



A Bayesian Model for Chronic Pain

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- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
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PHILIPPS-UNIVERSITY MARBURG

Abstract

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by Anna-Lena ECKERT

Introduction. Pain is ubiquitous in most living creatures and ensures survival through its protective function. Chronic pain, however, has lost its functionality. Recent ideas regarding the etiology of chronic pain originate in statistical and computational frameworks. Here, pain perception is viewed as emerging from a Bayesian combination of prior expectations and sensory information. Chronic pain conditions might develop from suboptimal settings or events within this computational process. As a consequence, patients find themselves in a persistent state of threat-signaling pain.

Methods. To test this idea, we describe a machine-learning model for chronic pain which is based on a hierarchical Hidden Markov Model (HMM). In this probabilistic Bayesian graphical model, belief propagation and free-energy learning is implemented to simulate dysfunctional changes towards a state of chronic pain over time.

Results. Simulations suggest that chronic pain can be simulated by a combination of increased prior expectations of pain and suboptimal associations between sensory information and pain. The models were fit to questionnaire data of N=35 children and adolescents with and without chronic pain who answered questions regarding their pain-related expectations. Results indicate that a hierarchical model where the expected pain is associated with a certain context or time of day represents patterns in the data most adequately. Further, the model selection suggests group differences regarding the association between interoceptive sensations and pain perception.

Conclusion. We propose a computational model for chronic pain, adopting an interoceptive predictive coding perspective on pain perception. Simulations and a model selection procedure are described and implications of these results for clinical practice are discussed. Extensions towards other mental conditions are outlined.

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Chapter 1

Theoretical Background

1.1 Introduction: Pain

To be in physical pain is to find yourself in a different realm - a state of being unlike any other, a magic mountain as far removed from the familiar world as a dreamscape. Usually, pain subsides, one wakes from it as from a nightmare, trying to forget it as quickly as possible. But what if pain that persists? The longer it endures, the more excruciating the exile becomes. Will you ever go home? you begin to wonder, home to your normal body, thoughts, life?

Melanie Thernstrom, *The Pain Chronicles: Cures, Myths, Mysteries, Prayers, Diaries, Brain Scans and the Science of Suffering*. (New York: Farrar, Straus and Giroux; 2010, p3)

Pain is a ubiquitous phenomenon in many creatures. The above quote from Melanie Thernstrom draws a rather pessimistic image of pain as a distressing experience, leaving the individual detached from its surroundings and consumed by its aversive experience. Despite its distressing emotional consequences, pain has a clear benevolent and adaptive function. Painful experiences demand immediate attention and a behavior that results in, or could result in, injury is withdrawn from reflexively. This type of pain is also referred to as nociceptive pain (Basbaum et al., 2009; Woolf, 2010). A lack of nociceptive pain, as present in individuals with 'congenital insensitivity to pain', illustrates its adaptive, threat-signaling function. Individuals with this very rare abnormality are not able to perceive pain from birth (Schon, Parker, and Woods, 1993). As a consequence of this, they frequently present to physicians with self-mutilation injuries of the fingers, cuts, burns and bruises (Nagasako, Oaklander, and Dworkin, 2003; Schon, Parker, and Woods, 1993). Hence, a lack of nociceptive pain poses serious threats to an individuals' physical integrity.

Further, pain can promote recovery after an injury by discouraging moving or touching the injured body part. This second type of pain is also referred to as inflammatory pain (Flor and Turk, 2015; Woolf, 2010). Healing processes are supported by means of a heightened sensitivity to pain after tissue damage, which makes otherwise innocuous stimuli subjectively aversive (Kidd and Urban, 2001). This is referred to as 'hyperalgesia' (i.e., increased pain responses to noxious or harmless stimuli) and discourages, for example, touching an open wound or sunburn which in turn can reduce the risk of bacteria transmission and infection.

However, pain experiences also occur without a clear underlying physical pathology. In this context, the pain experience is dysfunctional as it is devoid of the signaling function that characterizes nociceptive and inflammatory pain. Experts refer to this as persistent or chronic pain. Before turning to the nature and prevalence of chronic pain, basic concepts and terms related to pain are introduced in the next paragraph.

1.2 Pain: terminology and theoretical concepts

One widely used definition of pain is given by the International Association for the study of Pain (IASP) that describes pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Wall, 1979). This definition encompasses several interesting concepts. First, it defines pain as an ‘experience’ which highlights its subjective nature and makes it conceptually different from nociception. Nociception is the term used to describe the ‘transduction and transmission of a noxious stimulus to the brain via the pain pathway’ (Steeds, 2016). Secondly, the above definition does not incorporate a pain-initiating stimulus. Indeed, a large body of research suggests a non-linear, ambiguous relationship between pain perception and actual bodily damage, or nociception (Moseley and Butler, 2015; Tabor et al., 2017). Simple stimulus-response models are deemed inappropriate. Instead, pain perception is assumed to be subject to the modulatory influence of a multitude of interacting, individual and subjective (e.g., cognitive, attentional, motivational, individual) factors (Loeser and Melzack, 1999; Steeds, 2016).

The idea of a non-linear relationship between nociceptive stimulation and pain perception evolved over several millennia. Initial ideas date back to the Cartesian mind-body dualism. In his treatise about the human (*'l'homme'*), Descartes (ca. 1644) was one of the first to propose a detailed somatosensory pain system (Moayedi and Davis, 2013). Herein, he described pain as a perception within the brain that is distinctive from the neural transduction of the pain signal (today, a.k.a. nociception) via hollow nerve fibers. Very figuratively, Descartes proposed that pain had a function equivalent to a bell ringing in the brain in response to a pull on a thread (i.e. the nerve fiber) at the location where harmful stimulation occurred (Hadjistavropoulos and Craig, 2004; Melzack and Wall, 1965). Consequently, this signal motivates actions that serve to avoid damage (e.g., allocating overt attention to the harmful event, avoiding further damage).

Early Cartesian concepts were incorporated and refined within ‘specification theory’. This theory refers to pain as emerging from stimulation of a distinct sensory modality (comparable to vision or hearing) with its own physiological components such as specific receptors and associated nerve fibers (Hadjistavropoulos and Craig, 2004; Moayedi and Davis, 2013). This pain modality and its receptors are assumed to be sensitive to one specific stimulus. Within the theory, it is proposed that innocuous

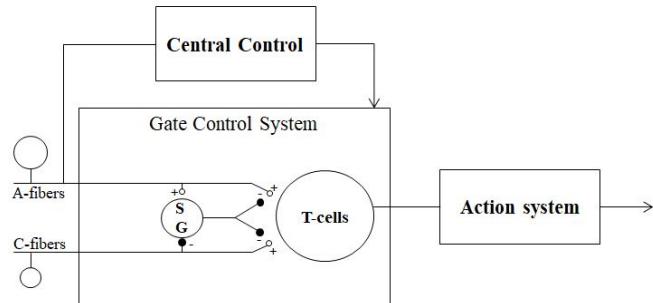
stimuli are encoded via low-threshold mechanoreceptors, whereas noxious stimuli would activate nociceptors that transduce the pain signal to designated pain areas via pain fibers.

In contrast to specificity theory, proponents of ‘pattern theory’ claimed that any somatosensory experience arises from a specific pattern of neural firing (Flor and Turk, 2015; Moayedi and Davis, 2013). The spatial and temporal profile of this pattern is then decoded by the brain which allows conclusions about stimulus type and intensity. According to this theory, the stimulation of any cutaneous nerve fibers (except those innervating hair cells, Lele, Sinclair, and Weddell, 1954) could in principle lead to the perception of pain. This theory ignored claims of specificity theory and any evidence of specialized receptors or a biomedical ‘pain system’ (Nafe, 1929).

Psychological factors (such as attention, cognition, emotion) were not given significant roles within specificity or pattern theory. Indeed, the contributions of psychological and physiological mechanisms for pain were subject of intense debate. For example, some clinicians arrived at the conclusion that psychological and physical pain mechanisms were mutually exclusive (with pain being either psychological or physical). Stigmatization of patients whose pain was categorized as ‘psychogenic’ occurred commonly and the aftereffects of this ideation are prevalent to this date (Katz, Rosenbloom, and Fashler, 2015; Liebeskind and Paul, 1977).

In 1965, Melzack and Wall proposed the seminal Gate-Control Theory which revolutionized pain research (Melzack and Wall, 1965; Moayedi and Davis, 2013; Sternbach, 1986). Their theory is largely influenced by the enhanced understanding of the neural mechanisms underlying pain. The theory claims that the transmission of a noxious stimulus to the central nervous system (CNS) is subject to a gating mechanism (see also figure 1.1). Specifically, the substantia gelatinosa in the dorsal horn of the spinal cord can either increase or decrease the transmission gain of incoming peripheral stimulation before pain perception emerges (Sternbach, 1986). This gate tends to be closed by large-fiber inputs and opened by small-fiber inputs. Further, Melzack and Wall assumed a central control component. The ‘central control trigger’ is thought to activate selective processes within the brain that exert control over incoming sensory data (Melzack and Wall, 1965). However, only little was known about descending pain modulation at the time (Sufka and Price, 2002). The authors claim that the theory is able to incorporate a wide range of phenomena. For example, they offer an explanation for Beecher’s observations of majorly wounded soldiers who are not reporting pain, but relief about returning from the battlefield alive (Melzack and Wall, 1965). Despite some conflicting findings and a major revision of some of the basic concepts of the gate control theory (Moayedi and Davis, 2013; Sufka and Price, 2002), the concept of input modulation is prevalent and influential in pain research and clinical pain management to this day (Dickenson, 2002; Steeds, 2016; Tabor et al., 2017).

FIGURE 1.1: Gate Control Theory



Notes The Gate Control Theory was proposed by Melzack & Wall, 1965. They propose that both large (A-) and small (C-) fibers synapse with neurons in the substantia gelatinosa (SG) and with first central transmission cells (T-cells). The SG has modulatory effects (represented by '-'; excitation: '+'). The T-cells project to cells of the action system. Once a critical level of firing in the T-cells is exceeded (e.g., after unexpected skin damage), a set of adaptive behavioral responses is triggered (e.g., startle response, flexion reflex, etc.). The central control trigger mechanisms are associated with A-fiber activity and the effect of this central control mechanism project back to the Gate Control system. Figure adapted from Moayedi & Davis, 2013 and Melzack & Wall, 1965

Methodological advances have shed light on cellular and molecular mechanisms underlying nociceptive and inflammatory processes (as described in Basbaum et al., 2009; Davis, 2011; Kidd and Urban, 2001; Steeds, 2016). These insights have further determined the way researchers view pain. Firstly, there are two types of nociceptors (i.e., receptor cells that respond specifically to noxious information): high-threshold mechanoreceptors (HTM), which respond to mechanical stimulation and -deformation; and polymodal nociceptors (PMN), which respond to a variety of potentially damaging substances and factors (such as hydrogen ions, 5-hydroxytryptamine, cytokines, prostaglandins, histamines or leucotrienes; see Steeds, 2016). These nociceptors are free nerve endings of two different types of fibers. A δ -fibers are myelinated, of a relatively large diameter (2-5 μm) and allow rapid signal transduction (5-15 $\mu\text{m}/\text{second}$). The associated pain experience is often described as pricking and well-localized. In contrast, C fibers are smaller in diameter ($>2 \mu\text{m}$) and unmyelinated. Transduction velocity is a lot slower (0.5-2 $\mu\text{m}/\text{second}$) and the associated pain is usually experienced as diffuse, dull and aching (Basbaum et al., 2009; Steeds, 2016). Most of these fibers terminate in the dorsal horn of the spinal cord. In the spinal cord, these afferent fibers form synapses with second-order neurons which bifurcate in up- and downstream neural pathways. Further, complex interactions with excitatory and inhibitory interneurons take place here (Basbaum et al., 2009).

The outlined theoretical and biological considerations have advanced our understanding of pain, especially acute nociceptive and inflammatory pain. However, understanding the basis of chronic pain might require additional theoretical attention.

1.3 Chronic Pain

1.3.1 Definition

The distinction between acute (i.e., nociceptive or inflammatory pain) and chronic (or persistent) pain is often given by means of an arbitrary period of time during which pain experiences have to persist after an inciting event. Most commonly, periods of between 3 to 6 months are used to define chronicity (Johannes et al., 2010; Katz, Rosenbloom, and Fashler, 2015). However, pain that persists for more than 6 months can be considered acute when a physical pathology can be identified. Hence, another approach is to define pain as chronic when no underlying pathology can be identified (Flor and Turk, 2015). This definition allows diagnosing chronic pain even if it has been persisting for less than 3 months but no underlying medical explanation can be identified (Flor and Turk, 2015; Turk and Okifuji, 2002).

The DSM-5 offers criteria to diagnose clinical forms of chronic pain under the category 'Somatic Symptom and Related Disorders' (American Psychiatric Association, 2013). This allows diagnosing somatic symptoms which are related to significant distress and impairment, such as chronic physical pain. Instead of focusing on the absence of an underlying pathology, the re-conception of the DSM-5 focuses on the individual's response to the symptoms (i.e., cognitive, emotional and behavioral responses to pain perception). The diagnostic criteria for somatic symptom disorder are listed in Table 1.1. These criteria are helpful in defining clinical chronic pain as there is no consensual definition of chronic pain per se. However, they have been criticized for 'overpsychologizing' chronic pain (Katz, Rosenbloom, and Fashler, 2015).

1.3.2 Epidemiology and impact

Chronic pain is one of the most challenging health problems in the world today. Studies in western countries identified high, but varying prevalence rates of chronic pain. Between 19 to 34% in the general population seem to be affected by it, with increasing incidences in women and at an older age (Andersson et al., 1993; Breivik et al., 2006; Johannes et al., 2010; Moulin et al., 2002). However, also a significant proportion of children and adolescents are affected by chronic pain. Here, similar prevalence rates are reported (between 20 and 35%, Friedrichsdorf et al., 2016; King et al., 2011). Persistence of chronic pain into adulthood is observed in about one third of all pediatric chronic pain patients (Walker, Deugler-Crish, and Rippel, 2010). The economic impact of chronic pain in the U.S.A. is severe with estimated costs of \$560 to \$635 billion annually for patients' healthcare utilization and productivity losses ("The Economic Costs of Pain in the United States"). Pediatric chronic pain is estimated to cause an economic burden of approximately \$19.5 billion per year in the U.S.A. (Groenewald et al., 2014). High rates of comorbid disorders further decrease quality of life and overall psychosocial functioning in these patients (Bair

TABLE 1.1: DSM-5 Somatic Symptom and Related Disorders

| | |
|---------|--|
| A | ≥ 1 somatic symptoms that are distressing and result in significant disruption of daily life |
| B | Excessive thoughts, feelings or behavior related to the symptoms or associated health concerns as manifested by at least one of the following: |
| | 1. Disproportionate and persistent thoughts about the seriousness of one's symptoms |
| | 2. Persistently high levels of anxiety about health or symptoms |
| | 3. Excessive time and energy devoted to symptoms or concerns |
| C | Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (Typically ≥ 6 months) |
| Specify | With predominant pain (previously: pain disorder) Persistent: severe symptoms, marked impairment and long duration (≥ 6 months) |
| | Mild: Only one of the symptoms specified in B is fulfilled |
| | Moderate: Two or more symptoms specified in B are fulfilled |
| | Severe: ≥ 2 symptoms of B are fulfilled, plus there are multiple somatic complaints (or one very severe symptom) |

et al., 2003; Tunks, Crook, and Weir, 2008). For example, 30-40% of chronic pain patients also meet diagnostic criteria for major depression (Bair et al., 2003; Rayner et al., 2016).

1.3.3 Etiology: The psychology of chronic pain

In a purely medical framework, chronic pain is difficult - if not impossible - to explain as a distinct physical pathology is usually hard to identify (Flor and Turk, 2015). Alternatively, in case there is a somatic pathology, some individuals respond to the symptom with disproportionate amounts of distress and disability while others do not. Research suggests that the type and extent of the individual injury are not reliable predictors for the development of chronic pain (Chou and Shekelle, 2010). Pharmacological approaches to treat individuals with chronic pain have shown only limited success in the longer term and might cause serious adverse side effects, such as substance abuse disorders (Ballantyne and Mao, 2003). Genetic research in the field has produced many heterogeneous, conflicting results - a multitude of genes and their interactions seem to be involved in chronic pain (Mogil, 2012). All these observations suggest an important role of psychological factors for the development of chronic pain.

Conditioning and Learning Behavioral formulations largely advanced the understanding of mechanisms underlying a chronicification of pain experience (Fordyce, Fowler, and DeLateur, 1968; Fordyce et al., 1968; Fordyce, Roberts, and Sternbach RA, 1985). Here, non-associative and associative learning processes are considered important etiologic factors. Habituation and sensitization are important *non-associative learning mechanisms* potentially underlying chronic pain development (Flor and Turk, 2015). While habituation is defined as the reduction of response intensity when a stimulus is presented repeatedly, sensitization is the process that leads to increased response intensity towards a stimulus that is presented multiple times (Domjan, 2014). Noxious stimuli usually do not lead to habituation, but rather sensitization and hence an increased response (physiological, behavioral and subjective) to the stimulus (Arntz and Lousberg, 1990). Important determinants of sensitization vs. habituation towards noxious stimuli seem to be psychological factors such as the organisms' background arousal and the individual's ability to accurately predict the noxious stimulation: the better an individual is able to anticipate a stimulus and the concurrent sensations, the more likely habituation towards the painful stimulus will take place (Arntz and Lousberg, 1990). Interestingly, researchers identified differences in non-associative learning processes within healthy individuals and chronic pain patients. When confronted with a painful stimulus in a laboratory setting (such as electrical stimulation or cold pressor pain), healthy controls seem to habituate whereas chronic pain patients tend to show signs of sensitization (Arntz and Lousberg, 1990; Arntz et al., 1991; Colloca, Benedetti, and Pollo, 2006; Kleinböhl et al., 1999). Further signs of sensitization in chronic pain patients are allodynia and hyperalgesia. Chronic pain patients seem to perceive stimuli as painful when healthy subject did not ("allodynia", defined as perceiving pain after stimulation that usually does not lead to pain perception, Jensen, Day, and Miró, 2014) and rated physical stimuli of lower intensity as more painful ("hyperalgesia", increased pain perception in response to a stimulus that usually does provoke pain, Jensen, Day, and Miró, 2014).

Further, *associative mechanisms* such as classical and operant conditioning received much attention in behavioral pain research (Fordyce, Fowler, and DeLateur, 1968; Vlaeyen and Linton, 2012; Gentry and Bernal, 1977). Gentry and Bernal proposed that acute pain, especially pain that is associated with muscle tension (the unconditioned stimulus or US), can develop into a chronic pain problem by means of classical conditioning (Gentry and Bernal, 1977). By experiencing a frequent coupling between innocuous stimuli (e.g., a certain environment or body position, here: the conditioned stimulus or CS) and pain states (US), individuals respond with increased muscle tensioning (conditioned response or CR) to these previously neutral stimuli. According to the authors, this process is able to explain the persistence of pain independent

from the original tissue damage. Linton and colleagues (Linton, 1985; Linton, 1986) further developed this conditioning perspective on pain by examining the role of anxiety for sensitization processes. They argue that not neurological pain, but rather anxiety and related physiological activation are subject to conditioning processes. For example, a patient might have learned to associate a specific body position or movement with increases in muscle tension and pain. These movements (or even thoughts about these movements) then elicit anticipatory fear and increases in muscle tension. The fear of movement is also termed “kinesiophobia” and discussed as a core factor for the exacerbation of chronic pain and the disability associated with chronic pain states (Flor and Turk, 2015; Picavet, Vlaeyen, and Schouten, 2002; Vlaeyen et al., 1995; Crombez et al., 1999).

The above behavioral perspectives have led Vlaeyen and Linton to introduce their fear-avoidance model of chronic pain (Vlaeyen and Linton, 2000). In their model (see 1.2), they propose that an aversive event such as an injury is associated with fear (e.g., kinesiophobia) through classical conditioning. This fear leads to the avoidance of all movements or environmental cues that are related to the original injury and further generalizes towards similar movements or situations. Consequently, the patient’s disability and depression increases. This model is the most important theoretical basis for the cognitive-behavioral treatment rationale and is widely used in clinical practice to this day (Vlaeyen and Linton, 2000; Leeuw et al., 2007).

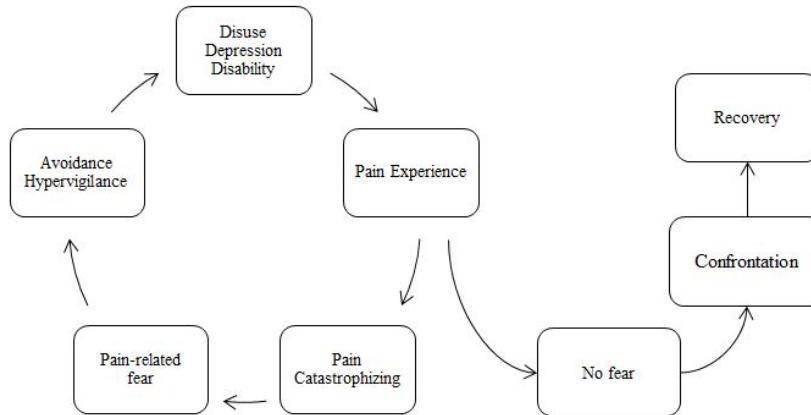


FIGURE 1.2: The Fear-Avoidance model as proposed by Vlaeyen and Linton

Attention Besides learning processes, other cognitive factors seem to play an important role for the perception of pain on the one hand and development of chronic pain on the other hand. Attentional focus is a prominent mechanism in the fear-avoidance model described above, where chronic pain patients are assumed to put an excessive attentional focus on their pain symptoms and tend

to catastrophize the experience of pain. Attention here means the mechanism by which sensory events are selected and enter awareness (Legrain et al., 2009). The dysfunctional attentional style associated with the development of chronic pain is referred to as hypervigilance. This is assumed to maintain and amplify bodily sensations and the perception of pain (Van Damme et al., 2010). Hypervigilance has been observed (among others) in patients with chronic low back pain and fibromyalgia, a medically unexplained syndrome that is characterized by whole body pain (Peters, Vlaeyen, and Drunen, 2000). In a study with pain patients referred to a university clinic, McCracken (1997) was able to associate increased attention or observation of pain symptoms with higher pain intensity, emotional distress, psychosocial disability and pain-related healthcare-utilization. In their neurocognitive model, Legrain and colleagues (2009) distinguish between top-down (i.e., intentional prioritization of certain stimuli for action selection) and bottom-up (i.e., salience or stimulus-driven selection) attentional mechanisms in pain perception. The authors argue that while an automatic attentional capture by pain experiences is an important feature of its threat-signaling function, top-down modulation of pain experiences has the potential to either aggravate or reduce pain. Consequently, the authors recommend focusing on top-down attentional mechanisms and excessive expectations of pain in clinical research, further exploring the 'psychoanalgesic' role of distraction (or attention-based pain relief strategies) for chronic pain patients (Legrain et al., 2009; Eccleston, 1995). However, rumination and dysfunctional attentional focus could also be determined by an individual's affective state.

