MIT Press, Mar. 2022, ISBN: 9780262369978. DOI: 10.7551/mitpress/12441.001.0001.

[121] C. Milde, L. S. Brinskelle, and J. A. Glombiewski, *Does Active Inference Provide a Comprehensive Theory of Placebo Analgesia?* 2024. DOI: 10.1016/j.bpsc.2023.08.007.

[122] A. Sabrina Patania Tutor Giuseppe Boccignone, "ON THE PROBABILISTIC MODELLING OF PAIN SSD 01/B1," ISSN: 2022-2023.

[123] B. Seymour, "Pain: A Precision Signal for Reinforcement Learning and Control," *Neuron*, vol. 101, no. 6, pp. 1029–1041, Mar. 2019, ISSN: 0896-6273. DOI: 10.1016/j.neuron.2019.01.055.

[124] B. Seymour et al., "Temporal difference models describe higher-order learning in humans," *Nature*, vol. 429, no. 6992, pp. 664–667, 2004, ISSN: 1476-4687. DOI: 10.1038/nature02581.

[125] B. Seymour et al., "Opponent appetitive-aversive neural processes underlie predictive learning of pain relief," *Nature Neuroscience*, vol. 8, no. 9, pp. 1234–1240, 2005, ISSN: 1546-1726. DOI: 10.1038/nn1527.

[126] O. Wang, S. W. Lee, J. O'Doherty, B. Seymour, and W. Yoshida, "Model-based and model-free pain avoidance learning," *Brain and Neuroscience Advances*, vol. 2, 2018, ISSN: 2398-2128. DOI: 10.1177/2398212818772964.

[127] R. Freynhagen, R. Baron, U. Gockel, and T. R. Tölle, "painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain," *Current Medical Research and Opinion*, vol. 22, no. 10, pp. 1911–1920, Oct. 2006, ISSN: 0300-7995. DOI: 10.1185/030079906X132488.

[128] R. Portenoy, "Development and testing of a neuropathic pain screening questionnaire: ID Pain," *Current Medical Research and Opinion*, vol. 22, no. 8, pp. 1555–1565, Aug. 2006, ISSN: 0300-7995. DOI: 10.1185/030079906X115702.

[129] D. Bouhassira et al., "Development and validation of the Neuropathic Pain Symptom Inventory," *PAIN*, vol. 108, no. 3, 2004, ISSN: 0304-3959. DOI: 10.1016/j.pain.2003.12.024.

[130] A. L. McDaniel et al., "Psychophysics of Pain: A Methodological Introduction," *Pain Management Nursing*, vol. 24, no. 4, 2023, ISSN: 15249042. DOI: 10.1016/j.pmn.2023.02.006.

[131] A. V. Apkarian, *The brain adapting with pain: Contribution of neuroimaging technology to pain mechanisms*. 2015.

[132] R. D. Lange, A. Chattoraj, J. M. Beck, J. L. Yates, and R. M. Haefner, "A confirmation bias in perceptual decision-making due to hierarchical approximate inference," *PLOS Computational Biology*, vol. 17, no. 11, e1009517, Nov. 2021.

[133] D. A. P. Nunes, J. Ferreira-Gomes, F. Neto, A. V. Apkarian, P. Branco, and D. Martins De Matos, "Language as a Predictor of Multiple Clinical Chronic Pain Assessments," Tech. Rep.

[134] A. Stankevicius, S. B. Wallwork, S. J. Summers, B. Hordacre, and T. R. Stanton, "Prevalence and incidence of phantom limb pain, phantom limb sensations and telescoping in amputees: A systematic rapid review," *European Journal of Pain*, vol. 25, no. 1, pp. 23–38, Jan. 2021, ISSN: 1090-3801. DOI: https://doi.org/10.1002/ejp.1657.

[135] B. W. Friedman et al., "Predicting the Transition to Chronic Pain 6 Months After an Emergency Department Visit for Acute Pain: A Prospective Cohort Study," *The Journal of Emergency Medicine*, vol. 59, no. 6, pp. 805–811, 2020, ISSN: 0736-4679. DOI: https://doi.org/10.1016/j.jemermed.2020.07.016.