Depression In about 30-40% of patients who present for treatment of chronic pain, a comorbid depression is diagnosed (Bair et al., 2003; Rayner et al., 2016). The comorbidity with depression further decreases functioning and treatment response in these patients (Holmes, Christelis, and Arnold, 2013). It is not always trivial to distinguish between symptoms of chronic pain and depression – features such as rumination, magnification of distress or catastrophisation and helplessness are characteristic symptoms of both disorders (Holmes, Christelis, and Arnold, 2013). This overlap in both symptoms and prevalence has led researchers to introduce the term "depression-pain-syndrome" (Bair et al., 2003). Research on the depression-pain syndrome implies that pain and depression frequently exacerbate one another, share a similar biological mechanism (i.e., the involvement of serotonergic and noradrenergic neurotransmitter systems) and respond to similar treatments (Blier and Abbott, 2001; Gallagher and Verma, 1999). The two disorders might hence emerge from a common underlying process (Holmes, Christelis, and Arnold, 2013) – some researchers have even suggested formalizing chronic pain as a subtype of depression (Blumer and Heilbronn, 1982).

1.4 Current developments in clinical psychology

Computational and cognitive neuroscientists argue that the brain must be viewed as an elaborate information-processing system (Lachman, Lachman, and Butterfield, 2015). Researchers in clinical psychology have adapted this notion in order to further the understanding of mental disorders and underpin clinical research with neuroscientific evidence (Beck and Clark, 1997; Ingram, Kendall, and In, 1986; Ingram, 1986). Viewing pain perception from an information-processing perspective seems to be promising and emerges as a novel field of research (Tabor et al., 2017; Büchel et al., 2014).

When analyzing information processing systems, David Marr has suggested doing so under consideration of three distinct, complementary levels of analysis (Marr, 1982). Marr's so-called Tri-Level Hypothesis was initially based on his ideas on information processing in visual perception (McClamrock, 1991). However, this conceptualization can be expanded to perception and action in general (Peebles and Cooper, 2015). The three levels suggested by Marr are

1. the **computational level**. This level encompasses the non-trivial analysis of what problem the system solves (the goal of the computation) and the reasons the system has to cope with that specific problem. It also encompasses the logic of the strategy with that the computation is carried out.
2. the **algorithmic level**. On this level, it is specified the processes and representations that the system uses in order to implement the computational theory. For example, analyses on this level would be concerned with the representation of the input a system gets and the output it generates as well as the algorithm necessary for this transformation.
3. the **implementational level**. Research on this level of analysis is concerned with the physical instantiation of the system's representations and processes (e.g., its neural basis).

Information processing approaches might also expand the current knowledge on the etiology and maintenance of chronic pain states. For example, an abundance of research on the neural basis of chronic pain is available (i.e., the implementational level, see Brown, El-Deredy, and Jones, 2014; Diatchenko et al., 2005; Dickenson, 2016). Yet, these studies are very heterogeneous regarding their focus (genetics, neurotransmitter systems, hormonal responses etc.) and they do not aim at explaining mechanisms underlying chronic pain. Modern psychiatry and clinical psychology face the tremendous challenge of integrating this neuroscientific insight with physiological, psychological and behavioral evidence into unifying nosological theories. Computational models can potentially bridge the gaps between these disciplines (Adams, Huys, and Roiser, 2016; Huys, Maia, and Frank, 2016; Wang and Krystal, 2014; Wiecki, Poland, and Frank, 2015). Advances in computational psychiatry rely

heavily on the notion that phenomena of the human mind result from Bayesian inference. The next paragraph introduces the most prevalent concepts, theories and frameworks related to the idea of the Bayesian brain.

1.4.1 The Bayesian Brain hypothesis and Predictive Coding

In recent years, the notion of the brain as a ‘Bayesian inference machine’ has become the predominant theoretical framework in neuroscience (Dayan et al., 1995; Doya et al., 2007; Friston, 2012). The basic idea underlying this concept is that the brain is trying to infer the causes for a given state (or sensation) by means of an internal generative model of the world (Friston, 2012). A generative model entails the dependencies between causes and consequences probabilistically (Friston, 2010). To put it in other words, the brain needs a representation of the world (a model) in order to identify the most likely environmental cause of the sensory information it receives (e.g., firing of retinal cells or auditory neurons) and interact with the world in a meaningful way (Hohwy, 2012; Friston, 2010). The model of the world is not innate or fixed – it is shaped and constrained by the information the brain gets from the environment. The search for the ‘real’ cause of sensory input is often paralleled to a scientific-style hypothesis-testing process (Gregory, 1980; Hohwy, 2012; Friston, 2012).

The idea of perception as an active hypothesis-testing process however is not novel. Philosophers like Immanuel Kant (1724-1804) argued that only the combination of ‘understanding’ and ‘sensing’ can give rise to knowledge. Helmholtz (1860) was probably the first to express this idea explicitly:

How do we escape from the world of sensations of our own nervous system into the world of real things? We are guided by the answers nature delivers when we query it, using unconscious perceptual inference based on prior learning.

Helmholtz, 1860, in *Treatise on Physiological Optics*

Sensory information, selected by individual strategies, is met with prior knowledge to give rise to perception - an idea which evolved over decades (Lee and Mumford, 2003; Gregory, 1980). Nevertheless, Helmholtzian ideas are still at the core of more modern approaches to perceptual inference, such as predictive coding and the Bayesian Brain hypothesis (Dayan et al., 1995; Hohwy, 2013).

The Bayesian Brain hypothesis puts the probabilistic combination of prior knowledge and current sensory information at the core of inference about hidden causes in the world. The theorem introduced by Bayes forms the mathematical basis of this idea. It states that the information about a model M (e.g., a belief about the state of the world) and the sensory information a system receives D (e.g., visual, auditory or tactile stimulation) are combined so that

$$P(M | D) = \frac{P(D | M) P(M)}{P(D)} \quad (1.1)$$

Where $P(M|D)$ is the posterior probability, $P(D|M)$ the likelihood of the sensory information given a certain model and $P(D)$ and $P(M)$ are the probabilities of the data and the model, respectively. Applied to perception, the theorem implies that the sensory information D is integrated in the light of existing internal models M of the world (Fortier, Friedman, and Friston, 2018). A statistical process then guides the inference about the circumstances in the external world which are most likely to have caused the sensory input.

An example: hearing a ticking sound in the library, one might have different beliefs (or models) about what causes that noise. The hypothesis that a clock on the library wall is causing this noise has a very high likelihood $P(D | M)$ (it is highly likely to hear a ticking sound in case there actually is a clock on the wall). The probability of a clock hanging on the wall is a lot higher than, for example, the probability of a squirrel rhythmically beating a hazelnut against the library's window. The hazelnut-beating squirrel might produce a similar sound as the clock; resulting in a comparable $P(D | M)$ in both models. However, after all one might know about the world, the marginal probability of a clock hanging at the library wall (model A, $P(M_A)$) is a lot higher than the probability of a hazelnut-beating squirrel (model B, $P(M_B)$). Hence, the posterior probability of model A, $P(M_A | D)$, is higher than the posterior probability of model B, $P(M_B | D)$ and the clock-hypothesis determines the individual's inference about what generates the ticking sound. This example illustrates how the credibility of a model is weighted by how well it fits with the sensory data as well as how likely the model is a priori.

The following paragraph introduces important concepts and quantities of the predictive coding framework, where Bayesian principles introduced above are applied to perception, cognition and action.

Predictions. In predictive coding, perception is an active process. Sensory information is always met with *predictions* about the nature of that information (Hohwy, 2013; Rao and Ballard, 1999). Predictions cascade down the cortical hierarchy, where they are met by sensory input. A comparison between prediction and the subsequent input emerges as the central task for the brain in causal inference (Friston, 2009).

Prediction Error. The divergence between the prediction and the sensory input can be quantified and is proposed as the central quantity in causal inference. This quantity, in the following referred to as 'prediction error', is a measure for the fit of the internal model for the incoming sensory data: a small error indicates a good capture of the circumstances in the external world by the model, whereas a large error suggests that substantial aspects of the sensory information were not well predicted by the brain.

Prediction Error Minimization. A large *prediction error* motivates a revision of the internal model so that subsequent model predictions match the sensory data better (Hohwy, 2012). Other ways of minimizing the prediction error include moving the body in order to get the expected sensory input. It is also possible to sample (e.g., attending to) sensory information differently ('active inference') on order to (Clark, 2013; Hohwy, 2013; Friston, Daunizeau, and Kiebel, 2009) minimize the error. Following this idea, perception and action are closely intertwined as both serve to minimize prediction error (Friston, 2009).

Hierarchies. An important feature of the predictive coding framework is the idea of *hierarchies* within the cortex (Ballard, 2015; Hohwy, 2012; Mumford, 1992; Kiebel, Daunizeau, and Friston, 2008). A prediction error that cannot be predicted at a lower level in the cortical hierarchy is passed up to a higher level. Basic sensory attributes are predicted at a low level with a fast timescale, whereas more abstract and complex regularities are processed on higher cortical levels and on a slower time scale (Friston, 2009; Kiebel, Daunizeau, and Friston, 2008). Prediction error minimization occurs on all levels of the cortical hierarchy which gives rise to causal inference on very fast (e.g., change of lighting leads to change in brightness) and slow (e.g., meat consumption accelerates climate change) time-scales (Hohwy, 2012).

Precision. A pertinent prediction error indicates a failure to explain circumstances in the world - not, for example, a lack of explanation for the noise in the sensory information. In order to determine which prediction error to 'trust' (i.e., which prediction error indicates a 'true' violation of model predictions), the brain relies on its estimated *precision*. A very precise prediction error is assigned a high priority and travels through the cortical hierarchies with a higher gain than errors with a lower estimated precision (Kiebel, Daunizeau, and Friston, 2008; Hohwy, 2012). Modifications of internal models are determined by precise errors while imprecise errors will not lead to adaptations of the internal model. The precision estimate balances the extent to which perceptual inference relies on the sensory information vs. more on prior beliefs about the world.

1.4.2 Predictive Coding, interoception and pain

Recent evidence suggests that not only perception (i.e., processing of signals from the external world) emerges from the minimization of prediction error - the processing of signals from the internal milieu of the body seems to follow this principle as well (Barrett and Simmons, 2015; Seth, 2013; Seth and Gray, 2016). The sensation and integration of signals that originate from inside the body is referred to as **interoception** (Khalsa and Lapidus, 2016). It seems that interoception, too, emerges from a comparison of bodily signals with top-down predictions of them, with prior beliefs

that were constructed from experience (Barrett and Simmons, 2015; Hechler, Endres, and Thorwart, 2016; Tabor et al., 2017). Following this approach, the brain tries to infer the causes of the bodily information by generating hypotheses about them. The "winning" hypothesis, or prediction, consequently determines interoceptive inference. Following this idea, Barrett and Simmons (2015) propose an interoceptive system (probably in the agranular visceromotor cortices) from where visceromotor and viscerosensory predictions are sent down the cortical hierarchy as hypotheses that are then tested against the arriving sensory information (Barrett and Simmons, 2015; Hechler, Endres, and Thorwart, 2016).

Bodily signals that are sensed through interoception include heart rate, glucose levels, build-up of carbon dioxide in the blood, temperature and markers of inflammation (Barrett and Simmons, 2015). Interoception does not only include the processing and representation of these signals, but also the attentional capture by, appraisal of and response towards them (Farb et al., 2015). For example, interoceptive sensations that are proximal to the body part affected by chronic pain seem to elicit increased fear responses in pediatric patients (Flack et al., 2017).

The concept of interoception hence encompasses many aspects of psychological research on chronic pain - it entails not only the processing of the nociceptive signal, but also its appraisal and modulation by a multitude of additional information. In a predictive framework, pain has the role of a generative model that explains threatening sensory information. The data this inferential process relies on is of multisensory, ambiguous and noisy nature, which makes interoceptive inferences probabilistic. This data has to be integrated with other information in order to estimate the behavior that will most likely serve the organism's current objective (Tabor; Friston, Kilner, and Harrison, 2006) As outlined in section 1.2, the most common trigger of pain is activity in nociceptors; however, pain perception is modulated by many antecedent, non-nociceptive inputs (Tabor et al., 2017). Experimental evidence suggests that event-related information that increases expectations about threat to body tissue increases consequent pain perception, while a decrease in pain perception is observed after safety signals (Anchisi and Zanon, 2015; Büchel et al., 2014; Moseley and Arntz, 2007; Moseley and Butler, 2015). Hence, pain can be viewed as an internal model, signaling "something is wrong" with the body and prompting a higher-order objective of bodily protection.

In their perspective paper, Hechler, Endres and Thorwart (2016) proposed that pain perception follows the Bayesian balancing of prior knowledge and current information:

$$P(\text{pain}|\text{sensations}) = \frac{P(\text{sensations}|\text{pain}) \times P(\text{pain})}{P(\text{sensations})} \quad (1.2)$$

Pain perception ($P(\text{pain}|\text{sensations})$, the posterior) is evaluated in the light of prior beliefs about the probability of pain ($P(\text{pain})$, the prior; or prediction of pain) and the likelihood of the current sensory information given the hypothesis of pain (or

no pain), ($P(\text{sensations}|\text{pain})$). In clinical populations with chronic pain, all parameters in equation 1.2 might contribute to the patient arriving in a state of persistent pain perception. A heightened prior prediction of pain (an increased pain prior) might be the consequence of repeated exposure to painful experiences. Also, patients might (subconsciously) perform active inference when experiencing less pain than expected and act on the likelihood model, for example through pinching or pressuring the body part affected by pain ($P(\text{sensations}|\text{pain})$). In the case of the sensory information being adequately explained by the "pain"-model, an inference in favor of pain perception is made and the posterior probability of $P(\text{pain}|\text{sensations})$ increases.

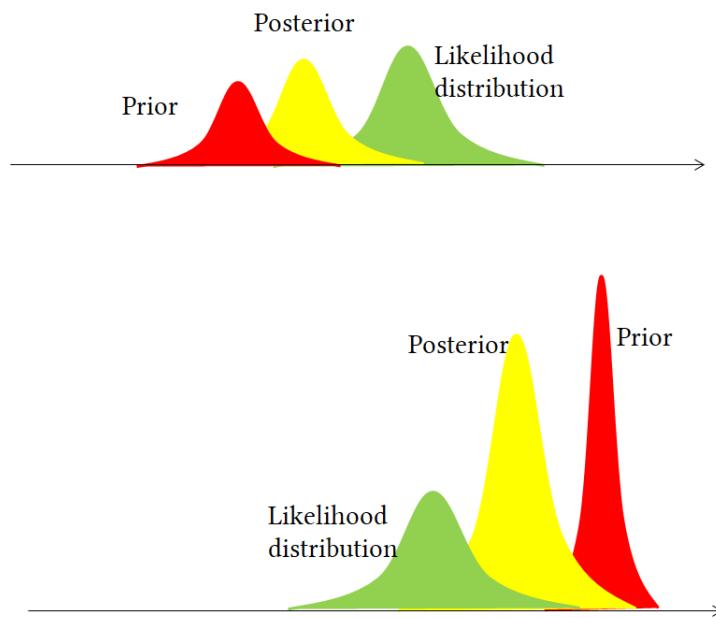
Another important feature for an interoceptive predictive coding model of chronic pain is the *precision*(Feldman and Friston, 2010; Hohwy, 2013). In psychology and psychiatry, precision is the key mechanism that is used to model attention and clinical phenotypes such as schizophrenia (Fletcher and D., 2009), autism-spectrum disorders (Pellicano and Burr, 2012; Van Boxtel and Lu, 2013), functional motor symptoms (such as hyperkinesia and tremor, Edwards et al., 2012) or pain (Edwards et al., 2012). In their review, Edwards and colleagues (2012) assume that the prior probability of pain ($P(\text{pain})$) is afforded too much precision in chronic pain patients via an abnormal attentional gain from levels higher up in the cortical hierarchy, leading to an increased posterior probability of pain which is hardly influenced by any innocuous bottom-up signals. A schematic illustration of this idea, adapted from Edwards et al., 2012, Büchel et al., 2014, Farb et al., 2015, Tabor et al., 2017 as well as Hechler, Endres, and Thorwart, 2016, can be found in figure 1.3.

1.4.3 The Free Energy Principle

The predictive coding framework described above can be considered a special instantiation of the Free Energy Principle (FEP) as introduced by Friston and colleagues (Friston, 2009; Friston, Kilner, and Harrison, 2006). The FEP attempts to unify neuroscientific, physiological and psychological perspectives by using ideas and techniques from information theory (as proposed by Shannon, Shannon, Weaver, and Burks, 1951), Bayesian statistics and machine learning. (Friston, 2010; Friston, Kilner, and Harrison, 2006; Friston, 2009). It is discussed as a global theory of how the brain works as it accounts for perception, action and learning in adaptive systems. An adaptive system is any system that successfully resists the natural tendency to disorder, such as humans, animals or brains (Friston, 2010). In order for a brain to achieve this type of adaptive exchange with the environment (that is, both the external and the internal environment), it has to minimize its free energy (Friston, 2010; Buckley et al., 2017; Friston, 2009).

It is imperative for an adaptive system to avoid surprising states in the longer term. A whale, for example, should avoid forsaking the ocean. To express it more formally, the whale should avoid being in states that have a high *entropy* and remain in low-entropic states as much as possible. States with a low entropy are determined by

FIGURE 1.3: An illustration of pain from a Bayesian perspective



Notes. An illustration of pain from a Bayesian perspective, corresponding to equation 1.2. *Top:* healthy inference on the pain state arises from a combination of a flat prior probability of pain and a likelihood distribution that captures sensory information and their relationship with pain well. *Bottom:* The prior probability of pain in patients might be more peaky (overly precise), resulting in a posterior probability of pain that exceeds normal sensation as shown in the top illustration. Inference on the pain state here is biased towards the prior expectation of pain, regardless of the sensory information the system is exposed to.

the agent's phenotype and are also referred to as an agent's *expected states*. However, an agent cannot know whether its sensations in a specific situation are surprising or not (Friston, Kilner, and Harrison, 2006; Hohwy, 2013). Free energy is proposed as a quantity that is both related to surprise (i.e., free energy is an upper bound on surprise) and accessible for the brain (Friston, 2010). Hence, by minimizing free energy, an agent implicitly minimizes surprise. Although the general idea underlying the FEP is rather straightforward, its implications are very complex.

The FEP is of particular importance for the implementation of Bayesian models in machine learning. Here, it allows a conversion of complicated integrations over probability densities into an optimization problem (Friston, 2010). Consider the goal of evaluating the posterior probability $P(M|D)$. In psychological terms, this evaluation underlies perception and learning. In the case of continuous variables, an exact solution quickly becomes intractable (e.g., evaluating densities instead of probability distributions, Friston, Kilner, and Harrison, 2006; Bishop, 2006). When restating the problem as a problem of optimization, it is possible to approximate the target posterior density. The goal here is to derive a lower bound $\mathcal{L}(D, Q(M))$ on the posterior, where $Q(M)$ is an approximation of the target posterior $P(M|D)$.

The two main mathematical components that make this optimization possible are the Kullback-Leibler divergence and Jensen's inequality for convex functions. The Kullback-Leibler (KL) divergence, or *relative entropy*, describes the divergence D between two distributions (e.g., probability distributions $Q(x)$ and $P(x)$) and is given by equation 1.3:

$$D(Q||P) = \sum_x Q(x) \log \left(\frac{Q(x)}{P(x)} \right) \quad (1.3)$$

the divergence is strictly positive or equal to zero ($D(Q||P) \geq 0$). The divergence is zero if and only if $Q(X) = P(X)$.

A further ingredient is Jensen's inequality for convex functions (proven by Jensen, 1906, see also Bishop, 2006) which is given by

$$f(E(X)) \leq E(f(X)) \quad (1.4)$$

where E denotes the expectation of a probability distribution over a variable x . It states that the weighted arithmetic mean of the function values in n locations is larger or equal to the function value at the mean of these n locations.

Both the KL-divergence (1.3) and Jensen's inequality (1.4) ensure that the target posterior is approximated "from below" and never exceeded. It can be shown (Bishop, 2006) that after deriving a lower bound on $P(M|D)$ using these components, $\mathcal{L}(D, Q(M))$ is given by:

$$\mathcal{L}(D, Q(M)) = \log(P(D)) - D(Q(M)||P(M|D)) \quad (1.5)$$

Another very practical property of this lower bound is that its elements are interpretable and meaningful. In the predictive coding framework, the negative lower bound $-\mathcal{L}(D, Q(M))$ refers to the prediction error. $-\log(P(D))$ can be interpreted as the surprisal caused by the sensory information (e.g., unexpected data has a low prior $P(D)$ and is hence surprising the system) and $D(Q(H)||P(H|D))$ is the divergence between the actual percept and the Bayes-optimal percept (one which is approximating the true, external cause of the percept best). Both elements are hard to compute and therefore approximated through the lower bound. In Bayesian terms, minimizing $-\mathcal{L}(D, Q(M))$ also makes it imperative for an agent to explain incoming sensory information well (maximize $\log(P(D))$) while also maintaining prior beliefs as much as possible (keep $D(Q(M)||P(M|D))$ small).

To conclude, free energy is currently discussed as a key quantity that might have the potential to unify neuroscientific evidence with psychology, physics and biology. It adopts an information-processing perspective on action, perception and learning and can account for various phenomena on computational, algorithmic and implementational levels. It also provides a practicable means of approximating a posterior probability density through optimization - instead of solving complicated integrals. The resulting lower bound and its components, $\mathcal{L}(D, Q(M)) = \log(P(D)) - D(Q(M)||P(M|D))$, are interpretable from a predictive coding perspective. These properties are of particular interest when implementing complex Bayesian models of brain computations.

1.5 Outlook and hypotheses

Approaches within the predictive coding- or free energy framework might have the potential to unify the numerous findings and disciplines concerned with the etiology of chronic pain. Specifically, framing pain perception in Bayesian terms, i.e., as arising from perceptual inference on the causes of a given percept by balancing prior experiences (boiled down into the pain prior) and the current sensory information and its likelihood distribution. In this context, pain is viewed as an internal model suggesting bodily threat and advising protective behavior. This approach might also be able to account for aspects of learning and conditioning in the development of chronic pain, attention and active inference.

In the present work, important requirements for an interoceptive predictive coding model of chronic pain will be introduced and an implementation will be proposed. Using simulations and a model selection procedure, the following hypotheses will guide the exploration of computational, predictive mechanisms underlying the development of chronic pain:

- 1. Heightened Pain Priors.** Some studies suggest that chronic pain patients might have an increased prior expectation of pain in general (Crombez et al., 1996). With the computational model outlined in the next section, it will be possible

to test under what circumstances an increased prior probability of pain leads to a state of chronic pain.

2. **Abnormal likelihood distribution.** In the present work, the role of an abnormal likelihood function ($P(\text{sensation}|\text{pain})$) will be explored so that settings which lead to a state of persistent pain perception will be identified.
3. **Achieving and sustaining (virtual) therapeutic change.** We will deduce features of psychotherapy that have to be implemented in order to achieve a sustained change in symptoms.

Chapter 2

Methods

2.1 Modeling preliminaries

We develop a Bayesian model for chronic pain for which central model requirements are drafted in the following paragraphs.

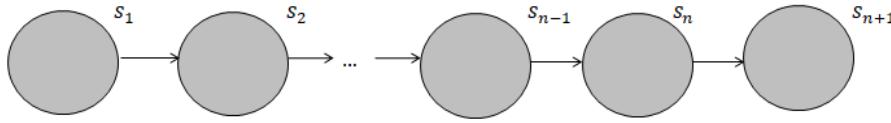
Sequential data. When simulating the development of chronic pain, it is crucial to incorporate a time-component into the model. The processing and evaluation of external signals from the environment (e.g., harmful or innocuous stimulation) or signals from within the body (e.g., inflammatory processes) is based on changes in these signals over time. Hence, the data that the system is processing is not independent or identically distributed (i.i.d.), but sequential. Following a predictive coding perspective, the brain is constantly trying to predict the sensory information it will receive during the next time-step. Hence, an important model requirement is to account for time-series and allowing predictions of future input. However, it is unlikely that the brain considers the wealth of all previous time-points in order to make a prediction concerning the near future. Data from the recent past might determine current predictions to a greater extent than observations from many time-steps ago. Further, models in which the entire history of data-points is considered are computationally expensive (Bishop, 2006).

Markov models are applied across numerous disciplines when modeling time-sequence data (such as speech recognition or handwriting sequences, see Bishop, 2006; Hastings, 1970; Norris, 1998). When considering a time-series of observations x_n , Markov models exploit sequential structures. By applying the product rule, the joint probability distribution for x_n is given by:

$$p(x_1, \dots, x_n) = \prod_{n=1}^N p(x_n | x_1, \dots, x_{n-1}) \quad (2.1)$$

A graphical model of a simple Markov chain with $x = 4$ time-steps is illustrated in figure 2.1.

FIGURE 2.1: A first-order Markov chain



Notes. Illustrated in this figure is a Bayesian graphical model of a first-order Markov chain. Filled circles in graphical models illustrate an observable random variable. The edges in this graph are unidirected.

An important characteristic of Markov chains is the **Markov property** which states that an observation is independent from all but the previous observation:

$$x_{n+1} \perp\!\!\!\perp x_{n-1} | x_n \quad (2.2)$$

Applying the d-separation property to Markov chains (Bishop, 2006), it can be shown that the conditional distribution for x_n given all previous x is given by

$$p(x_n | x_1, \dots, x_{n-1}) = p(x_n | x_{n-1}) \quad (2.3)$$

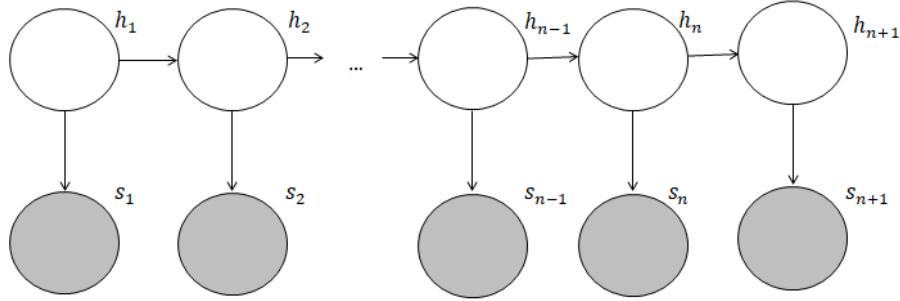
That is, only the model state at x_{n-1} is determining the present state x_n . In other words, a prediction of x_n depends only on x_{n-1} . In machine learning, models complying with the Markov property are also referred to as “memorylessness” (Feller, 2008). An important advantage of this is an improved tractability. Further, message passing between the variables is facilitated which will be discussed later in this section.

Perceptual hierarchies. All definitions of pain discussed above make a distinction between the nociceptive stimulus and the perception of pain, indicating that the relationship between the intensity of the noxious stimulus and pain perception is intricate and depends on unknown individual characteristics. This differentiation is an important requirement for any model of chronic pain. Here, a hierarchical structure is simulated by introducing different types of random variables in the model. The sensation can be quantified and observed; however, pain is a non-observable, hidden state. Therefore, observable and latent random variables are introduced into the model.¹

Given the two different types of random variables (observable and latent) as well as the opportunity to model sequential data, a hierarchical structure of the proposed Markov model seems favorable. One hierarchy level represents the sensory input (in the following referred to as S) whereas another level contains

¹A random variable X is a function that maps from a set of possible worlds W to a range Z . In machine learning, random variables are used to deal with uncertainty. Every random variable has a probability distribution which is a function $P : Z \rightarrow [0, 1]$. The probability distribution over a random variable is denoted by $P(X)$.

FIGURE 2.2: Hidden Markov Model (HMM)



Notes. In this exemplary HMM, a Markov chain of latent variables h_N is associated with corresponding observable variables s_N .

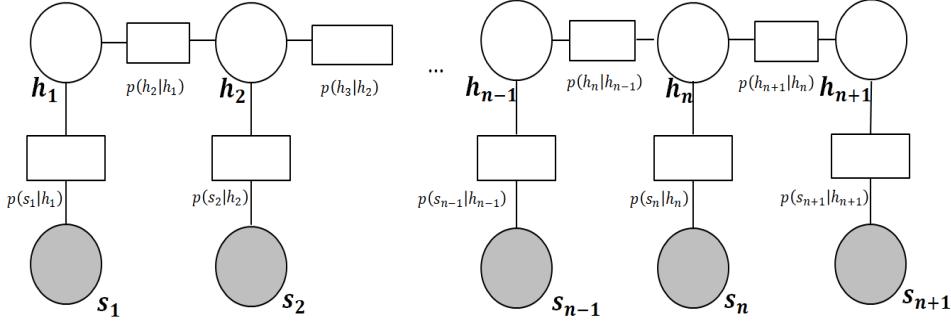
the latent variables and represent unobservable states (in the following: H for hidden). From a predictive coding perspective, the unobservable variable represents the generative model responsible for explaining the sensory information the system receives. In the present implementation, pain is considered a model that the brain is identifying as responsible for the sensory input the system is currently exposed to. To further explain this logic: an individual might have to infer the cause of a given (interoceptive) sensory information via an internal model which is then compared to the actual sensory information. ‘Pain’ is the most obvious model following nociceptive stimulation, indicating a potential threat to the body’s integrity. In individuals with chronic pain, this logic might however be disrupted in a way in that also innocuous stimulation is “explained” by the internal model of “pain” or threat. By implementing hierarchies, this becomes a testable hypothesis. **Hidden Markov Models** (HMMs) incorporate observable as well as latent variables (e.g., Reynolds et al., 1994; Young, 1992). The basic structures underlying HMMs are a Markov chain of latent variables h_n and corresponding observable variables s_n that are conditioned on the state of the associated latent variable (see figure 2.2). This model structure is also known as a state space model (Bishop, 2006), whereas the HMM is a special case of as its latent variables are discrete. The latent variables further fulfill the Markov property described above:

$$h_{n+1} \perp\!\!\!\perp h_{n-1} | h_n \quad (2.4)$$

That is, h_{n+1} is independent of h_{n-1} , given h_n .

Inference and message passing Probabilistic graphical models are useful for the expression of the conditional dependence- and independence relationships between random variables. After instantiating a network with fixed relationships between the variables, it is possible to perform inference in this model (Bishop, 2006; D’Ambrosio, 1999). In technical terms, inference allows determining the

FIGURE 2.3: Factor graph



Notes. In a factor graph, factor nodes are represented through boxes. Variable nodes are represented as circles. Factors contain conditional probability distributions and are the basis for message passing algorithms such as the sum-product algorithm. See also Bishop, 2006.

extent to which a variable changes once the knowledge about the value of another variable changed. In the present case, it is of interest to what extent the probabilities of the latent variables change once an observation has been made. For this purpose, it is necessary to infer the marginal probabilities of the latent variables from the value of the observed variables. A marginal probability distribution results from summing out all variables except the one of interest. In the case of two random variables X and Y, the marginal probability of X is given by

$$p(X = x) = \sum_Y p(X|Y) \quad (2.5)$$

An efficient means of performing inference in singly connected graphical models is given by the Sum-Product algorithm (Bishop, 2006). Before applying the sum-product algorithm, it is necessary to transform the Bayesian network into a factor graph. A factor graph contains variable- and factor nodes. It is bipartite, which means that edges connect a given variable node only with other factor nodes (never connecting variable nodes to other variable nodes). Conditional probability distributions are represented in factor nodes (see figure ??). A further prerequisite in order to run the sum-product algorithm on a given graphical model is *single connectedness*. A graph is singly connected when any two nodes are connected only through one path which is true for tree- and polytree-structured models (Jordan, 1998; Bishop, 2006).

Message passing via the Sum-Product algorithm is also known as belief-propagation. It allows obtaining the marginal probability of any hidden nodes' states (here: h), given the observed nodes (here x), (Pearl, 1982). The calculation of marginal probability distributions following the equation in 2.5 becomes computationally prohibitive even with a low number of binary variables as one would have to sum over many possible values in order to get marginal distributions. The Sum-Product algorithm allows efficient marginalization because it exploits the

tree-structure of the graphical model (Bishop, 2006; Pearl, 1982). The exact computation of the messages depends on whether the message is passed from a variable node to a factor node, where the product of all incoming messages is calculated and sent to all neighboring nodes ne_Y except the node the message came from:

$$\mu_{t \rightarrow Y}(Y) = \prod_{I \in ne_Y \setminus Y} \mu_{z \rightarrow t}(Z) \quad (2.6)$$

Or whether the message is send from a factor node to a variable node, where all incoming messages from neighboring nodes are collected and multiplied with a local factor before passing the message to neighboring variable nodes (except the node the factor node has received messages from):

$$\mu_{t \rightarrow Y}(Y) = \sum_{Z_1} \dots \sum_{Z_M} t(Y, Z_1, \dots, Z_M) \prod_{Z \in ne_t \setminus Y} \mu_{Z \rightarrow t}(Z) \quad (2.7)$$

The marginal distribution of the variable Y is then given by

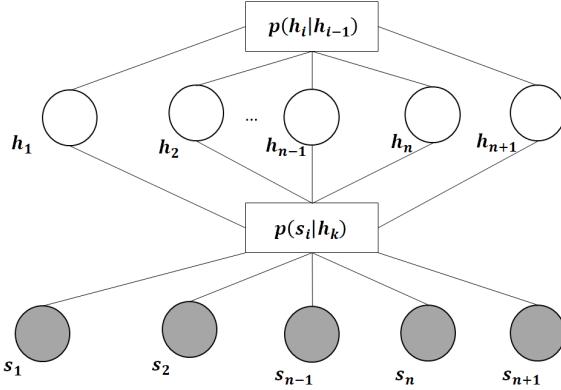
$$f(Y) = \prod_{t \in ne_Y} \mu_{t \rightarrow Y}(Y) \quad (2.8)$$

With the sum-product algorithm, it is also possible to obtain the surprise – $\log P(D)$ introduced before in the context of predictive coding and the FEP. For that, the marginal probability of the data D is computed in any variable node after observations were made. With the sum-product algorithm, it is possible to obtain the marginal probability distributions of the variables Y , $P(Y)$. After observing data (that is, obtaining a fix value for D), the sum-product algorithm computes $P(Y, D)$ at the node Y which is marginalized over Y and leads to $P(D)$, the marginal probability of the data, which is also necessary when computing posterior probabilities of a model using Bayes theorem.

A graphical model as depicted in figure 2.3 represents some assumptions underlying the Bayesian Brain hypothesis (Doya et al., 2007; Friston, 2012): it illustrates how future predictions are shaped by the comparison of sensory information and the generative model of the present time-step.

Learning from data and variational inference A drawback of the graphical model in figure 2.3 is the necessary new instantiation of the model's parameters (e.g. $p(x_i|h_k)$ and $p(h_i|h_{i-1})$) after every time-step. On a computational level, this approach is inefficient. It further is psychologically implausible as it does not represent an agent who is able to learn from past experiences. However, when trying to avoid repeated new instantiations, a factor graph with numerous loops results (see Figure 2.4). Applying the belief-propagation algorithm introduced before is not possible in the graph in 2.4 as it can run only on tree- or

FIGURE 2.4: Conventional factor graph with learning from past experiences



Notes. When learning from the past is implemented in a conventional factor graph (i.e., no new instantiation of the model after each time-step), a graph with numerous loops results. Belief propagation in this model is intractable, as established algorithms for message-passing (such as the sum-product algorithm) run only on tree- or poly-tree structured graphical models. An approximating solution is needed.

polytree-structured graphical models.

A solution to this is variational inference and the lower bound inspired by the free energy framework. Using variational inference, it is possible to eliminate the loops in 2.4 by transforming the factor nodes into free energy nodes where natural parameters η given λ and v are uncoupled from specific factor nodes. This results in a factor graph without loops (see figure 2.5), where the lower bound implicitly connects hidden and observable variable nodes and belief-propagation is possible.

Infinitely long messages. Message-passing in Bayesian models becomes impossible when the messages to be sent are infinitely long. This is the case for continuous random variables. The update of the new posterior parameters after belief propagation would be very complicated and effectively intractable. Variational inference schemes with identities vastly facilitate parameter updates by re-parameterizing the messages (Bishop, 2006; Endres, 2018). In particular, exponential family distributions and their conjugate priors are used for this purpose. A distribution or density belongs to the exponential family if it complies with the following form:

$$p(x|\eta) = h(x)g(x)\exp(\eta^T u(x)) \quad (2.9)$$

with the random variates x , the sufficient statistics which are functions of x $u(x)$, the natural parameters η and $h(x)$ which is used to constrain parameter space. The normalization constant $g(\eta)$ is (in case of continuous x) given by

(Endres, 2018)

$$g(n) \int dx h(x) \exp(\eta^T u(x)) = 1 \quad (2.10)$$

By introducing the conjugate prior to exponential family distributions, message passing and belief propagation becomes feasible. The effect of a conjugate prior is that the posterior has the same shape as the prior after observations were made - as a consequence, inference or learning data changes from solving complicated integrals into rather simple parameter updates. A conjugate prior on exponential family distributions is given by

$$p(\eta|\lambda, \nu) = f(\lambda, \nu)m(\eta)g(\eta)^{\nu} \exp(\nu\eta^T\lambda) \quad (2.11)$$

with the parameters of the prior and/or the posterior λ and ν , an arbitrary positive function that is different from $g(\eta)$, $m(\eta)$; and the normalization constant $g(\eta)$, see Equation 2.10. Endres (unpublished) has then shown that after observing N data points, the posterior parameters can be obtained by updating the prior parameters according to the following rules:

$$\tilde{\nu} := \nu + N \quad (2.12)$$

$$\tilde{\lambda} := \frac{\nu\lambda + \sum_n u(x_n)}{\tilde{\nu}} \quad (2.13)$$

$\tilde{\nu}$ in this context is also referred to as the *pseudocount* as it counts the number of observed datapoints while also containing information on the prior via ν . Considering this, $\tilde{\lambda}$ can now be interpreted as a weighted mean of the prior λ and the observed data.

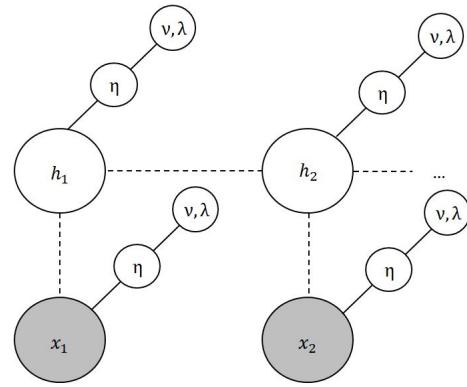
In the present model, we used the multinomial distribution given by

$$P(x|q) = \prod_{k=1}^{K-1} q_k^{x_k} \left(1 - \sum_{k=1}^{K-1} q_k\right)_K^x \quad (2.14)$$

which is a generalization of the beta distribution to K possible outcomes. The conjugate prior on the multinomial distribution is given by the Dirichlet distribution with $\alpha = \alpha_1, \dots, \alpha_K$ and $\alpha_k \geq 0$ and the standard form

$$\frac{\Gamma(\sum_{k=1}^K \alpha_k)}{\prod_{k=1}^K \Gamma(\alpha_k)} \prod_{k=1}^{K-1} q_k^{\alpha_k-1} \left(1 - \sum_{k=1}^{K-1} q_k\right)^{\alpha_K-1} \quad (2.15)$$

FIGURE 2.5: A fragment of an HMM with free energy factor nodes



Notes. In this graph, factor nodes were replaced by free energy factor nodes. This implementation solves the problem of loops in the factor graph (see 2.4) by breaking the direct connections between the variable- and factor nodes. However, connections between the nodes are still existent through the definition of the lower bound \mathcal{L} .

Chapter 3

Simulations

3.1 Methods and models

The implementation of all models is conducted using Python, version 3.6.0 (Van Rossum, 2007). All plots are created using the `matplotlib.pyplot` library (version 2.0.0, Hunter, 2007) for Python. A library for belief propagation in Bayesian graphical models written by D. Endres was used (see enclosed disc for details).

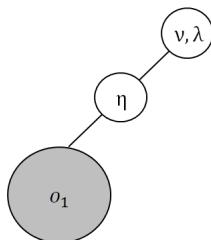
3.1.1 Basic Model

A model with only one observable variable node o_1 , connected to a free energy factor node $P(o_1)$, is implemented to explore the development of the model parameters in a simple scenario. Here, the observable node has the possible outcomes $o \in \{pain, nopain\}$. An illustration of this model can be found in figure 3.1.

3.1.2 Latent Model

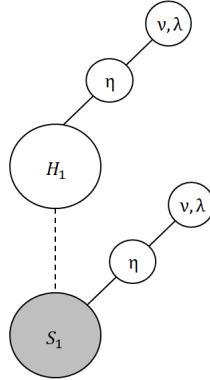
A model with an additional latent variable is implemented. It incorporates a hidden node H_1 and an observable node S_1 . They are connected through a free energy factor node which contains the likelihood distribution. In the following, this factor node will be referred to as the **top-down factor**. Further, a prior on the hidden variable is implemented (i.e. at the observable node). Possible states of the hidden variable are

FIGURE 3.1: Basic Model



Notes. A basic model, consisting of one observable variable node with two possible outcomes (pain and no pain). The prior on this node is a free energy factor node with natural parameters η and prior (= posterior, conjugate prior) parameters ν and λ

FIGURE 3.2: Latent model without time-steps



Notes. This model contains one observable variable node s_1 and one hidden variable node h_1 . They are connected (denoted by the dashed line) via a free energy factor node that contains the likelihood distribution. Further, a prior on H_1 is implemented.

$$H_1 \in \{ \text{pain}, \text{nopain} \} \quad (3.1)$$

and possible observations are

$$S_1 \in \{ \text{nociception}, \text{tickle} \} \quad (3.2)$$

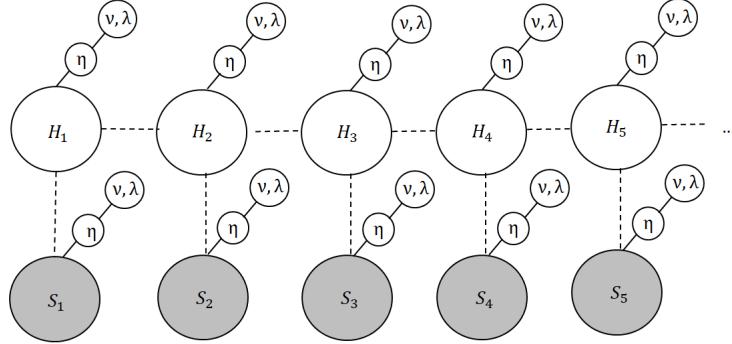
where tickle stands for innocuous stimuli that usually do not lead to a pain experience whereas nociceptive input represents any input following actual or potential tissue damage.