[136] J. M. Stevans et al., "Risk Factors Associated With Transition From Acute to Chronic Low Back Pain in US Patients Seeking Primary Care," *JAMA Network Open*, vol. 4, no. 2, e2037371–e2037371, Feb. 2021, ISSN: 2574-3805. DOI: 10.1001/jamanetworkopen.2020.37371.

[137] C. Gummesson et al., "The transition of reported pain in different body regions – a one-year follow-up study," *BMC Musculoskeletal Disorders*, vol. 7, no. 1, p. 17, 2006, ISSN: 1471-2474. DOI: 10.1186/1471-2474-7-17.

[138] M. Ramne, L. Steinmeier, and S. Damercheli, *Phantom sensations and pain in non-limbs: a systematic literature search*, 2025. DOI: 10.5281/zenodo.15573482.

[139] A. N. Graham, C. G. Ryan, A. MacSween, G. Atkinson, S. Smith, and D. J. Martin, "The Test–Retest Reliability of Pain Outcome Measures in People With Phantom Limb Pain," *Clinical Journal of Pain*, vol. 40, no. 8, pp. 490–496, Apr. 2024, ISSN: 15365409. DOI: 10.1097/AJP.0000000000001219.

[140] G. A. Dumanian et al., "Targeted Muscle Reinnervation Treats Neuroma and Phantom Pain in Major Limb Amputees: A Randomized Clinical Trial," *Annals of Surgery*, vol. 270, no. 2, 2019, ISSN: 15281140. DOI: 10.1097/SLA.0000000000003088.

[141] S. L. Woo, T. A. Kung, D. L. Brown, J. A. Leonard, B. M. Kelly, and P. S. Cederna, "Regenerative peripheral nerve interfaces for the treatment of postamputation neuroma pain: A pilot study," *Plastic and Reconstructive Surgery - Global Open*, vol. 4, no. 12, 2016, ISSN: 21697574. DOI: 10.1097/GOX.0000000000001038.

[142] E. Pettersen et al., "Surgical treatments for postamputation pain: study protocol for an international, double-blind, randomised controlled trial," *Trials*, no. 24, May 2023. DOI: 10.1186/s13063-023-07286-0.

[143] N. Birbaumer et al., "Effects of Regional Anesthesia on Phantom Limb Pain Are Mirrored in Changes in Cortical Reorganization," *The Journal of Neuroscience*, vol. 17, no. 14, 5503 LP –5508, Jul. 1997. DOI: 10.1523/JNEUROSCI.17-14-05503.1997.

[144] A. Vaso et al., "Peripheral nervous system origin of phantom limb pain," *Pain*, vol. 155, no. 7, pp. 1384–1391, 2014, ISSN: 18726623. DOI: 10.1016/j.pain.2014.04.018.

[145] B. Borghi et al., "The Use of Prolonged Peripheral Neural Blockade After Lower Extremity Amputation: The Effect on Symptoms Associated with Phantom Limb Syndrome," *Anesthesia & Analgesia*, vol. 111, no. 5, 2010, ISSN: 0003-2999.

[146] P. E. Grant et al., "Analgesia after dorsal root ganglionic injection under CT-guidance in a patient with intractable phantom limb pain," *Pain Medicine*, pnad039, Mar. 2023, ISSN: 1526-4637. DOI: 10.1093/pm/pnad039.

[147] Q. Zheng et al., "Synchronized cluster firing, a distinct form of sensory neuron activation, drives spontaneous pain," *Neuron*, vol. 110, no. 2, pp. 209–220, Jan. 2022, ISSN: 0896-6273. DOI: 10.1016/j.neuron.2021.10.019.

[148] H. Flor et al., "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation," *Nature*, vol. 375, no. 6531, pp. 482–484, 1995, ISSN: 1476-4687. DOI: 10.1038/375482a0.

[149] A. Karl, N. Birbaumer, W. Lutzenberger, L. G. Cohen, and H. Flor, "Reorganization of Motor and Somatosensory Cortex in Upper Extremity Amputees with Phantom Limb Pain," *The Journal of Neuroscience*, vol. 21, no. 10, 3609 LP –3618, May 2001. DOI: 10.1523/JNEUROSCI.21-10-03609.2001.

[150] M. Lotze, H. Flor, W. Grodd, W. Larbig, and N. Birbaumer, "Phantom movements and pain An fMRI study in upper limb amputees," *Brain*, vol. 124, no. 11, pp. 2268–2277, Nov. 2001, ISSN: 0006-8950. DOI: 10.1093/brain/124.11.2268.

[151] E. Huse, W. Larbig, H. Flor, and N. Birbaumer, "The effect of opioids on phantom limb pain and cortical reorganization," *Pain*, vol. 90, no. 1-2, 2001, ISSN: 03043959. DOI: 10.1016/S0304-3959(00)00385-7.

[152] S. M. Grüsser et al., "The relationship of perceptual phenomena and cortical reorganization in upper extremity amputees," *Neuroscience*, vol. 102, no. 2, 2001, ISSN: 03064522. DOI: 10.1016/S0306-4522(00)00491-7.

[153] J. Foell, R. Bekrater-Bodmann, M. Diers, and H. Flor, "Mirror therapy for phantom limb pain: Brain changes and the role of body representation," *European Journal of Pain*, vol. 18, no. 5, pp. 729–739, May 2014, ISSN: 1090-3801. DOI: https://doi.org/10.1002/j.1532-2149.2013.00433.x.

[154] E. Raffin, N. Richard, P. Giraux, and K. T. Reilly, "Primary motor cortex changes after amputation correlate with phantom limb pain and the ability to move the phantom limb," *NeuroImage*, vol. 130, pp. 134–144, Apr. 2016, ISSN: 10959572. DOI: 10.1016/j.neuroimage.2016.01.063.

[155] K. MacIver, D. M. Lloyd, S. Kelly, N. Roberts, and T. Nurmikko, "Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery," *Brain*, vol. 131, no. 8, 2008, ISSN: 00068950. DOI: 10.1093/brain/awn124.

[156] T. R. Makin, J. Scholz, N. Filippini, D. Henderson Slater, I. Tracey, and H. Johansen-Berg, "Phantom pain is associated with preserved structure and function in the former hand area," *Nature Communications*, vol. 4, no. 1, p. 1570, 2013, ISSN: 2041-1723. DOI: 10.1038/ncomms2571.

[157] T. R. Makin, J. Scholz, D. Henderson Slater, H. Johansen-Berg, and I. Tracey, "Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation," *Brain*, vol. 138, no. 8, pp. 2140–2146, Aug. 2015, ISSN: 0006-8950. DOI: 10.1093/brain/awv161.

[158] S. Kikkert, H. Johansen-Berg, I. Tracey, and T. R. Makin, "Reaffirming the link between chronic phantom limb pain and maintained missing hand representation," *Cortex*, vol. 106, pp. 174–184, 2018, ISSN: 0010-9452. DOI: https://doi.org/10.1016/j.cortex.2018.05.013.

[159] P. Schwenkreis et al., "Assessment of reorganization in the sensorimotor cortex after upper limb amputation," *Clinical Neurophysiology*, vol. 112, no. 4, pp. 627–635, 2001, ISSN: 1388-2457. DOI: https://doi.org/10.1016/S1388-2457(01)00486-2.

[160] B.-X. Zheng et al., "Altered Cortical Reorganization and Brain Functional Connectivity in Phantom Limb Pain: A Functional MRI Study," *Pain Practice*, vol. 21, no. 4, pp. 394–403, Apr. 2021, ISSN: 1530-7085. DOI: https://doi.org/10.1111/papr.12966.

[161] P. Schwenkreis et al., "Reorganization in the ipsilateral motor cortex of patients with lower limb amputation," *Neuroscience Letters*, vol. 349, no. 3, 2003, ISSN: 03043940. DOI: 10.1016/S0304-3940(03)00838-3.

[162] M. M. Merzenich, J. H. Kaas, J. Wall, R. J. Nelson, M. Sur, and D. Felleman, "Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation," *Neuroscience*, vol. 8, no. 1, 1983, ISSN: 03064522. DOI: 10.1016/0306-4522(83)90024-6.