The resulting graphical model is represented in figure 3.2. Model parameters will be varied in order to explore interactions between different factor settings. This model already entails many important aspects of the Bayesian brain hypothesis discussed above (i.e., an integration of observed sensory information with prior assumptions or knowledge).

3.1.3 Model with N time-steps

An HMM with N time-steps and free energy learning over time is implemented. Possible states of the hidden (or latent) variables and possible observations lower in the hierarchy are equal to the latent model described previously ($H \in \{ \text{pain}, \text{nopain} \}$ and $S \in \{ \text{nociceptiveinput}, \text{tickle} \}$). The top-down factor, as above, contains the likelihood which allows modeling the association between a certain type of sensory input and pain. The hidden variable nodes form a Markov chain in this model. For this purpose, an additional free energy factor node is implemented, connecting two hidden variables with each other and modeling $P(h_t|h_{t-1})$. In psychological terms, these nodes allow simulating the development of pain expectations (or the pain prior) over time. An example of this model's structure in the case of 5 time-steps is illustrated in figure 3.3

FIGURE 3.3: Model with 5 time-steps



Notes A model with 5 (or N, as indicated by ...). The hidden variables form a Markov chain, which simulates the development of pain expectations over time. They contain information about $P(h_t|h_{t-1})$. The top down factor contains the likelihood, i.e. associations between a specific type of sensory information and the respective hidden state (pain, no pain) and hence information about $P(\text{sensation}| \text{pain})$. The hidden variables can take on the two values $H \in \{\text{pain}, \text{nopain}\}$ and the sensation nodes can take on the values $S \in \{\text{nociceptiveinput}, \text{tickle}\}$.

3.1.4 Transition probabilities in the time-step model

Per definition, patients with chronic pain perceive pain persistently despite changes in the nociceptive input, medication use or psychotherapy. In machine-learning, the state of being in constant pain would translate to a system or model arriving in a steady, asymptotic state. The dynamics of the model would not show any state-wise fluctuations once arrived at the asymptote. In the discussed, HMM-based approach,

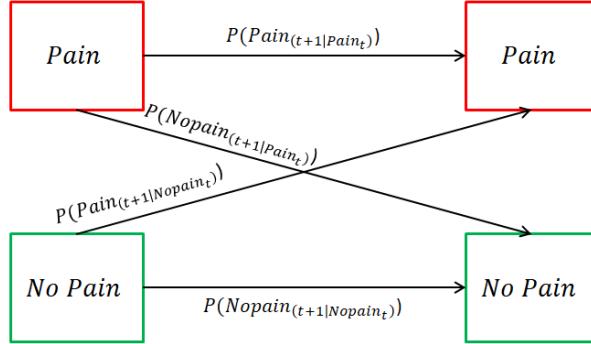
this can be modeled via the hidden variable nodes $H_n = \begin{cases} \text{pain} \\ \text{nopain} \end{cases}$.

In model 3.3 the probability distribution $P(h_n)$ depends on the previous state through the conditional distribution $P(h_n|h_{n-1})$. These are also referred to as transition probabilities. Transition probabilities are conditional probabilities that are usually represented in a matrix A . They determine the state of a variable H_i given its previous variable H_{i-1} in a Markov chain so that $A_{j,k} \equiv p(z_{nk} = 1|z_{n-1,j} = 1)$. Put differently, transition probabilities indicate the probability of transitioning from one state to another and the probability of a specific state being maintained in the next time-step. In the present case, there are four transition probabilities that determine message passing in the Markov chain (see also figure 3.4):

The transition probabilities are

1. $P(\text{Pain}_{t+1})|\text{Pain}_t$, the probability of remaining in a state of pain when pain was perceived in the state before
2. $P(\text{Nopain}_{t+1})|\text{Pain}_t$, the probability of transitioning from a pain-state into a no pain state

FIGURE 3.4: Lattice diagram of the hidden states



Notes. Transition diagram of the HMM, unfolded over time. There are 4 transition probabilities that need to be specified in order to constrain the requirements for reaching an asymptotic state of pain. Note that this is not a probabilistic graphical model.

3. $P(Pain_{t+1})|Nopain_t$, the probability of perceiving pain in the next time-step in case the current state is no pain
4. $P(Nopain_{t+1})|Nopain_t$ the probability of remaining in a pain-free state

The possible transition probabilities for the states of the hidden variables are summarized in figure 3.4.

In chronic pain, moving forward in time does not change the pain experience. Translated to machine-learning, this means that a linear system of equations has to be solved to get transition probabilities (e.g., with a $P(Pain) = 0.8$):

$$\begin{pmatrix} 0.8 & 0 & 0.2 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0.8 & 0 & 0.2 \\ 0 & 0 & 1 & 1 \end{pmatrix} \begin{pmatrix} P(Pain_{t+1})|Pain_t \\ P(Nopain_{t+1})|Pain_t \\ P(Pain_{t+1})|Nopain_t \\ P(Nopain_{t+1})|Nopain_t \end{pmatrix} = \begin{pmatrix} 0.8 \\ 1 \\ 0.2 \\ 1 \end{pmatrix}$$

The transition from one state to the next does not change the probabilities of pain ($P(pain) = .8$) or no pain ($P(nopain) = .2$). Hence, when trying to predict the developments of this model, the transition probabilities of the HMM are necessary (Bishop, 2006).

The following assumptions held for the construction of the matrix:

1. $P(Pain) = P(Pain_{t+1})|Pain_t \cdot P(Pain) + P(Pain_{t+1})|Nopain_t \cdot P(Nopain)$
2. $P(Nopain) = P(Nopain_{t+1})|Pain_t \cdot P(Pain) + P(Nopain_{t+1})|Nopain_t \cdot P(Nopain)$
3. $P(Pain_{t+1})|Pain_t + P(Nopain_{t+1})|Pain_t = 1$
4. $P(Pain_{t+1})|Nopain_t + P(Nopain_{t+1})|Nopain_t = 1$

However, the description of this system is ambiguous due to a redundancy which originates from the linear dependence between $P(Pain)$ and $P(noPain)$: $\sum(P(Pain), P(noPain)) = 1$.

In order to solve this system, additional constraints have to be identified. For that purpose, all probabilities are expressed in dependence of $P(Nopain)$:

$$P(Nopain) = 1 - P(Pain) \quad (3.3)$$

In the following, the terms are sorted and reshaped with the goal of expressing $P(Nopain_{t+1}|Nopain_t)$ in dependence of $P(Pain)$:

$$= (1 - P(Pain_{t+1}|Pain_t) \cdot P(Pain) + (1 - P(Pain_{t+1})|Nopain_t) \cdot (1 - P(Pain))) | - 1 \quad (3.4)$$

$$- P(Pain) = -P(Pain_{t+1}|Pain_t) \cdot P(Pain) + P(Pain_{t+1}|Nopain_t)(P(Pain) - 1) \quad (3.5)$$

$$P(Pain) = P(Pain_{t+1}|Pain_t) \cdot P(Pain) + P(Pain_{t+1}|Nopain_t) \cdot P(Nopain) \quad (3.6)$$

Now, all terms are expressed in dependence of $P(Pain)$:

$$P(Pain) = P(Pain_{t+1}|Nopain_t) \cdot P(Pain) + (1 - P(Pain_{t+1}|Nopain_t) \cdot (1 - P(Pain))) \quad (3.7)$$

$$P(Pain) = P(Pain_{t+1}|Pain_t) \cdot P(Pain) + 1 - P(Pain) - P(Nopain_{t+1}|Nopain_t)(1 - P(Pain)) \quad (3.8)$$

reshape 3.8 by taking $| - P(Pain) + P(Nopain_{t+1}|Nopain_t)(1 - P(Pain))$

$$P(Nopain_{t+1}|Nopain_t)(1 - P(Pain)) = 1 - 2P(Pain) + P(Pain_{t+1}|Pain_t) \quad (3.9)$$

reshape 3.9 by $| \div (1 - P(Pain))$

$$P(Nopain_{t+1}|Nopain_t) = \frac{1 + P(Pain)(P(Pain_{t+1}|Pain_t) - 2)}{1 - P(Pain)} \quad (3.10)$$

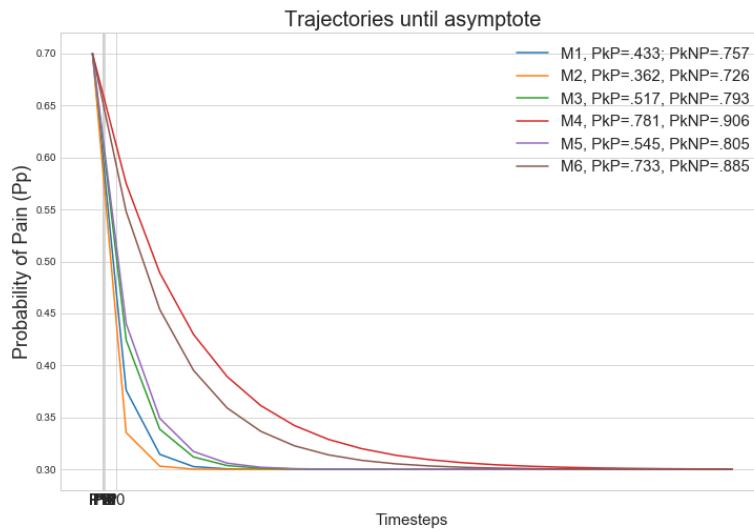
We then receive for $P(Nopain_{t+1}|Nopain_t)$:

$$P(Nopain_{t+1}|Nopain_t) = \frac{1 - 2 \cdot P(Pain)}{1 - P(Pain)} + \frac{P(Pain)}{1 - P(Pain)} \cdot P(Pain_{t+1}|Pain_t) \quad (3.11)$$

The result in equation 3.11 shows that once all terms are expressed in dependence of $P(\text{Pain})$, a line holding potential values for $P(\text{No} \text{pain}_{t+1} | \text{No} \text{pain}_t)$ makes the linear equation system above solvable.

An implication of this is that any values for $P(\text{No} \text{pain}_{t+1} | \text{No} \text{pain}_t)$ that are a sample of the line $\frac{1-2 \cdot P(\text{Pain})}{1-P(\text{Pain})} + \frac{P(\text{Pain})}{1-P(\text{Pain})} \cdot P(\text{Pain}_{t+1} | \text{Pain}_t)$ would allow the model to reach a state of persistent pain in the longer run. This phenomenon is illustrated in figures 3.5 and 3.6.

FIGURE 3.5: Course of trajectories $P(\text{Pain})$



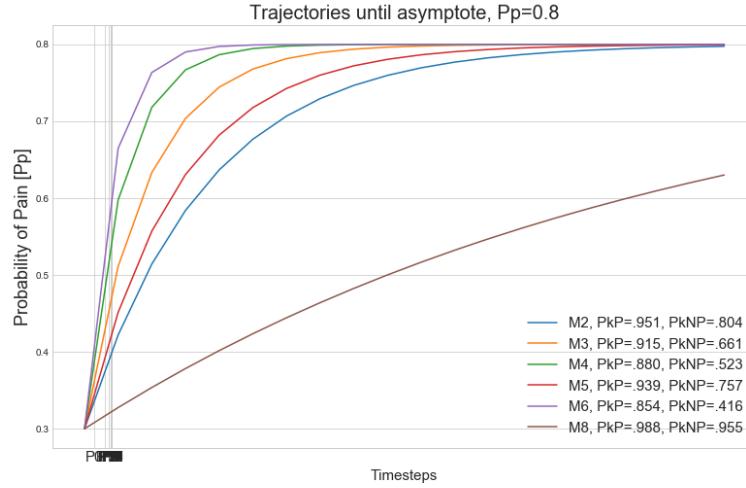
Notes. Plotted here are the trajectories over the course of time for transition probabilities that were sampled from the line derived above (Eq. 3.11). Of note, all trajectories arrive at the baseline value of $P(\text{Pain})$, regardless of the prior or the exact nature of the probabilities. $\text{PkP} = P(\text{keepPain}) = P(\text{Pain}_{t+1} | \text{Pain}_t)$, $\text{PkNP} = P(\text{keepNoPain}) = P(\text{No} \text{pain}_{t+1} | \text{No} \text{pain}_t)$.

3.2 Results

3.2.1 Basic model

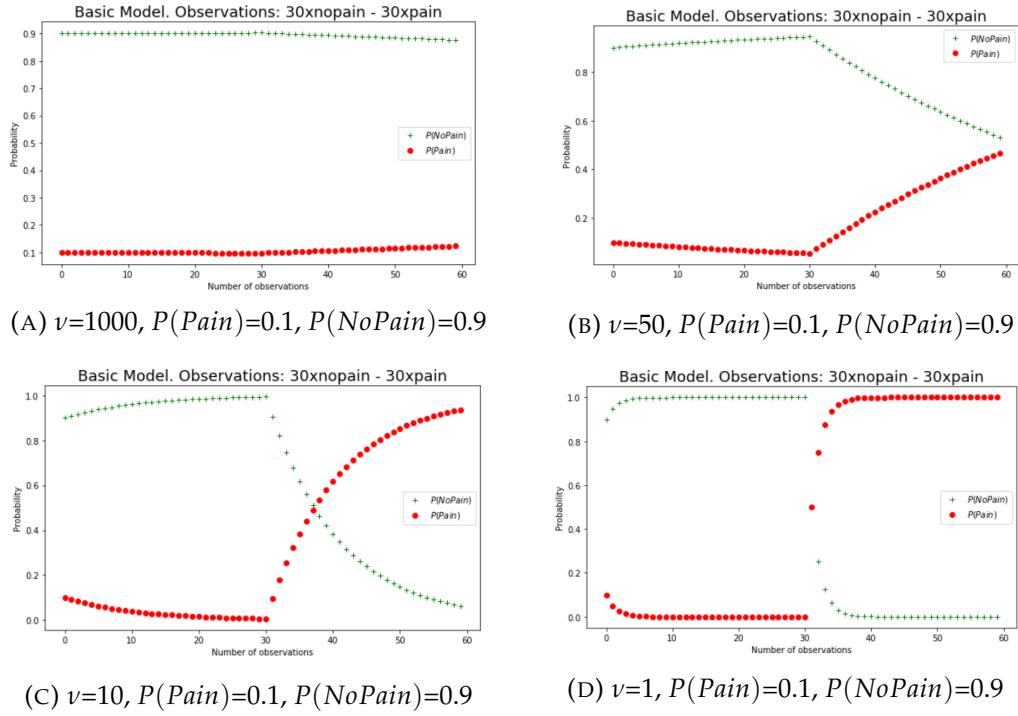
Prior. Varying the *precision* of the prior leads to the results plotted in figure 3.7.

Four different settings for the prior precision were tested and the model was exposed to 60 observations (30x pain, 30x no pain). A model with a highly precise prior ($\nu = 1.000$) was hardly influenced by the observations - the probabilities of Pain and No pain (as seen in the natural parameters of the free energy factor node) remained very close to the prior settings of 0.1 and 0.9, respectively. In contrast, the influence of a very imprecise prior ($\nu = 1$) on the posterior probability of pain is very small as it is overridden by the observations immediately.

FIGURE 3.6: Course of trajectories $P(Pain)$ 

Notes. Similar to figure 3.5, this plot shows the trajectories over the course of time for transition probabilities that were sampled from the line in equation 3.11. This time, the prior probability of pain is higher, potentially simulating a patient with chronic pain. Despite an initial $P(Pain)$ that is much lower than the prior, over the course of time, the probability to experience pain reaches baseline values.

FIGURE 3.7: Basic Model: Prior precision.



Different precision values of the prior parameter are operationalized through the pseudocount ν while keeping constant observations and likelihood parameters. For all experiments, 60 observations were made: 30 trials of no pain followed by 30 trials of pain.

3.2.2 Latent model.

Three aspects of this model were manipulated in order to simulate pain. Firstly, the **prior** on the hidden variable and the probabilities of its respective states can be adjusted. Secondly, the prior setting of the **top-down factor** ($P(sensation|pain)$) can be adjusted regarding its precision and the likelihood distribution. Thirdly, different types of **observations** can be made (harmless, nociceptive). The following parameter combinations are of particular interest for modeling chronic pain related behavior:

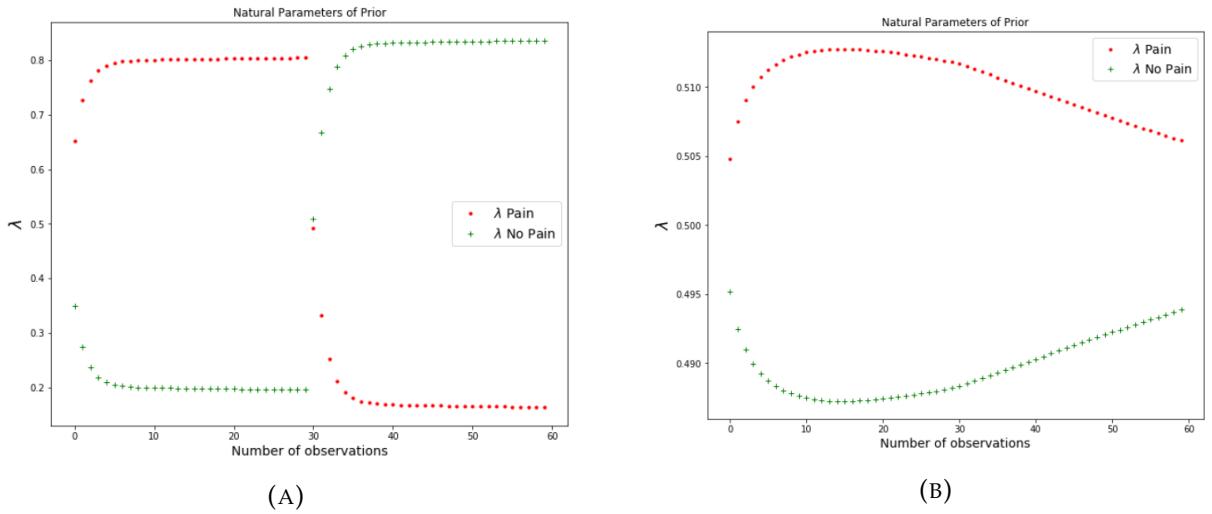
Prior $P(pain)$. The precision of the prior parameter on the first hidden node h_1 was varied to be significantly larger or smaller than the prior precision of the likelihood parameter ($\nu = 1$ vs. 100), see figure 3.8. The pseudocounts, or the parameter ν , are evaluated per state of the variable and can be interpreted as observations that are explained by the respective state. For example, if the prior ν is 100 and nociceptive input is observed, the pseudocount of "pain" will increase by approximately one (given a normal likelihood which contains a clear association between pain and nociceptive input).

60 observations were made (30x noci, 30xtickle). The prior probabilities $P(Pain)$ and $P(Nopain)$ were set to 0.5 . The likelihood distribution was $P(nociceptiveinput|Pain) = 0.8$ and $P(harmlessinput|Nopain) = 0.8$. A precise likelihood distribution in combination with an imprecise prior lead to the sensations determining the state of the hidden variables; e.g., when exposed to nociceptive stimuli, the probability of pain increases instantly. To the contrary, an imprecise likelihood function combined with a precise prior leads to slower deviations of λ from the prior probabilities.

Likelihood $P(sensation|pain)$ pseudocounts. In case the precision of the top-down factor ($\nu_{Likelihood} = 100$) is higher than the precision of the prior on the latent variable ($\nu_{Prior} = 1$), the pseudocounts of the top-down factor grow quickly with the observations of nociceptive or innocuous stimuli (3.9). In case of nociceptive input, ν_{Nopain} plateaus; in case innocuous stimuli are observed, ν_{Pain} reaches a plateau. To the contrary, if the prior on the hidden variable is assigned a higher precision than the top-down factor, the different states "share" the explanation of the observations according to the probabilities set in the prior factor, as observed in the pattern of the growth in pseudocounts (see figure 3.9 B).

Healthy interoception. Healthy interoceptive inference was simulated by setting the prior parameters to $\nu_{prior} = 100, P(Pain) = 0.2, P(Nopain) = 0.8$ and implementing a likelihood distribution with $\nu = 80, P(Nociception|Pain) = P(harmlessinput|Nopain) = 0.8$, see figure 3.10. These settings simulate "healthy" individuals who expect to find themselves in a pain-free state rather than in pain ($P(Nopain) > P(Pain)$). This expectation is rather certain ($\nu = 100$);

FIGURE 3.8: Latent Model: precise likelihood vs. precise prior.



Precise likelihood distribution and imprecise prior.

Prior: $\nu = 1$, $P(Pain) = P(Nopain) = 0.5$

Likelihood: $\nu = 100$,

$$P(Noci|Pain) = 0.8, P(Tickle|NoPain) = 0.8$$

Observations in both cases were 30 trials of nociceptive input, followed by 30 trials of harmless input.