[163] P. Sörös et al., "Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography," *Neuroscience Letters*, vol. 298, no. 3, pp. 195–198, 2001, ISSN: 0304-3940. DOI: https://doi.org/10.1016/S0304-3940(00)01752-3.

[164] D. B. Wesselink et al., "Malleability of the cortical hand map following a finger nerve block," *Science Advances*, vol. 8, no. 16, eabk2393, Jun. 2022. DOI: 10.1126/sciadv.abk2393.

[165] S. Kikkert, M. Mezue, D. Henderson Slater, H. Johansen-Berg, I. Tracey, and T. R. Makin, "Motor correlates of phantom limb pain," *Cortex*, vol. 95, pp. 29–36, 2017, ISSN: 0010-9452. DOI: https://doi.org/10.1016/j.cortex.2017.07.015.

[166] M. Diers, C. Christmann, C. Koeppe, M. Ruf, and H. Flor, "Mirrored, imagined and executed movements differentially activate sensorimotor cortex in amputees with and without phantom limb pain," *PAIN*, vol. 149, no. 2, 2010, ISSN: 0304-3959.

[167] J. Andoh et al., "Assessment of cortical reorganization and preserved function in phantom limb pain: a methodological perspective," *Scientific Reports*, vol. 10, no. 1, pp. 1–15, 2020, ISSN: 20452322. DOI: 10.1038/s41598-020-68206-9.

[168] H. R. Schone et al., "Stable cortical body maps before and after arm amputation," *Nature Neuroscience*, Oct. 2025, ISSN: 15461726. DOI: 10.1038/s41593-025-02037-7.

[169] T. R. Makin and H. Flor, "Brain (re)organisation following amputation: Implications for phantom limb pain," *NeuroImage*, vol. 218, p. 116 943, 2020, ISSN: 1053-8119. DOI: https://doi.org/10.1016/j.neuroimage.2020.116943.

[170] A. J. Harris, "Cortical origin of pathological pain," *The Lancet*, vol. 354, no. 9188, pp. 1464–1466, Oct. 1999, ISSN: 0140-6736. DOI: 10.1016/S0140-6736(99)05003-5.

[171] V. S. Ramachandran and D. Rogers-Ramachandran, "Synaesthesia in phantom limbs induced with mirrors," *Proceedings of the Royal Society of London. Series B: Biological Sciences*, vol. 263, no. 1369, pp. 377–386, Jan. 1997. DOI: 10.1098/rspb.1996.0058.

[172] C. S. McCabe, R. C. Haigh, P. W. Halligan, and D. R. Blake, "Simulating sensory–motor incongruence in healthy volunteers: implications for a cortical model of pain," *Rheumatology*, vol. 44, no. 4, pp. 509–516, Apr. 2005, ISSN: 1462-0324. DOI: 10.1093/rheumatology/keh529.

[173] L. Herrador Colmenero et al., "Effectiveness of mirror therapy, motor imagery, and virtual feedback on phantom limb pain following amputation: A systematic review," *Prosthetics and Orthotics International*, vol. 42, no. 3, 2018, ISSN: 0309-3646. DOI: 10.1177/0309364617740230.

[174] M. Gagné, K. T. Reilly, S. Hétu, and C. Mercier, "Motor control over the phantom limb in above-elbow amputees and its relationship with phantom limb pain," *Neuroscience*, vol. 162, no. 1, pp. 78–86, Aug. 2009, ISSN: 0306-4522. DOI: 10.1016/j.neuroscience.2009.04.061.

[175] M. Ortiz-Catalan et al., "Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: a single group, clinical trial in patients with chronic intractable phantom limb pain," *The Lancet*, vol. 6736, no. 16, 2016. DOI: 10.1016/S0140-6736(16)31598-7.

[176] T. Weiss, H. Koehler, and I. Croy, "Pain and Reorganization after Amputation: Is Interoceptive Prediction a Key?" *Neuroscientist*, vol. 29, no. 6, 2023, ISSN: 10894098. DOI: 10.1177/10738584221112591.

[177] C. Peirs et al., "Dorsal Horn Circuits for Persistent Mechanical Pain," *Neuron*, vol. 87, no. 4, pp. 797–812, Aug. 2015, ISSN: 0896-6273. DOI: 10.1016/j.neuron.2015.07.029.