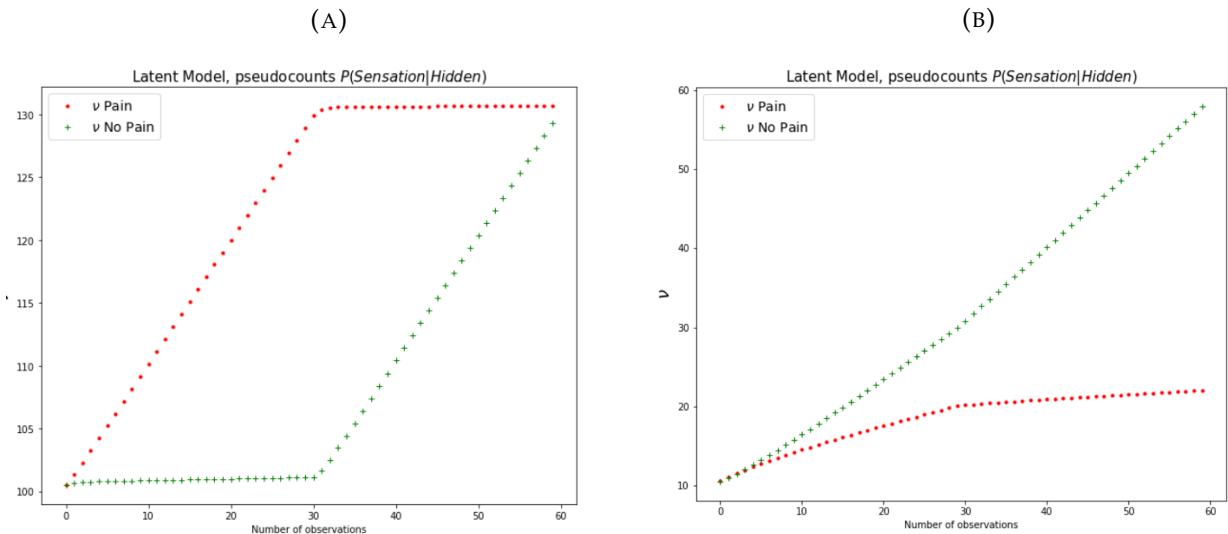
Precise prior and imprecise likelihood distribution.
 $P(\text{prior}) = 100$, $P(P_{\text{prior}}) = P(N_{\text{prior}}) = 0.5$

Prior: $\nu = 100$, $P(\text{Pain}) = P(\text{No pain}) = 0.5$.

Likelihood: $\nu = 1$,

$$P(\text{No}ci|\text{Pain}) = 0.8, P(\text{Tickle}|\text{No}pain) = 0.8$$

FIGURE 3.9: Latent Model: Likelihood: ν and λ



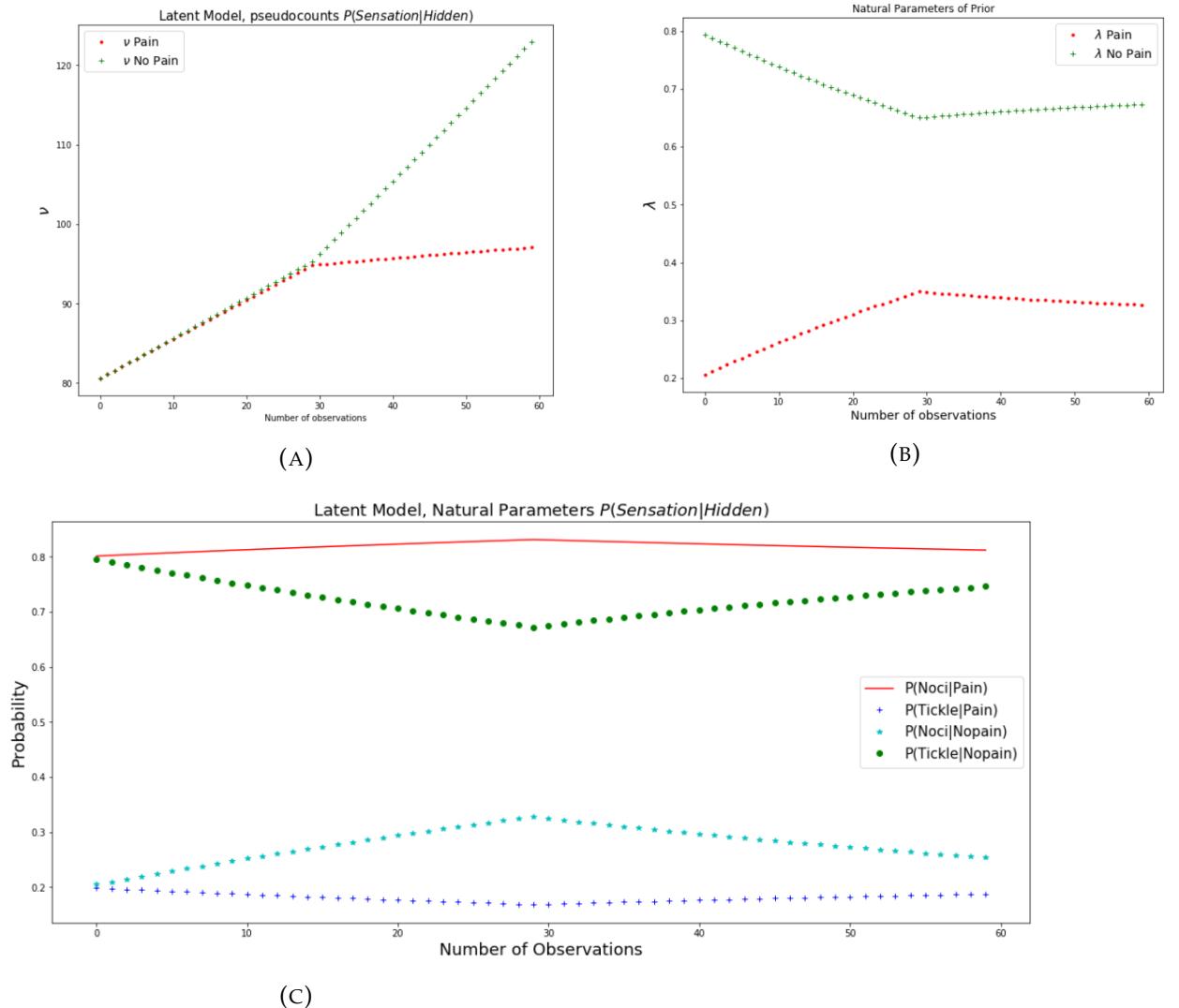
A. Pseudocounts of the top-down factor. The combination of an imprecise prior ($v = 1$, $P(\text{Pain}) = P(\text{No pain}) = 0.5$) and a precise likelihood distribution ($P(\text{Noci}|\text{Pain}) = P(\text{Tickle}|\text{No pain}) = 0.8$, $v = 100$) lead to the observed pattern in pseudocount growth after 30 observations of nociceptive input followed by 30 observations of innocuous input.

B. Pseudocounts of the top-down factor grow with observations - there is no plateau in the function as the states (pain and no pain) share the explanation of each observation according to the prior setting (here: $P(\text{pain}) = 0.2, P(\text{nopain}) = 1 - P(\text{pain})$).

however, it can be overwritten by prolonged observation of nociceptive input (100 trials or highly precise information). These individuals are able to distinguish between the types of sensory information they received and establish

relatively clearly to what extent these observations are associated with pain ($P(noci|pain)$, $P(tickle|nopain)$) are high). As seen in figure 3.10, with these settings, more of the observed data (30x nociceptive input followed by 30X innocuous stimuli) is explained by, or interpreted in the sense of, a pain-free state (see subfigure A, representing growth in ν). Further, both types of observations can be distinguished and associated with the pain- or pain-free state: upon observation of nociceptive input, the probability of $P(\text{nociceptiveinput}|pain)$ increases, whereas the probability of $P(\text{nopain}|\text{harmlessinfo})$ increases when harmless information is observed. Both of these probabilities are much higher than their complements, $P(\text{Nociceptiveinput}|Nopain)$ and $P(\text{harmlessinput}|pain)$, which suggests that the associations are learned and will become tighter when more observations are made.

FIGURE 3.10: Latent Model: Healthy interoception.



A. The pseudocounts of the top-down prior increase when 60 observations are made. Starting from a prior precision of $\nu = 80$, the first 30 observations of nociceptive input are explained by both the pain- and the pain-free state, which is due to the high prior expectation of the pain-free state ($P(\text{nopain}) = 0.8$). When harmless input is observed, the probability of the pain-free state increases further, whereas the probability of being in pain decreases over time.

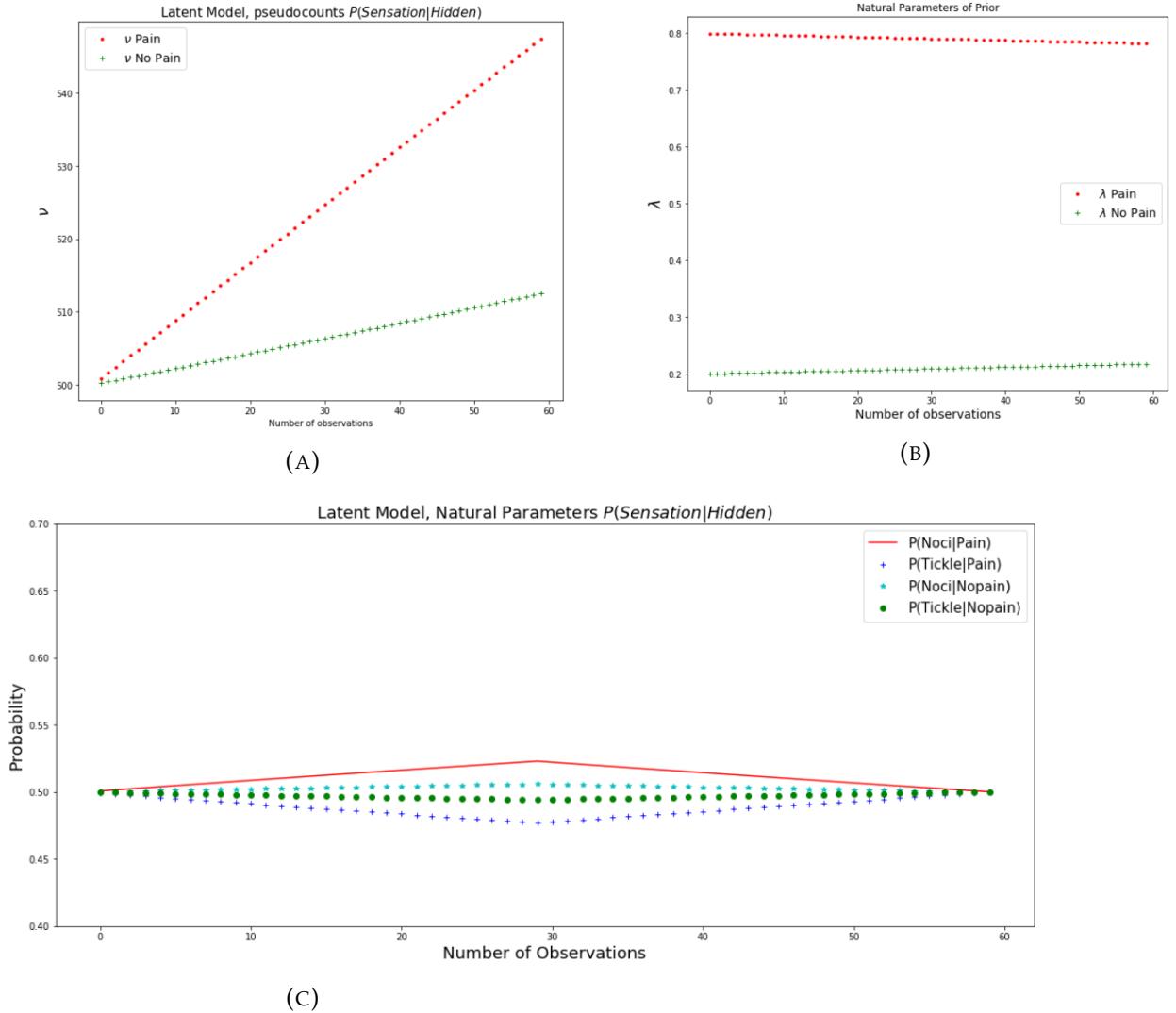
B. In B, the natural parameters of the prior factor on the hidden variable are illustrated. Starting at a high expectation of a pain-free state (0.8), this decreases slightly as nociceptive input is observed. The decrease is relatively high as top-down prior and hidden state prior have similar precisions ($\nu_{\text{prior}} = 100.0$, $\nu_{\text{top-down}} = 80.0$).

C. In this simulation, both types of observation (noci = nociceptive input; tickle= harmless input) are distinguished and associated with pain in a "normal" manner. It is learned here that nociceptive input is more probable than harmless input given pain and vice versa.

Chronic pain. Dysfunctional interoceptive inference was modeled by setting the prior parameters to be very precise and towards an increased expectation of pain before any observations are made ($\nu_{\text{prior}} = 1000$, $P(\text{Pain}) = 0.8$, $P(\text{Nopain}) = 0.2$) and by implementing a likelihood distribution that models an inability to distinguish between sensations; with $\nu = 500$, $P(\text{Nociception}|\text{Pain}) = P(\text{Tickle}|\text{Nopain}) =$

0.5, see figure 3.11. In this case, the pseudocounts for the hidden state of pain grow significantly faster than those for the pain-free state (see figure 3.11 (A)), which means that more observations are interpreted in the sense of a pain state. Even harmless sensations are associated with pain in this model. Moreover, the increased expectation of pain is hardly deviated from - even after observing different types of sensory input (see figure 3.11 (B)), which is due to the highly precise prior expectation of pain. Lastly, the simulated individual is rather uncertain about the distinction between different types of sensory input, which can be seen in the natural parameters of the top-down factor, depicted in figure 3.11 (C): observations have a rather small impact and they cannot be distinguished from each other clearly.

FIGURE 3.11: Latent Model: Chronic Pain.

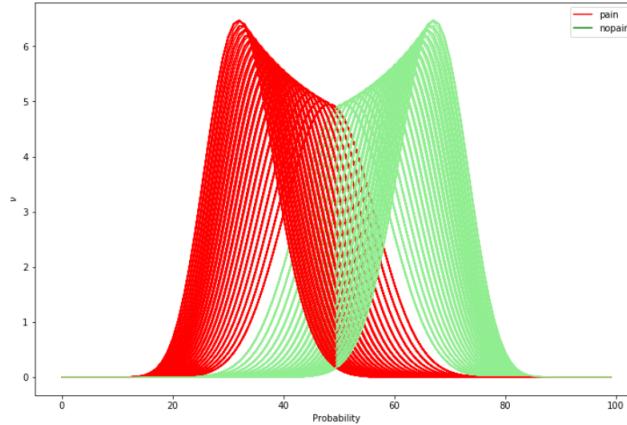


- A. The observations (30x nociceptive input followed by 30x harmless input) are accounted for by a pain state; which is due to the precise and increased prior expectation of pain.
- B. Making different types of observations hardly influences the prior expectation of pain and pain-free states.
- C. The different conditional probabilities cannot be distinguished from another and do not change significantly upon learning new observations.

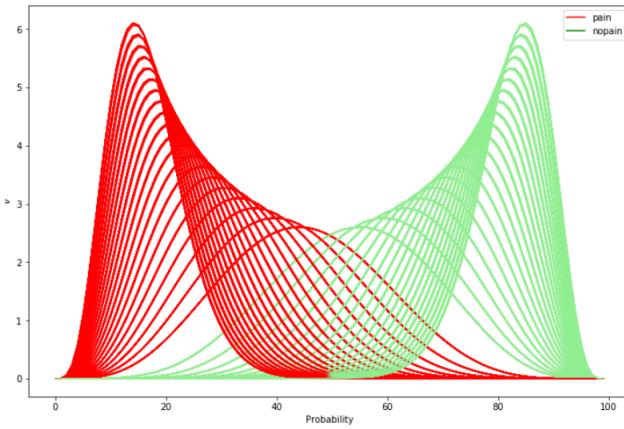
3.2.3 Model with N time-steps

In the model with N time-steps (implemented here: 20 time-steps), there are four starting points which can be manipulated in order to adapt the model's behavior. Like in the models before, the **prior** on the first hidden variable and the **top-down factor** were varied. Further, the prior on the **transition probabilities** within the Markov chain was modified. Lastly, different types of **observations** can be made.

FIGURE 3.12: Learning plots



(A) Precise prior



(B) Imprecise prior

Notes. In all cases, a hierarchical model with 20 time-steps was exposed to 20 trials of harmless sensory input per node. red curves represent the probability of pain, whereas green curves illustrate the probability of no pain (through the natural parameters alpha and beta). Precise prior expectations (simulated via a high prior pseudo count) are determined by observations a lot less than more imprecise prior information (B).

3.2.4 Learning in the HMM

Figure 3.12 illustrates learning in this model. When the system receives and recognizes sensory information, the precision of the hidden state generative model increases. A more dramatic increase in precision can be observed when the prior parameter is initially imprecise (3.12b), which represents uncertainty about what internal state to expect. Observations here determine the future expectations to a greater extent (higher information-theoretic entropy). To the contrary, very precise prior knowledge is hardly deviated from after observing sensory data (see 3.12a).

3.2.5 Chronic pain and healthy inference

Additional result plots can be found in the supplementary material. The following settings were used to simulate normal, or healthy, interoceptive inference:

Prior on first hidden variable. A pain-free state was expected to be more likely than pain ($P(pain) = .2, P(nopain) = 1 - P(pain)$) with a relatively high prior precision of $\nu = 100$.

Top-down prior. $P(nociceptiveinput|pain)$ and $P(harmlessstimulus|nopain)$ are set to be relatively high in the case of normal inference, with .8 and .9, respectively. The prior precision of the top down prior is $\nu = 100$.

Transition prior. Experiencing pain after being pain-free in a previous time-steps is relatively unlikely in the simulation of healthy inference $P(pain|nopain) = .2$. Likewise, pain is likely to subside quickly in case it is experienced, with $P(nopain|pain) = .7$. The precision of these probabilities is, however, moderately soft with $\nu = 50$.

Observations. Mixed observations are made with innocuous stimulation from node 1 through to node 5 and nociceptive input from node 12 to 18.

The resulting marginal probabilities of pain are shown in figure 3.13. The marginal probability of pain increases only when the system is confronted with nociceptive sensory information. In this case, the pain-state is assigned a very high probability. The probability of pain quickly drops to its prior levels after nociceptive stimulation ceases.

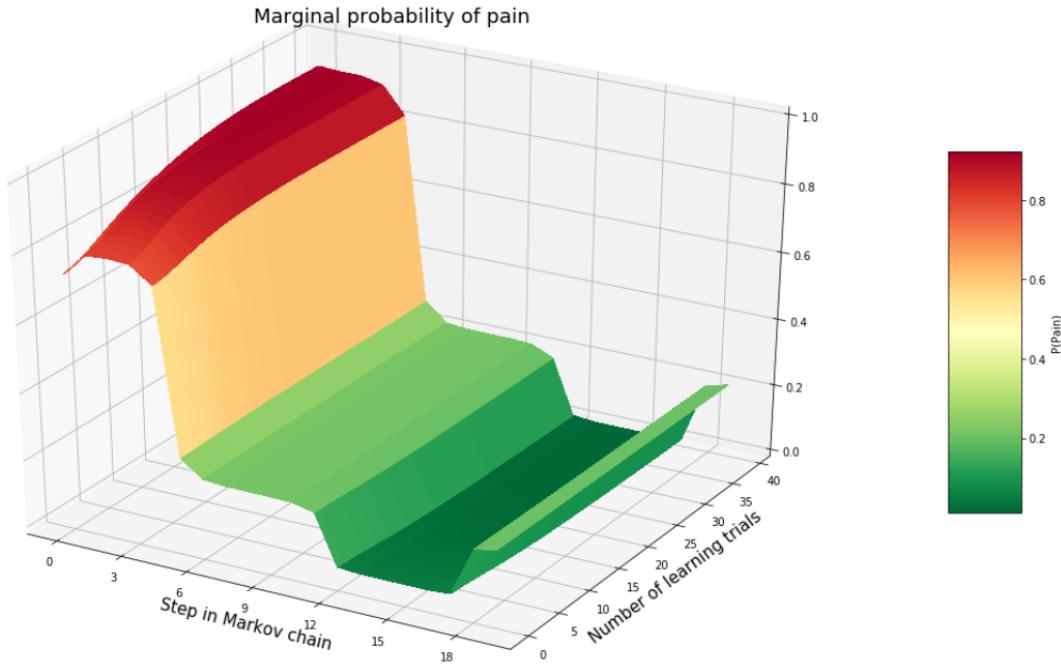
To simulate a patient with chronic pain, the parameter were set as follows:

Prior on first hidden variable. The prior was rather precise ($\nu = 100$) and contains an increased prior expectation of pain over no pain ($P(Pain) = 0.8$). Individuals with this prior expect to find themselves in a state of pain more regularly.

Top-down prior. The precision of the top-down prior is adjusted to be relatively imprecise ($\nu = 20$) and the associations between the different observable sensory stimuli and pain are unclear ($P(pain|noci) = 0.6, P(nopain|noci) = 0.6$). This translates into an individual who is unable to distinguish well between the sensory information it perceives. Also, sensory information is not "sampled" very much as the information from prior knowledge is weighted much more (higher precision of prior expectations).

Transition prior. The precision of the transition prior is assigned a rather high value ($\nu = 100$). The probability of remaining in a pain-state after perceiving pain is high ($P(pain_t|pain_{t-1}) = 0.8 > P(nopain_t|pain_{t-1}) = 0.2$). The probability of perceiving pain after being in a pain-free state in the previous time-point are also set to be higher ($P(pain_t|nopain_{t-1}) = 0.7 > P(nopain_t|nopain_{t-1}) =$

FIGURE 3.13: Simulation of healthy inference



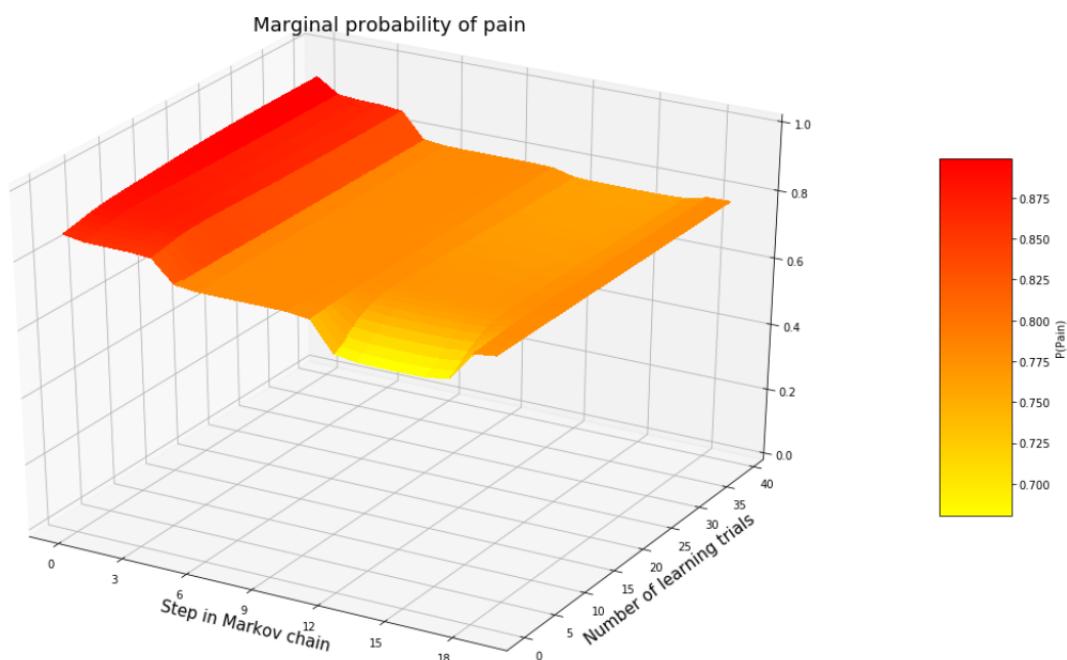
Notes. Marginal probabilities of pain in a simulation of healthy interoceptive inference after mixed observations (nociceptive stimulation at nodes 0 to 5 and harmless sensory input from nodes 12 to 18, 40 trials per node.) A quick increase in the probability of pain upon observation of nociceptive input is observed which decreases after nociceptive input stops.

0.3). These settings simulate individuals who expect to remain in pain, or to experience pain in the future even when they are currently pain free.

Observations. All models are exposed to 10 trials of harmless sensory information at the observable nodes 0 to 5 and 10 trials of nociceptive input from observable node 12 through to node 18. The rest of the nodes remain unobserved.

The resulting pain probabilities over time are shown in figure 3.14. There are two interesting aspects of these results. Firstly, the probability of being in pain (operationalized over the marginal probabilities of pain in the hidden variable nodes) remains more or less at its prior level of 0.8. Upon observing something, this is deviated from; however, the probability returns to its a priori levels when no sensory input is observed. Secondly, both types of sensory information (nociceptive input at the first 5 nodes; harmless input from nodes 12 through 18) lead to an increased marginal probability of pain.

FIGURE 3.14: Chronic pain patient - mixed observations



The plots simulate the marginal probability of pain (summed over all irrelevant variable states and factors) in a chronic pain patient after observing 40 trials of nociceptive stimulation at nodes 0 to 5 and 40 trials of harmless sensory information at nodes 12 to 18. The node number is shown on the x-axis, the y-axis indicates the trial number and the z-axis as well as the color bar indicate the probability of pain. The marginal probability of pain remains relatively stable at the prior levels of .8. When nociceptive input is observed, the marginal probability of pain increases. A decrease in $P(\text{pain})$ is observed when harmless sensory information is observed; however, $P(\text{pain})$ remains at a very high level. With additional trials of observing harmless sensory information, $P(\text{pain})$ increases.

Chapter 4

Modeling data

4.1 Methods and participants

The PI-ANNA ("Pain and Interoception: ANNAhmen in Kindern und Jugendlichen mit und ohne chronische Schmerzen", engl. interoceptive expectations in children and adolescents with and without chronic pain) questionnaire was designed by T. Hechler, A. Thorwart and D. Endres specifically to measure pain-related expectations in children and adolescents, adopting an interoceptive predictive coding view of chronic pain. The questionnaire consists of 14 items of which 10 items are of particular interest for the present work (see also supplementary material). These items are designed to assess the prior expectation of pain (e.g. Item 1: "Imagine waking up in the morning- how likely are you going to be in pain?") and the self-reported likelihood model $P(\text{sensation}|\text{pain})$ (e.g. Item 7: "When you are in pain, how likely are you going to feel a tension in your stomach?"). Prior expectations of pain were assessed retrospectively at four time-points during a typical day (morning, during school, afternoon, evening). Responses were given by marking an X on a 10cm long line where the line's two end-points are marked with the words "No, I dont' have pain" on the left and "Yes, I have pain" on the right. The distance from line start to the X marked by the participants was measured and transformed into percentage values. The questionnaire data was kindly provided by Tanja Hechler and colleagues, who assessed N=35 (11-18 years of age, mean age: 14.2 years) children and adolescents with chronic abdominal pain or headache (N=15) and without chronic pain (N=20) who presented for treatment of their pain symptoms in the Vestische clinic for children in Trier, Germany or at the University Clinic of the Ruhr-university Bochum. All participants and their parents gave their written informed consent before taking the survey.

4.2 Modeling $P(\text{pain})$

Three different models and two different versions per model are fitted to the response data of the first four items in the PI-ANNA questionnaire, which assess the probability of pain at a certain time of the day (morning, afternoon, evening) or context (at school).

Whenever two models are compared to each other directly, this was done using Bayes factors (Goodman, 1999). Bayes factors allow Bayesian model comparison by quantifying the evidence in the data for one model over another one. This does not imply that the more supported model is the true model. It is given by the ratios of the posterior probabilities of two different models M_A and M_B :

$$K = \frac{P(M_A|D)}{P(M_B|D)} \quad (4.1)$$

Whenever $K > 1$, M_A is supported more by the data. According to the taxonomy given by Jeffreys, 1998, a $0 > K < 1.6$ is 'barely worth mentioning', $1.6 > K < 3.3$ indicates 'substantial support', $3.3 > K < 5.0$ is 'very strong' support and $K > 6.6$ is 'decisive'.

(Bishop, 2006). They are given as the ration of two models

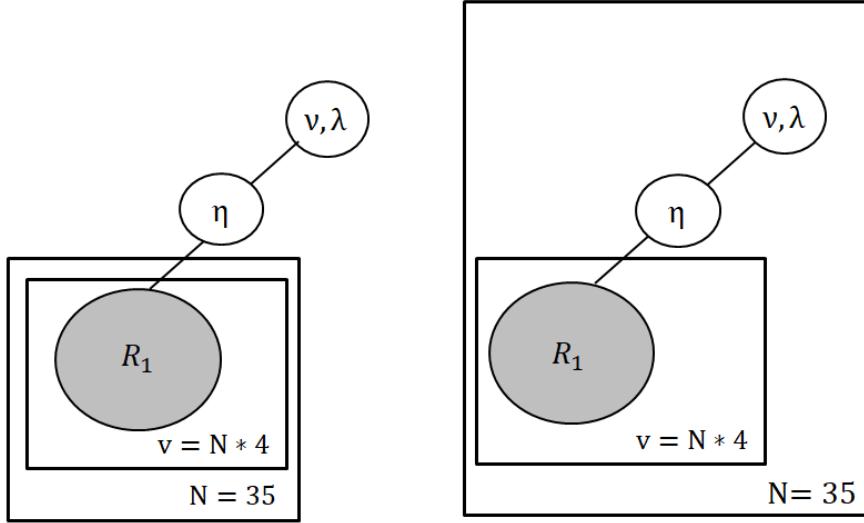
4.2.1 Basic model

The first and most simple model consists of one variable node and an implementation of free energy to learn from the observed data (i.e., the questionnaire responses). The variable node is implemented to have three different values: Response (R_k) = { no pain, moderate pain, pain }. The graphical models are shown in figure 4.1. The two different subtypes of the basic model represent assumptions about the homogeneity vs. heterogeneity of the participants. In the first scenario, there is one model for all participants which implies that all individual parameters are samples from the same distribution (i.e., equal mean, variance etc of $P(Pain)$, see the left figure in 4.1). The group level is either considered here (modeling sick and healthy control participants separately) or all participants are modeled together regardless of group identity. A slightly modified model assumes that not only the responses per participant are determined individually, but also the distributions the parameters are drawn from can be individual per patient (see right in 4.1).

4.2.2 Hierarchical model

The second model incorporates associations between context or time of the day (morning, school, afternoon, evening) and the pain response R_k . These time-points are treated as if they were more or less independent from another. In the first subtype of this model, the value of the observable variable R_k is individual whereas the parameters are equal for all participants or per group (see left, figure ??). In the second subtype, the model parameters are assumed to be unique for each patient - one individual model per participant is learned.

FIGURE 4.1: Basic Model



Notes. In the most simple scenario, the parameters η , v and λ are learned from the questionnaire responses alone. The parameters are either learned from the entire dataset (not considering potentially differing parameters per person, left) or per participant (where the parameters per participant are learned from individual distributions, right).

4.2.3 Markov chain model

[h] The third model consists of a **Markov chain** of four observations, combined with free energy learning. The graphical model is shown in figure 4.3. The variables represent the reported pain probabilities which are learned over time. In this model, the state of a variable depends on the states and probabilities of the previous variable. The evidence for two different subtypes of this model will be evaluated (see the upper and lower figures in 4.3). The first model (upper figure in 4.3) contains the assumption that an individual model per participant captures the data best. In the other case (lower figure in figure 4.3), all parameters are assumed to be equal for all participants (or all participants within a certain group)

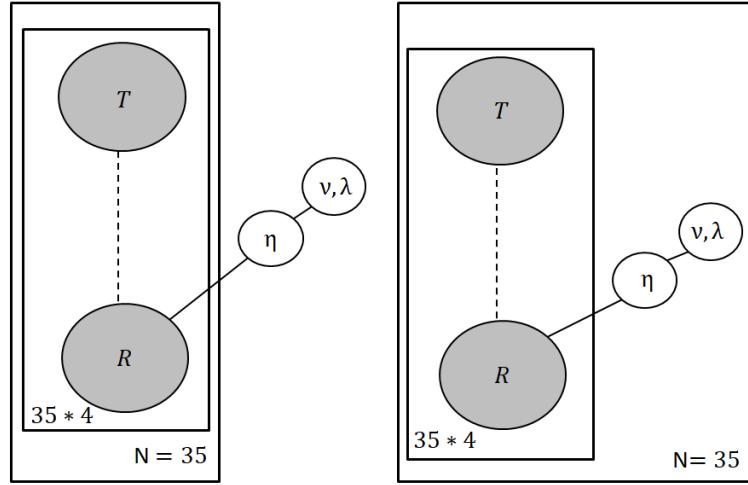
4.3 Evaluation of model evidence

The model evidence is evaluated by calculating the model's free energy, given by

$$\mathcal{L}(D, Q(M)) = \underbrace{E_{Q(M)} \log P(D|M)}_{\text{log } P(D|M)} - \underbrace{D(Q(M)||P(M))}_{\text{divergence from prior}} \quad (4.2)$$

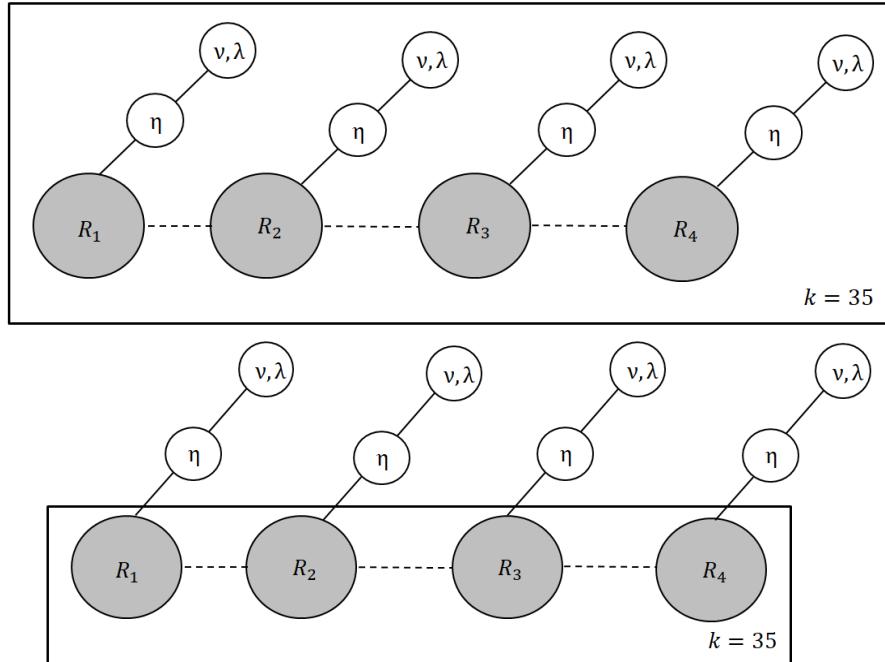
For each model, the log-probability of the data given the model, $\log P(D|M)$ is evaluated after observing the data. In addition, the KL-divergence between the approximating function $Q(M)$ and the true posterior is added to the evidence score each

FIGURE 4.2: Hierarchical model



Notes. In these two models, the pain questionnaire responses are modeled in association with the time-point or context the response is referring to. In the present case, the variable T , or time point, is set to have four values (morning, during school, afternoon, evening). Pain responses were, as before, no pain, moderate pain, pain. The parameters η , v and λ are learned from the entire dataset and hence treated as equal for all participants (left), or the parameters are learned individually per participant (which translates to one individual model per participant).

FIGURE 4.3: Markov chain model



Notes. All responses taken from the participants over the course of a day form a Markov chain of observable random variables. The free-energy learned natural parameters η and λ, v are modeled either per participant (upper case) or learned from all data, not considering the individual structure per participant.

time after parameters were learned.

This can be combined with the prior probabilities of both the data $P(D)$ and the model $P(M)$ in order to obtain the posterior probability $P(M|D)$ per model via Bayes' theorem:

$$P(M|D) = \frac{P(D|M) \cdot P(M)}{P(D)} \quad (4.3)$$

The marginal probability of the data $P(D)$ is obtained by summing the evidence over all models, i.e., by marginalizing out the models:

$$P(D) = \sum_M P(D|M) \quad (4.4)$$

The prior probability of the model $P(M)$ in this case is given by

$$\frac{1}{\#models} \quad (4.5)$$

where $\#models$ is the number of models that are considered in the model selection. One of the models will be considered as the 'true' model at the end of the selection procedure - for this reason, the sum of all model evidences is 1. Here, $P(M) = \frac{1}{6}$ as there are six models to be considered.

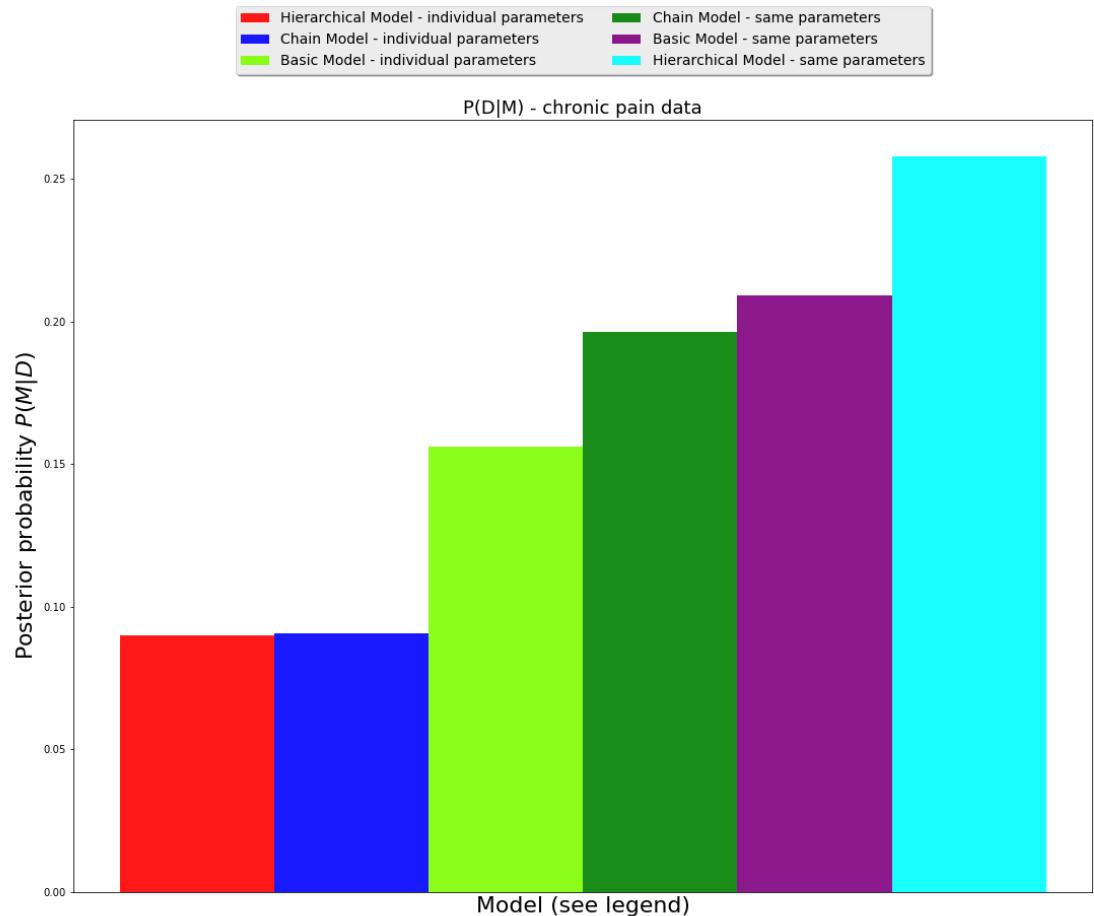
4.4 Results

The frequency of responses to the first 4 items in the PI-ANNA suggested to categorize the pain responses into three categories: expectation of being in a pain-free state at the time suggested in the questionnaire (<25%), expectation of moderate pain (25-55%), and expectation of severe pain at that time of the day (>55%, for a histogram, see supplementary material).

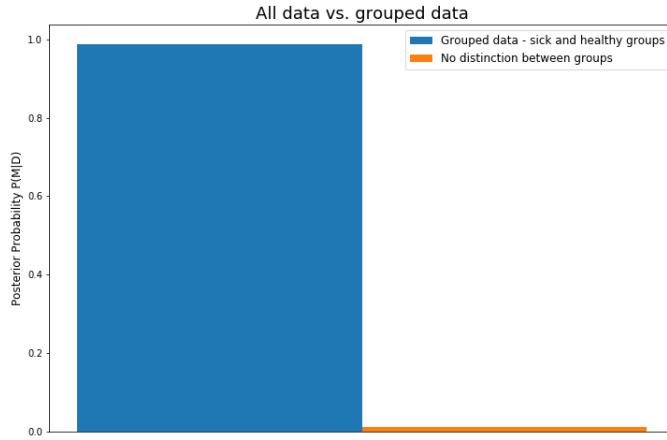
As expected, an initial analysis of the model evidence scores suggested significant group differences between healthy and control participants, which is why the two groups were treated separately in all subsequent models. Regarding patients with chronic pain, the evaluation of the posterior probability $P(M|D)$ favors the hierarchical model where all participants share a hypothetical parameter distribution (see figure 4.4) with a $P(M_{hierarchical}|D) = .2577$. The hierarchical model is followed by the basic model with $P(M_{basic}|D) = .2091$ and the Markov chain model ($P(M_{chain}|D) = .1964$). All models which treat each participant as unique have a smaller posterior probability. The hierarchical model has a $P(M_{hierarchical}|D) = .1560$ and the Markov chain model and the Basic model have a $P(M_{chain}|D = .0905)$ and $P(M_{basic}|D) = .0901$ when uniqueness is assumed.

A similar picture emerges for healthy participants (also see supplementary material). All models where participants are not considered individually, but per group score higher than those where each participant is treated as unique. Like before, the hierarchical model has the highest posterior probability with a $P(M_{hierarchical}|D) = .2828$. It is followed by the Markov chain model which has a posterior of $P(M_{chain}|D) =$

FIGURE 4.4: Model comparison - participants with chronic pain



Notes. Illustrated here are the posterior probabilities of all models given the data of only patients with chronic pain, $P(M|D)$. As shown, the hierarchical model where all parameters are assumed to be equal for all participants accounts best for the observed data.

FIGURE 4.5: $\sum_M P(M_{sick+healthy}|D)$ vs. $\sum_M P(M_{alldata}|D)$ 

Notes. All posterior probabilities of two different modeling approaches were summed according to equation 4.6. As seen here, the sum of the posterior probabilities of models where the data was grouped is higher than the sum of the posterior probabilities of models where the data was not grouped.

.2399 and the basic model with $P(M_{basic}|D) = .1864$. When each participant is considered individually, the basic model reaches the highest posterior probability with $P(M_{basic}|D) = .1452$. This is followed by the Markov chain model with $P(M_{chain}|D) = .0728$ and lastly the hierarchical model with $P(M_{hierarchical}|D) = .0727$.