[178] M. Ortiz-Catalan, "The stochastic entanglement and phantom motor execution hypotheses: A theoretical framework for the origin and treatment of Phantom limb pain," *Frontiers in Neurology*, vol. 9, no. SEP, Sep. 2018, ISSN: 16642295. DOI: 10.3389/fneur.2018.00748.

[179] K. Fisher, S. Oliver, I. Sedki, and R. Hanspal, "The effect of electromagnetic shielding on phantom limb pain: A placebo-controlled double-blind crossover trial," *Prosthetics and Orthotics International*, vol. 40, no. 3, 2016, ISSN: 17461553. DOI: 10.1177/0309364614568409.

[180] M. Alrabayah, A. B. Qaswal, A. Suleiman, and L. Khreesha, "Role of Potassium Ions Quantum Tunneling in the Pathophysiology of Phantom Limb Pain," DOI: 10.3390/brainsci10040241.

[181] M. J. M. Alviar, T. Hale, and M. Dungca, *Pharmacologic interventions for treating phantom limb pain*, 2016. DOI: 10.1002/14651858.CD006380.pub3.

[182] L. Nikolajsen, *Postamputation pain: Studies on mechanisms*. 2012, vol. 59.

[183] E. Raffin, P. Giraux, and K. T. Reilly, "The moving phantom: Motor execution or motor imagery?" *Cortex*, vol. 48, no. 6, 2012, ISSN: 00109452. DOI: 10.1016/j.cortex.2011.02.003.

[184] C. Richardson, S. Glenn, T. Nurmikko, and M. Horgan, "Incidence of phantom phenomena including phantom limb pain 6 months after major lower limb amputation in patients with peripheral vascular disease," *Clinical Journal of Pain*, vol. 22, no. 4, 2006, ISSN: 07498047. DOI: 10.1097/01.ajp.0000177793.01415.bd.

[185] P. U. Dijkstra, J. H. B. Geertzen, R. Stewart, and C. P. van der Schans, "Phantom Pain and Risk Factors: A Multivariate Analysis," *Journal of Pain and Symptom Management*, vol. 24, no. 6, pp. 578–585, 2002, ISSN: 0885-3924. DOI: 10.1016/S0885-3924(02)00538-9.

[186] M. Poor Zamany Nejat Kermany, E. Modirian, M. Soroush, M. Masoumi, and M. Hosseini, "Phantom limb sensation (PLS) and phantom limb pain (PLP) among young landmine amputees," *Iranian Journal of Child Neurology*, vol. 10, no. 3, 2016, ISSN: 20080700.

[187] G. D. Shukla, S. C. Sahu, R. P. Tripathi, and D. K. Gupta, "Phantom limb: A phenomenological study," *British Journal of Psychiatry*, vol. 141, no. 1, 1982, ISSN: 00071250. DOI: 10.1192/bjp.141.1.54.

[188] P. L. Ephraim, S. T. Wegener, E. J. MacKenzie, T. R. Dillingham, and L. E. Pezzin, "Phantom pain, residual limb pain, and back pain in amputees: Results of a national survey," *Archives of Physical Medicine and Rehabilitation*, vol. 86, no. 10, 2005, ISSN: 00039993. DOI: 10.1016/j.apmr.2005.03.031.

[189] J. H. Davidson, K. E. Khor, and L. E. Jones, "A cross-sectional study of post-amputation pain in upper and lower limb amputees, experience of a tertiary referral amputee clinic," *Disability and Rehabilitation*, vol. 32, no. 22, 2010, ISSN: 09638288. DOI: 10.3109/09638281003734441.

[190] A. Gardetto et al., "Reduction of phantom limb pain and improved proprioception through a tsr-based surgical technique: A case series of four patients with lower limb amputation," *Journal of Clinical Medicine*, vol. 10, no. 17, 2021, ISSN: 20770383. DOI: 10.3390/jcm10174029.

[191] S. S. Srinivasan et al., "Neural interfacing architecture enables enhanced motor control and residual limb functionality postamputation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 118, no. 9, 2021, ISSN: 10916490. DOI: 10.1073/pnas.2019555118.