Another regarding the role of the group differences was conducted to establish whether differences between healthy controls and patients with chronic pain justify different modeling approaches. Posterior probabilities of all models were summarized to see if models that allow for a distinction between healthy and sick participants score higher than models that do not account for group differences, or to put it differently:

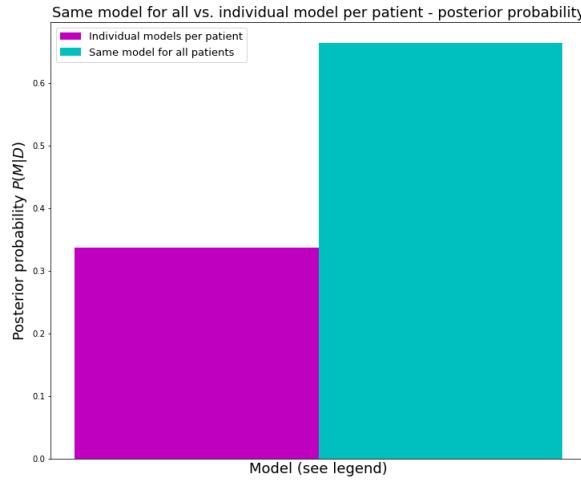
$$\sum_M P(M_{sick+healthy}|D) > \sum_M P(M_{alldata}|D) \quad (4.6)$$

In case the two groups are represented in the data in a meaningful way, all models which consider the distinction between the two groups combined should score higher than models where this distinction is not accounted for. Results of this analysis are shown in figure ???. The sum over all posteriors when group differences are modeled is $\sum_M P(M_{sick+healthy}|D) = .9877$. The sum over all posteriors when group differences are not accounted for is $\sum_M P(M_{alldata}|D) = .0123$. The Bayes factor for this comparison is

$$\frac{\sum_M P(M_{sick+healthy}|D)}{\sum_M P(M_{alldata}|D)} = 80.45 \quad (4.7)$$

which indicates very strong evidence in favor of the model where groups are accounted for.

FIGURE 4.6: Individual versus shared model per participant



Notes. The difference in posterior probability of models where participants are considered on an individual level (magenta) versus a group-wise modeling of the data (cyan).

A further analysis suggested modeling the data group-wise rather than modeling each participant individually (see figure 4.6). $\sum_M P(M_{individual}|D) = .337$ whereas $\sum_M P(M_{shared}|D) = .663$, which can be translated into a Bayes factor of

$$\frac{\sum_M P(M_{shared}|D)}{\sum_M P(M_{individual}|D)} = .663 / .337 = .663 / .337 = 1.96 \quad (4.8)$$

This can be interpreted as substantial evidence in favor of models that do not account for each participant individually, but group-wise.

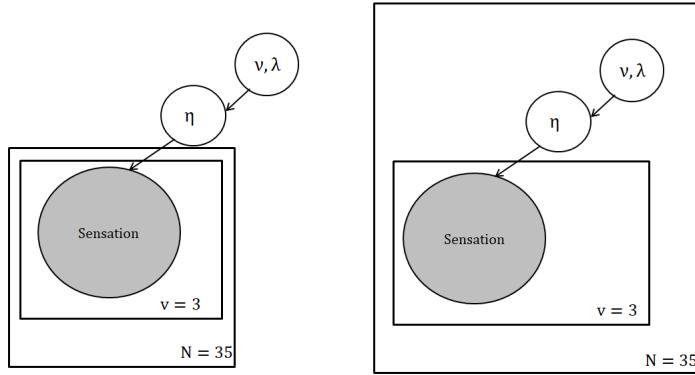
4.5 Modeling $P(sensation|pain)$ and $P(sensation|nopain)$

Three different models in two different versions are used to analyze the responses concerning the likelihood of $P(sensation|pain)$ and $P(sensation|nopain)$. The remaining questions in the PI-ANNA questionnaire assessed the probability of feeling an interoceptive sensation (stomach tension, neck tension, hand tension), given being in pain (or no pain).

4.5.1 Basic model for all sensations

In the first and most simple model, sensations were modeled independently of the pain-state. All sensations are modeled via one variable node with three different categories: $\{yes, maybe, no\} \in S$. This means that participant responses (probabilities of a sensation) were modeled as present, maybe present or absent. There was no distinction between the different types of sensations (stomach, neck and hand). The graphical model is represented in figure 4.7

FIGURE 4.7: Basic likelihood model



Notes. For the basic model, a variable node with three different observable states (sensation: yes, maybe, no) was connected to a free-energy factor node. Two different versions of this model were implemented: first, a mode where all responses were modeled irrespective of the participant (this corresponds to one model for all participants, left) and another model where an individual model was learned per participant (right).

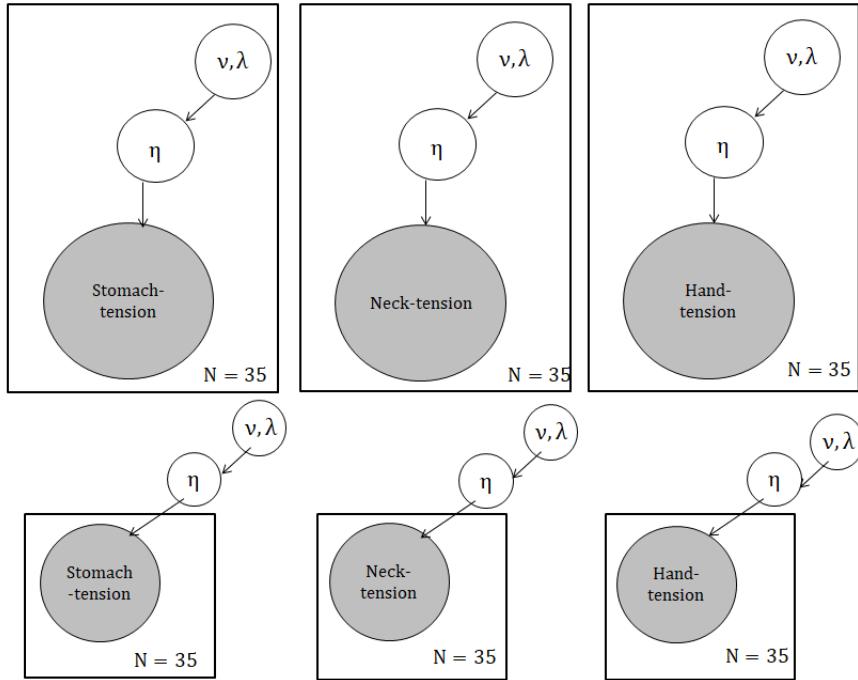
4.5.2 Basic model sensation specific

In the next model, responses are analyzed in more detail as the type of the sensation is considered. The sensation specific model (see 4.12) is an iteration of the basic model introduced above; however, one model accounts for one specific sensation (i.e., stomach-, neck- and hand-tension individually), not the sum of all sensations. Again, a sensation-specific model is tested on an individual level, so that each participant is modeled individually; or group-wise, where all participants in one group are modeled together. All three observable variables (stomach-tension, neck-tension and hand-tension) can take on three different values (yes, maybe and no) and are connected to a free energy factor which allows learning from the data.

4.5.3 Hierarchical model

A further model is implemented to account for potential associations between the pain-state and the sensation. For this purpose, responses to the three items assessing $P(\text{sensation}|\text{Pain})$ and the three remaining items assessing $P(\text{sensation}|\text{nopain})$ are modeled with an additional, superordinate observable variable node which is connected to the sensation nodes (stomach-, neck- and hand-tension). The superordinate node contains information about the pain state of the participant. In case of $P(\text{sensation}|\text{Pain})$ items, the 'pain' node is set to the value 'pain'; for $P(\text{sensation}|\text{nopain})$ responses, this node is set to 'no pain'. The information on whether or not a sensation is observed (yes, maybe, no) is processed within the corresponding sensation-node. As before, two different versions of this model are implemented. One model is used to account for each participant individually (figure 4.10); whereas in another approach, the data is modeled group-wise (4.9)

FIGURE 4.8: Sensation-specific model



Notes. The sensation specific model is an iteration of the basic model described above insofar as here, the sensations assessed in the questionnaire are modeled individually. In the upper three cases, stomach-, neck and hand-tension are modeled per participant. In the lower three cases, there is one model for each sensation; however, the data is not structured into the additional participant level.

4.6 Results: $P(\text{sensation}|\text{pain})$

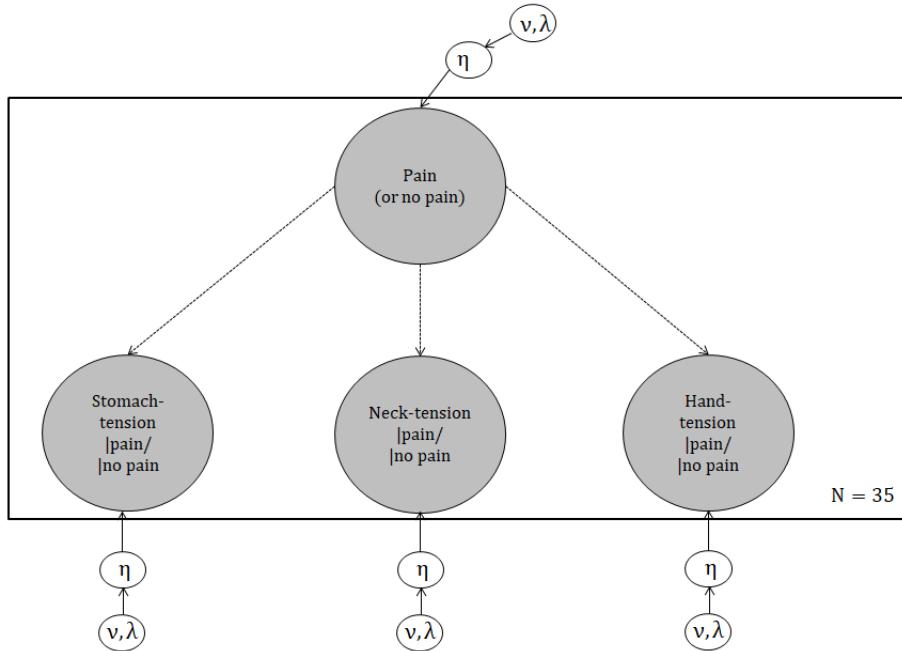
Response frequencies confirmed the three response categories introduced above (yes, maybe, no; see supplementary material).

Regarding the basic model (figure 4.7), the data supports an individual model per participant ($P(M_{\text{basic-individual}}|D) = .5616$, right figure in 4.7) over the model where group differences are accounted for ($P(M_{\text{basic-grouped}}|D) = .3187$) and the model where groups are not accounted for ($P(M_{\text{basic-all}}|D) = .1196$), see also figure ??

When fitting the sensation-specific model to the data (see 4.12), a model selection procedure suggests a preference for modeling grouped data ($P(M_{\text{specific-grouped}}|D) = .4633$). A modeling approach where the group differences were not considered ($P(M_{\text{specific-all}}|D) = .3497$) reached a smaller posterior probability, followed by the model where each participant is considered individually ($P(M_{\text{specific-individual}}|D) = .1870$), see also figure 4.12.

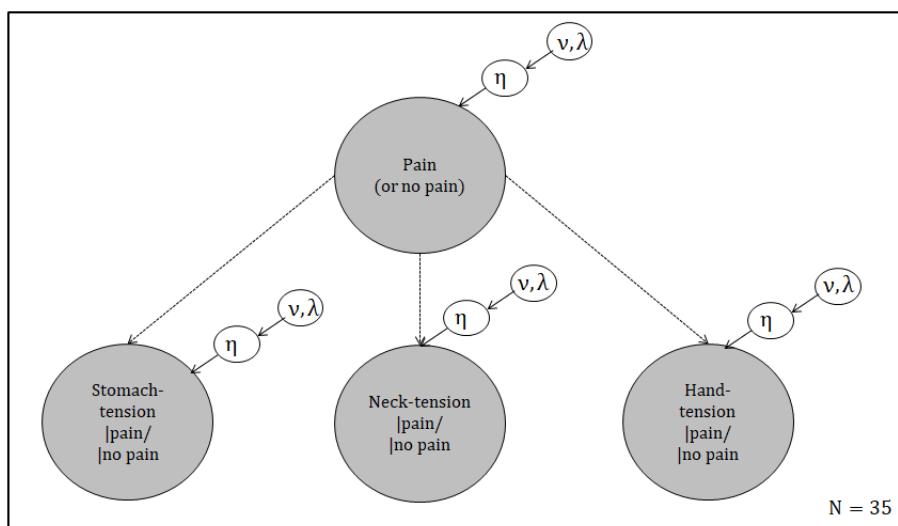
A similar picture emerges when fitting the hierarchical model to the data (see 4.9 and 4.10). Here, a group-wise modeling approach is preferred slightly over modeling the non-grouped data ($P(M_{\text{hierarchical-grouped}}|D = .4523, P(M_{\text{hierarchical-non-grouped}}|D) = .4160$). Modeling each participant individually here reached the smallest posterior probability ($P(M_{\text{hierarchical-individual}}|D) = .1317$, see also figure 4.13).

FIGURE 4.9: Hierarchical likelihood model



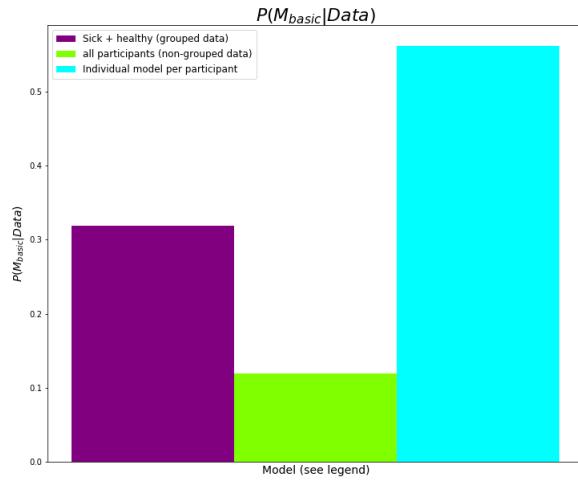
Notes. A superordinate variable node can take on the values 'pain' or 'no pain', depending on the specific items that are analyzed. It is connected to three variable nodes representing the three different types of observations assessed in the questionnaire. These can be present, maybe present, or absent. In this approach, the data is modeled group-wise, as indicated by the free-energy nodes outside of the box - the model is learned after all data is observed.

FIGURE 4.10: Hierarchical likelihood model



Notes. See above. This instantiation of the hierarchical model is approaching the data on a participant level, that is, all data from one participant is modeled and learned individually.

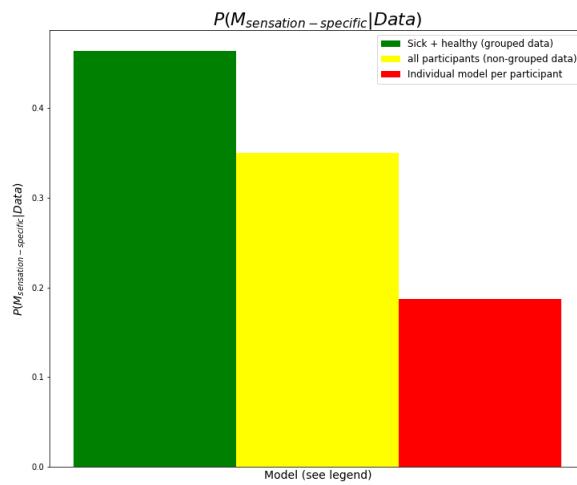
FIGURE 4.11: Evidence for basic likelihood model



Notes. Looking at the basic model, modeling each participant individually is supported most by the data. One model per group (purple bar) or one model for all responses (green bar) are less well supported by the data.

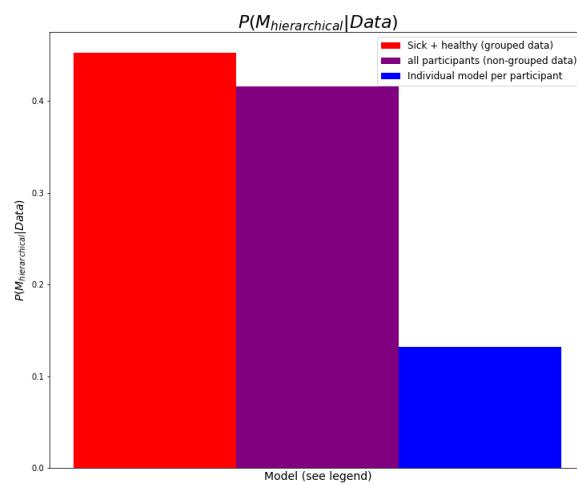
The posterior probability of all models suggests a clear advantage of the sensation-specific model when compared to the basic likelihood model or the hierarchical model (see figure 4.14). The sum of the posterior probabilities of the basic model is $\sum_{M= basic} P(M_{basic}|D) = 1.0576^6$, while for the hierarchical model, a posterior probability of $\sum_{M= hierarchical} P(M_{hierarchical}|D) = 1.500^{88}$. All three variations sensation-specific model reach a combined posterior probability of $\sum_{M= specific} P(M_{specific}|D) = \tilde{1.0}$. Bayes factors regarding the comparison of a sensation specific model on non-grouped versus on grouped data suggested a small advantage of modeling grouped data: $BF = P(M_{specific,grouped}|D \div P(M_{specific,non-grouped}) = 1.325)$. For a comparison of all grouped versus non-grouped data, see the supplementary material, figure 13.

FIGURE 4.12: Evidence for a sensation-specific likelihood model



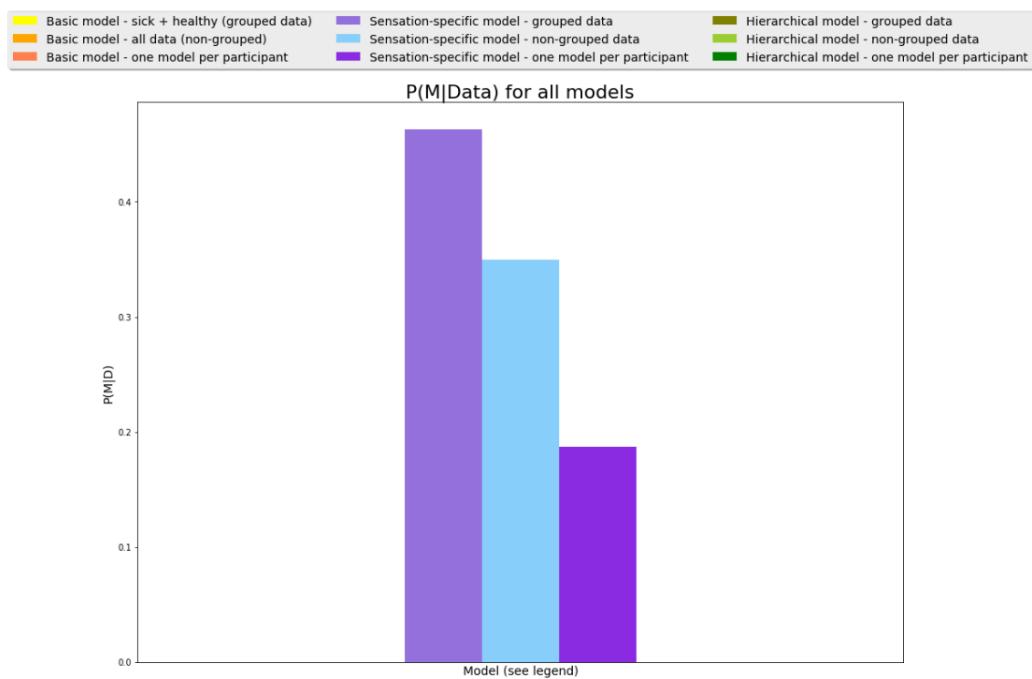
Notes. When modeling the responses specific to the assessed sensations, a group-wise approach seems to be preferable. This is followed by a model where the groups (patients and healthy controls) are not considered as distinct from another. Modeling each participant individually is least supported by the data.

FIGURE 4.13: Evidence for hierarchical likelihood model



Notes. Concerning the hierarchical model, a group-wise approach (e.g. modeling chronic pain patients and healthy controls separately) is preferred over a model where distinctions between the groups are not considered in the modeling process. The analysis yields that modeling each participant individually is the least favorable approach.

FIGURE 4.14: Posterior probabilities of all likelihood models



Notes. A model comparison between all likelihood models suggests a clear advantage of the sensation-specific likelihood model over a basic likelihood model and a hierarchical likelihood model. Within the sensation-specific model, a group-wise approach is preferred over non-grouped or individual models.

Chapter 5

Discussion

5.1 A Bayesian Model for Chronic Pain

In the present work, a Bayesian model for chronic pain is described. It uses machine-learning concepts and techniques in order to simulate processes that could underly the etiology of chronic pain on a computational level. Specifically, a hidden Markov model with two hierarchy levels (latent and observable random variables) was implemented for the purpose of simulating the dynamics potentially underlying the disorder. Learning over time and learning from observed data was implemented using variational free energy. We tested the effects of various parameter settings within this model for chronic pain.

Simulations of chronic pain were characterized by only small deviations from prior expectations when observations were made - indeed, sensory information hardly influenced the probability of perceiving pain in this case. Parallel to this, research in this field suggests that chronic pain patients might not attend to the actual sensory information they are confronted with, but rather rely on their increased prior expectation of pain (Tracey, 2010; Edwards et al., 2012). This is in line with a current discussion about the central role of expectations as key etiologic- and maintaining factors of numerous mental disorders (Rief et al., 2015; Hechler, Endres, and Thorwart, 2016). Several mental conditions, such as schizophrenia and conditions related to "hysteria", are currently discussed from a similar perspective (i.e., abnormal and inflexible reliance on prior expectations and internal models, which are insufficiently constrained by sensory information (Fletcher and D., 2009; Edwards et al., 2012)).