[192] J. T. Mauch, D. S. Kao, J. L. Friedly, and Y. Liu, "Targeted muscle reinnervation and regenerative peripheral nerve interfaces for pain prophylaxis and treatment: A systematic review," *PM&R*, vol. 15, no. 11, pp. 1457–1465, Nov. 2023, ISSN: 1934-1482. DOI: 10.1002/pmrj.12972.

[193] A. Hagiga, M. Aly, M. Gumaa, A. Rehan Youssef, and T. Cubison, *Targeted muscle reinnervation in managing post-amputation related pain: A systematic review and meta-analysis*, 2023. DOI: 10.1111/papr.13262.

[194] J. Bishay, I. Yeap, and T. Wang, *The effectiveness of targeted muscle reinnervation in reducing pain and improving quality of life for patients following lower limb amputation*, 2024. DOI: 10.1016/j.bjps.2024.03.013.

[195] J. Carter, P. Richardson, H. Stark, and J. Henton, *Regenerative peripheral nerve interface in the prevention and treatment of post-amputation pain: a systematic review*, 2024. DOI: 10.1007/s00238-024-02167-4.

[196] S. Goyal, A. Kumar, M. Kantha, R. S. Sharma, S. Agrawal, and G. K. Singh, "Ultrasound-guided Stellate Ganglion Block for Upper Extremity Phantom Limb Pain - A Case Series," *Indian Journal of Pain*, vol. 38, no. 1, 2024, ISSN: 23217820. DOI: 10.4103/ijpn.ijpn{_}111{_}23.

[197] B. N. Perry et al., "Clinical trial of the virtual integration environment to treat phantom limb pain with upper extremity amputation," *Frontiers in Neurology*, vol. 9, no. SEP, 2018, ISSN: 16642295. DOI: 10.3389/fneur.2018.00770.

[198] E. Lendaro et al., "Extended reality used in the treatment of phantom limb pain: a multicenter, double-blind, randomized controlled trial," *Pain*, vol. 166, no. 3, pp. 571–586, Mar. 2025, ISSN: 18726623. DOI: 10.1097/j.pain.0000000000003384.

[199] Chan B. L. et al., "Mirror Therapy for Phantom Limb Pain," *New England Journal of Medicine*, no. 357;21, Nov. 2007. DOI: 10.1056/nejmc071927.

[200] G. Beaumont, C. Mercier, P. E. Michon, F. Malouin, and P. L. Jackson, "Decreasing Phantom Limb Pain Through Observation of Action and Imagery: A Case Series," *Pain Medicine*, vol. 12, no. 2, 2011, ISSN: 15264637. DOI: 10.1111/j.1526-4637.2010.01048.x.

[201] K. Wiech, J. Vandekerckhove, J. Zaman, F. Tuerlinckx, J. W. S. Vlaeyen, and I. Tracey, "Influence of prior information on pain involves biased perceptual decision-making," *Current Biology*, vol. 24, no. 15, R679–R681, 2014, ISSN: 0960-9822. DOI: https://doi.org/10.1016/j.cub.2014.06.022.

[202] A. Grahl, S. Onat, and C. Büchel, "The periaqueductal gray and Bayesian integration in placebo analgesia," *eLife*, vol. 7, K. E. Stephan, Ed., e32930, 2018, ISSN: 2050-084X. DOI: 10.7554/eLife.32930.

[203] R. Hoskin, C. Berzuini, D. Acosta-Kane, W. El-Deredy, H. Guo, and D. Talmi, "Sensitivity to pain expectations: A Bayesian model of individual differences," *Cognition*, vol. 182, pp. 127–139, 2019, ISSN: 0010-0277. DOI: doi.org/10.1016/j.cognition.2018.08.022.

[204] A. Drusko et al., "A novel computational approach to pain perception modelling within a Bayesian framework using quantitative sensory testing," *Scientific Reports*, vol. 13, no. 1, p. 3196, 2023, ISSN: 2045-2322. DOI: 10.1038/s41598-023-29758-8.

[205] W. Yoshida, B. Seymour, M. Koltzenburg, and R. J. Dolan, "Uncertainty Increases Pain: Evidence for a Novel Mechanism of Pain Modulation Involving the Periaqueductal Gray," *The Journal of Neuroscience*, vol. 33, no. 13, 5638 LP –5646, Mar. 2013. DOI: 10.1523/JNEUROSCI.4984-12.2013.

[206] J. Zaman, W. Vanpaemel, C. Aelbrecht, F. Tuerlinckx, and J. W. Vlaeyen, "Biased pain reports through vicarious information: A computational approach to investigate the role of uncertainty," *Cognition*, vol. 169, 2017, ISSN: 18737838. DOI: 10.1016/j.cognition.2017.07.009.

[207] A. Strube, M. Rose, S. Fazeli, and C. Büchel, "The temporal and spectral characteristics of expectations and prediction errors in pain and thermoception," *eLife*, vol. 10, P. Kok, F. P. de Lange, and E. Schulz, Eds., e62809, 2021, ISSN: 2050-084X. DOI: 10.7554/eLife.62809.

[208] M. Habermann and C. Büchel, "Effects of Predictability and Controllability on Pain Perception," 2022. DOI: 10.32470/ccn.2022.1169-0.

[209] G. A. Cecchi et al., "Predictive Dynamics of Human Pain Perception," *PLoS Computational Biology*, vol. 8, no. 10, Oct. 2012, ISSN: 1553734X. DOI: 10.1371/journal.pcbi.1002719.

[210] F. Mancini, S. Zhang, and B. Seymour, "Computational and neural mechanisms of statistical pain learning," *Nature Communications*, vol. 13, no. 1, p. 6613, 2022, ISSN: 2041-1723. DOI: 10.1038/s41467-022-34283-9.

[211] T. C. Zhang, J. J. Janik, and W. M. Grill, "Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain," *Brain Research*, vol. 1569, pp. 19–31, 2014, ISSN: 0006-8993. DOI: 10.1016/j.brainres.2014.04.039.

[212] N. F. Britton and S. M. Skevington, "A Mathematical Model of the Gate Control Theory of Pain," Tech. Rep., 1989, pp. 91–105.

[213] W. Fink and R. B. Raffa, "A Pluripotent Progression of the Gate Control System Theory of Pain–Modeling Ascending & Descending Pain Pathways as a Lotka-Volterra Coupled Control & Feedback Loop," *Journal of Pain Research*, vol. 18, 2025, ISSN: 11787090. DOI: 10.2147/JPR.S525449.

[214] W. Fink and R. B. Raffa, "A Pain Memory "Trace": Cumulative Pain Perception and Damping During Fight-or-Flight Response Modeled with a Lotka-Volterra-Style Coupled Feedback Control Loop System," *Journal of Pain Research*, vol. 19, pp. 1–11, 2026, ISSN: 11787090. DOI: 10.2147/JPR.S561278.

[215] Y. A. Rho and S. A. Prescott, "Identification of molecular pathologies sufficient to cause neuropathic excitability in primary somatosensory afferents using dynamical systems theory," *PLoS Computational Biology*, vol. 8, no. 5, May 2012, ISSN: 1553734X. DOI: 10.1371/journal.pcbi.1002524.

[216] O. E. Dick, B. V. Krylov, and A. D. Nozdrachev, "Possible mechanism of bursting suppression in nociceptive neurons," *Doklady Biochemistry and Biophysics*, vol. 473, no. 1, 2017, ISSN: 16076729. DOI: 10.1134/S1607672917020120.

[217] O. E. Dick, "Mechanisms of dynamical complexity changes in patterns of sensory neurons under antinociceptive effect emergence," *Neurocomputing*, vol. 378, pp. 120–128, Feb. 2020, ISSN: 18728286. DOI: 10.1016/j.neucom.2019.10.004.

[218] F. Xu, T. Wen, K. Seffen, and T. Lu, "Modeling of skin thermal pain: A preliminary study," *Applied Mathematics and Computation*, vol. 205, no. 1, pp. 37–46, Nov. 2008, ISSN: 00963003. DOI: 10.1016/j.amc.2008.05.045.

Table 6.1: References from Table 4.2.

In table	In bibliography
(Nikolajsen, 2012)	[182]
(Limakatso et al., 2020)	[4]
(Stankevicious et al., 2021)	[134]
(Ramne et al., 2025)	[138]
(Gagne et al., 2009)	[174]
(Raffin et al., 2012)	[183]
(Raffin et al., 2016)	[154]
(Kikkert et al., 2017)	[165]
(Richardson et al., 2006)	[184]

Table 6.2: References from Table 4.3.

In table	In bibliography
(Nikolajsen, 2012)	[182]
(Limakatso et al., 2020)	[4]
(Richardson et al., 2006)	[184]
(Dijkstra et al., 2002)	[185]
(Poor Zamany Nejat Kermany et al., 2016)	[186]
(Shukla et al., 1982)	[187]
(Ephraim et al., 2005)	[188]
(Davidson et al., 2010)	[189]

Table 6.3: References from Table 4.4.

In table	In bibliography
(Gardetto et al., 2021)	[190]
(Srinivasan et al., 2021)	[191]
(Mauch & Kao, 2023)	[192]
(Hagiga et al., 2023)	[193]
(Bishay et al., 2024)	[194]
(Carter et al, 2024)	[195]
(Birbaumer et al., 1997)	[143]
(Vaso et al., 2014)	[144]
(Zheng et al., 2022)	[147]
(Grant et al., 2023)	[146]
(Goyal et al., 2024)	[196]
(Ortiz-Catalan et al., 2016)	[175]
(Perry et al., 2018)	[197]
(Lendaro et al., 2025)	[198]
(Chan et al., 2007)	[199]
(Beaumont et al., 2011)	[200]
(Foell et al, 2014)	[153]
(Herrador Colmenaro et al, 2017)	[173]

Table 6.4: References from Table 4.5.

In table	In bibliography
(Flor et al., 1995)	[148]
(Birbaumer et al., 1997)	[143]
(Lotze et al., 2001)	[150]
(Karl et al., 2001)	[149]
(Grusser et al., 2001)	[152]
(Foell et al., 2014)	[153]
(Raffin et al., 2016)	[154]
(Makin et al., 2015)	[157]
(Schone et al, 2025)	[168]
(MacIver et al., 2008)	[155]
(Makin et al., 2013)	[156]
(Schwenkreis et al., 2001)	[159]
(Zheng et al., 2021)	[160]
(Schwenkreis et al., 2003)	[161]
(Kikkert et al., 2017)	[165]
(Kikkert et al., 2018)	[158]
(Diers et al., 2010)	[166]
(Andoh et al., 2020)	[167]

Table 6.5: References from Figure 3.2.

In figure	In bibliography
(Wiech et al., 2014)	[201]
(Anchisi & Zanon, 2015)	[118]
(Jepma et al., 2018)	[75]
(Grahl et al., 2018)	[202]
(Hoskin et al., 2019)	[203]
(Drusko et al., 2023)	[204]
(Wang et al., 2018)	[126]
(Yoshida et al., 2013)	[205]
(Zaman et al., 2017)	[206]
(Strube et al., 2021)	[207]
(Habermann et al., 2022)	[208]
(Cecchi et al., 2012)	[209]
(Mancini et al., 2022)	[210]
(Seymour et al., 2004)	[124]
(Seymour et al., 2005)	[125]
(Eckert et al., 2022)	[74]
(Minamitani & Hagita, 1981)	[103]
(Boström et al., 2014)	[114]
(Aguiar et al., 2010)	[106]
(Zhang et al., 2014)	[211]
(Crodelle et al., 2019)	[110]
(Ropero Peláez & Taniguchi, 2016)	[112]
(Arle et al., 2014)	[108]
(Britton & Skevington, 1989)	[212]
(Fink & Raffe, 2025)	[213]
(Fink & Raffe, 2026)	[214]
(Crodelle & Maia, 2021)	[111]
(Medlock et al., 2022)	[109]
(Tigerholm et al., 2012)	[104]
(Rho & Prescott, 2012)	[215]
(Dick et al., 2017)	[216]
(Dick, 2020)	[217]
(Xu et al., 2008)	[218]

Part II

Papers