A further characteristic of the simulation of chronic pain is that innocuous stimuli become associated with pain. This is also observed in patients with chronic pain and referred to as allodynia (Flor and Turk, 2015). In the simulation, this is an effect of the increased prior probability of pain. Pain is the most likely cause of a wide range of sensory input that is usually explained by alternative models. Here, due to the increased prior probability, pain is automatically the most likely cause of nociceptive, but also harmless sensory input which in healthy inference is accounted for by a "no pain" model. Also, the recognition of and differentiation between types of sensory input is difficult in this simulation due to the low precision and more or less meaningless probabilities of $P(\text{sensation} \in \{\text{nociception}, \text{harmless input}\} | \text{pain}) = .5$

Contrarily, healthy interoceptive inference is characterized by a more flexible return to prior probabilities (a consequence of the "softer" prior on first hidden variable and the more precise top-down prior which associates sensory information with pain) and a more pronounced determination by sensory information rather than inflexible reliance on an increased prior expectation of pain. Upon observation of nociceptive stimuli, the probability of pain increases abruptly to very high levels. This circumstance is crucial for the warning function of pain: an individual who reliably infers "pain" as the cause for nociceptive information is able to react quickly and initiate protective behavior. In the ideal case, this protective behavior is refrained from once nociceptive stimulation stops, which supports general functioning of the individual in the longer term.

5.1.1 Modeling of pain data

Different models for the prior expectations of pain and the likelihood model were fitted to questionnaire data of children and adolescents with chronic pain.

Interestingly, this procedure suggests that models who do not account for every participant individually are preferred over models in which this is the case. On the one hand, this could suggest significant resemblances within the group regarding the prior expectation of pain. On the other hand, models who do not account for each participant individually are more parsimonious and hence preferred in Bayesian model selection.

For both healthy and control participants, a model that associates a specific response with the context the response is referring to, achieved the highest evidence. This means that the pain responses are determined by context, rather than by the previous time-step. There are several reasons for this observation. Conditioning paradigms and research in predictive coding suggest that expecting pain increases the probability to perceive pain (Tracey, 2010; Tabor et al., 2017; Büchel et al., 2014). If, for example, an individual was confronted with unusual amounts of nociceptive stimuli in school due to nervousness-related stomach problems, the results suggest that the prior expectation of pain is updated only for the context the observations were made, leading to increased expectations of pain only in this context (or at this specific time of the day).

An important clinical implication of this finding is to plan exposure sessions in the context where the pain is expected most, to work on lowering the prior expectation of pain context-specifically. This would also eliminate the risk of renewal effects once the therapeutic context is left.

However, the wording of the question could have encouraged participants to make associations between context and expected pain - even if there are none in reality.

Several reasons for the unsatisfactory fit of the Markov chain model are conceivable. First, it is possible that the time-points in the Markov model are on a much faster time-scale than the ones measured here (i.e., 10:00, 10:15, 10:30, .. instead of

morning, noon, afternoon, evening). The Markov model might be able to capture transitions within hours or minutes, while the questionnaire responses refer to differences over the course of several hours. One could test this argument by handing out portable devices which would allow a more frequent and mobile assessment of expectations over the course of a day in the patients day-to-day life. Secondly, the relationship between the responses given in the questionnaire and the "true" pain a participant is confronted with is more than unclear. Interoceptive ability is based on various processes prone to distortions and biases, e.g., interoceptive accuracy and -awareness (Garfinkel et al., 2015). Additional response biases (e.g., due to demand characteristics, extreme response bias etc.) are likely. For this reason, it must be assumed that the data are corrupted by a lot of noise, which is suboptimal for modeling Markov chain models and transition probabilities.

Regarding the participants' likelihood model, the model selection suggests modeling each sensation specifically, which suggests significant differences in the type of sensation and their association with pain. This was to be expected, as tension in stomach and neck is probably experienced as more aversive by patients with chronic abdominal pain or headache than a tension in the hand. Further, significant differences in the likelihood models of chronic pain patients and healthy controls are suggested, as a group-wise modeling approach achieved a higher evidence score than an approach where the group-level was not considered. This means that there are differences in the participants' sensation-specific likelihood models, i.e., $P(stomachtension|pain)$. Translated to clinical practice, this finding is evidence for an exposure to interoceptive sensations in patients with chronic pain - ideally, by exposing the patient to the sensation associated the closest with pain and hence working on the individual likelihood model $P(sensationA|pain)$. However, this finding needs further investigation. One, because the database is rather weak and results only indicate slight tendencies regarding group differences. This cannot be interpreted straightforwardly. Two, to further investigate the likelihood models of chronic pain patients, it would be necessary to assess data on $P(harmlessensation|pain)$ which is currently not considered.

Surprisingly, an association between pain-state and the probability of a specific sensation was not favored in the present work. A more or less tight association between pain and presence of interoceptive sensation was expected, for example because studies suggest that interoceptive fear conditioning is associated with the development of chronic pain (Flack et al., 2017). The lack of evidence for this type of model could again be related to the low resolution of the questionnaire data and the nature of Bayesian model selection, where simple models are preferred over more complex models (Myung and Pitt, 1997). Complex models only achieve a higher posterior probability than simpler models if the additional model parameters make a significant contribution to explaining the patterns in the data. This does not appear to be the case for the hierachal likelihood model.

5.1.2 Nullspace of psychotherapy

An important goal of the present work was to derive the transition probabilities¹ necessary for the simulation of persistent pain despite varying sensory input. For this purpose, all probabilities were expressed through a linear system of equations. This system, however, was not sufficiently described due to the dependencies between the baseline probabilities of 'pain' and 'no pain' ($P(\text{No pain}) = 1 - P(\text{Pain})$). The solution to the linear system of equations was a straight line given by (in the case of staying in a state of no pain when currently not perceiving pain, $P_{np_{t+1}|np_t}$)

$$P_{np_{t+1}|np_t} = \frac{1 - 2P_{\text{pain}}}{1 - P_{\text{pain}}} + \frac{P_{\text{pain}}}{1 - P_{\text{pain}}} P_{\text{pain}_{t+1}|P_t} \quad (5.1)$$

Consequent simulations have suggested that if the transition probabilities take on values that were sampled from this line, the virtual patient will maintain in a chronic pain state regardless of the prior expectation of pain. This could be the 'nullspace of psychotherapy'. Even if reductions are achieved and the patient's pain perception decreases for a while; given sufficient time (-steps in the model), the probability of perceiving pain will develop towards its original level. In other words: as long as the transition probabilities are not targeted substantially during psychotherapy, no sustained change in pain perception can be achieved. This finding needs more investigation, but could be of interest for cognitive-behavioral therapy which have repeatedly been confronted with the accusation of producing only short-term symptom-relief or a transient shift in symptoms ("Symptomverschiebung" in the psychoanalytic literature, see Perrez, 1978; Jacobi, 1999) rather than sustained, long-term therapeutic change.

5.2 Limitations and future research

The model presented in this work must be viewed as an explorative model that can be extended in numerous ways. For example, the latent nodes in this model contained only two states: "pain" and "no pain". Also, we set the possible observations to two (harmful stimulus vs. innocuous "tickle"). Of course, this is a very simplified approach to pain perception and a model that incorporates more states and possible observations would allow more complex conclusions. However, it is not trivial to define these states as a holistic understanding of all potential body states or observations contributing to pain perception is still lacking. Possible candidates are infinite, but one idea is to incorporate the six basic emotions into the model as additional states of the hidden variables (Ekman, 1992). Some research has focused on the relationship between emotions and interoceptive predictive coding (Seth, 2013; Seth

¹transition probabilities are the probabilities of transitioning from a pain- to a non-pain state ($P_{\text{no-pain}_{t+1}|\text{pain}_t}$) or vice versa ($P_{\text{pain}_{t+1}|\text{no-pain}_t}$); or remaining in a pain state ($P_{\text{pain}_{t+1}|\text{pain}_t}$) or a no-pain state ($P_{\text{no-pain}_{t+1}|\text{no-pain}_t}$), respectively, over the course of two time-steps in the HMM

and Gray, 2016). This suggests emotions as promising candidates for an extension of the present model.

Further, the data used for the purpose of model selection was self-report questionnaire data. Future research with the model presented here should focus on fitting this model to **experimental data**. For example, it would be interesting to investigate phenomena like allodynia and hyperalgesia in healthy controls vs. chronic pain patients. By exposing participants in both groups to nociceptive stimuli and fitting the presented model to the data (e.g., self-report data on pain intensity), further conclusions regarding the 'Bayesian' nature of pain might be possible. Also, it would be interesting to contrast the findings which are valid for children and adolescents with data from adult chronic pain patients.

Additionally, research with this model could be concerned with the isolation of **sub-types** of chronic pain. According to the simulations, the probabilities of remaining in pain or in a pain-free state, the ability to reliably recognize and categorize sensory information and an increased prior expectation of pain contribute to an individual developing chronic pain conditions. Certainly, it would be interesting to look at these differences in a clinical context as this could represent subtypes of chronic pain - for example, an increased prior expectation subtype, an interoceptive-unaware subtype and so forth. If this can be confirmed, it might be possible to derive personalized treatment recommendations. Finding ways to efficiently tailor treatments to the specific needs of an individual patient is a central public health concern of our time (Simon and Perlis, 2010; DeRubeis et al., 2014; Huibers et al., 2015). The question of 'what works for whom' is of utmost importance for psychotherapy researchers in particular - many clinical trials suffer from high ratios of non-responders or non-remitters which usually remain unexplained (Huibers et al., 2015; Redish and Gordon, 2016). Personalized medicine here aims at identifying which patient characteristics predict treatment outcome in order to match both individual and therapy received better (Simon and Perlis, 2010). If this model and the hypothesis about subtypes can be confirmed, it might be able to contribute to efficient and data-driven treatment selection.

Another promising approach would be a model selection on longitudinal data for the development of chronic pain. The presented model could help detecting patients who are at a high risk of developing chronic pain, for example after an injury (such as disc prolapses or after cancer therapy) as it could help estimating the patient's parameter values (e.g., pain prior, transition probabilities) and anticipate the dynamics of the inferential process underlying pain perception. This, in turn, could optimize theory-driven treatment selection.

A model comparison procedure could further be used to evaluate therapy effects in the future. This could help formalizing and evaluating therapy effects on a mathematical and/ or computational level, one of the main goals of the emerging field of

computational psychiatry (Huys, Maia, and Frank, 2016; Redish and Gordon, 2016). If this is successful, this model might help anticipating response to a therapy. The application of machine-learning techniques to treatment selection in clinical psychology and psychiatry has yielded some very promising results already. Machine learning and "big data" approaches might play an important role in the relatively new fields of precision medicine and personalized psychotherapy (DeRubeis et al., 2014; Collins and Varmus, 2015; Collins et al., 2015; Dwyer, Falkai, and Koutsouleris, 2018).

5.2.1 Extensions towards other mental conditions

Extensions of this model towards further mental conditions are conceivable. Given the remarkable rates of **comorbid disorders**, computational models of chronic pain should integrate comprehensible explanations of these relationships. Accounting for the high rates of comorbidity, which often remain unexplained and impede successful treatment, would vastly increase the credibility of computational models. Research in this area should, for example, focus on the tight conjunction between chronic pain and depression (Fishbain et al., 1997). Depression and chronic pain overlap and respond to the same treatment (Hameroff, 1982; Banks and Kerns, 1996). This is especially so as some experts consider chronic pain a subtype of depression (Blumer and Heilbronn, 1982). Integrating knowledge on a patient's comorbid disorders into treatment is crucial for treatment success. Any insights regarding common mechanisms underlying typically co-occurring mental conditions is necessary as potential implications for clinical practice are enormous.

Due to many commonalities reported in the literature, an evident extension of the current model would be towards **hypochondriasis** (Fishbain et al., 2009; Pauli and Alpers, 2002; Chapman, 1944). It might be possible to account for the self-reinforcing nature of the symptoms in both chronic pain and hypochondriasis with a similar model (by incorporating time-series and different levels of hierarchies). The dynamics underlying the development from increased expectations of disease towards hyperalgesia in these patients could be very interesting for computational studies (Hadjistavropoulos et al., 2001). Dysfunctional attentional biases are a key element of hypochondriasis (**Lautenbacher**; Hadjistavropoulos et al., 2001) and could be expressed in terms of increased precision of top-down beliefs, Bayesian belief updating- and propagation over time as well as free-energy learning from data.

5.3 Conclusion

The model demonstrated here allowed testing different hypotheses regarding potential computational mechanisms associated with the development of chronic pain.

It is an implementation of the idea that pain perception emerges from an inferential process as described within the framework of predictive coding. Machine-learning structures and techniques, such as hierarchical Markov models, belief-propagation algorithms and variational inference, allowed exploring different sets of parameters that might play a pivotal role in the dynamics underlying chronic pain. We have demonstrated how a hierarchical model with a sensation- and a superordinate perception-level shows behavior that has many parallels with phenomena observed in chronic pain patients, such as an increased prior expectation of pain, allodynia and hyperalgesia. Fitting different types of models to data of chronic pain patients suggested pain-related expectations to be context-specific - a finding that has important implications for therapeutic decisions. Chronic pain patients also seem to show abnormalities regarding their likelihood model when compared to healthy controls, which needs further investigation. Research in this area could advance the mechanistic understanding of chronic pain and related disorders. These insights could then inform treatment selection and response anticipation.

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Supplementary Material to Master's Thesis

Anna-Lena Eckert

September 2018

A Bayesian Model for Chronic Pain

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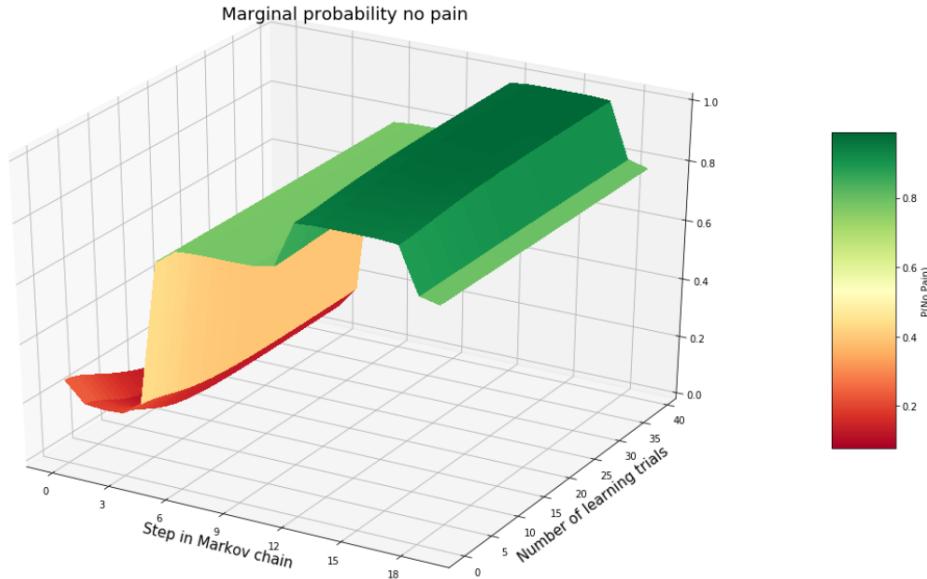
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1 Simulations: HMM with N time-steps

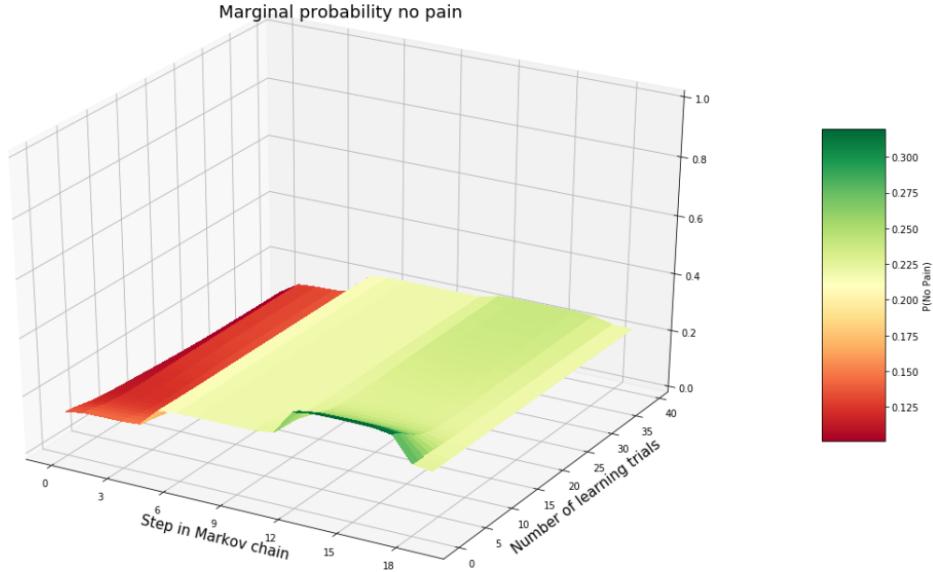
The additional plots in 1 and 2 illustrate the development of the marginal probability $P(\text{nopain})$ after making mixed observations in a simulation of healthy interoceptive inference and in the case of a chronic pain patient.

Figure 1: $P(\text{nopain})$ and healthy inference



This surface plot represents the development of $P(\text{nopain})$ in a simulated case of healthy interoceptive inference. The x-axis shows the node number (in a Markov chain of 20 hidden nodes of an HMM), the y-axis indicates the number of trials and the z-axis as well as the color bar represent the altitude of $P(\text{nopain})$. For the first 5 nodes, 40 trials of nociceptive stimulation were observed, resulting in a small marginal probability of being pain-free (and, consequently, a high $P(\text{pain})$, see thesis main text). This pattern is reversed when harmless sensory information is observed (from nodes 12 to 18), where a quick increase in $P(\text{nopain})$ can be observed.

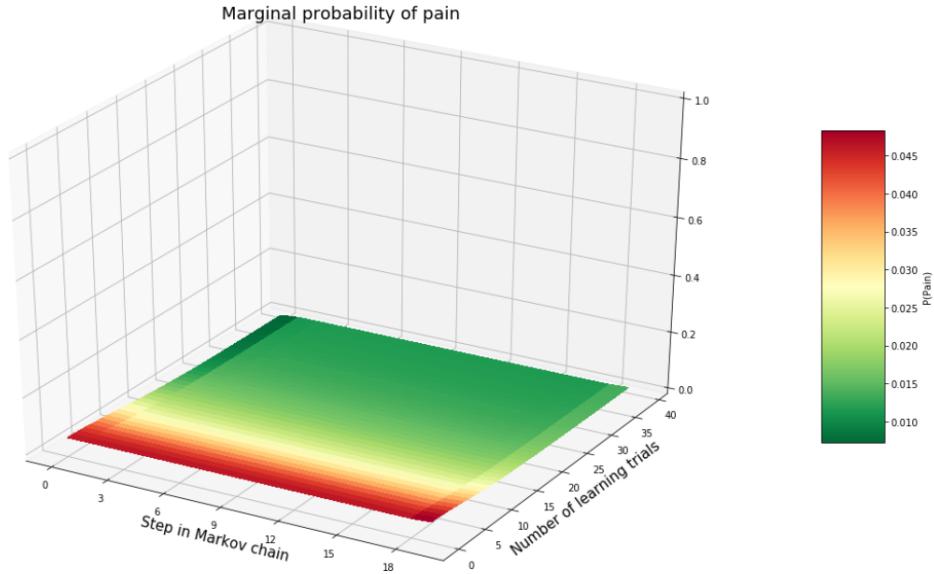
Figure 2: $P(\text{nopain})$ in a simulation of chronic pain patients



The probability of $P(\text{nopain})$, as simulated here for chronic pain patients. The x-axis indicates the node number (in a Markov chain of 20 hidden nodes of an HMM), the y-axis shows the number of trials and the z-axis as well as the color bar represent the altitude of $P(\text{nopain})$. For the first 5 nodes, 40 trials of nociceptive stimulation were observed, resulting in a decreased probability of being in a pain-free state. In chronic pain, this probability increases only lightly when harmless information is sampled - also, this increase is not very sustained when additional trials of harmless information are observed. In this case, $P(\text{nopain})$ decreases again.

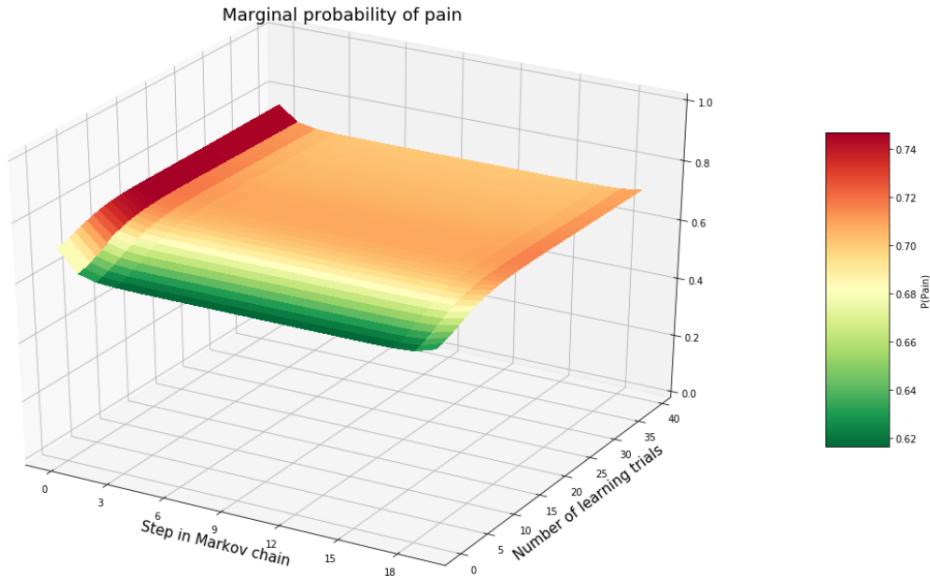
The two additional surface plots in figures 3 and 4 illustrate the development of $P(\text{pain})$ in normal and dysfunctional interoceptive inference after observing one trial of harmless information at node 0. The remaining nodes are not observed. This is used to illustrate the spontaneous dynamics of the two models where sensory information does not constrain inference.

Figure 3: Spontaneous development - healthy simulation



When simulating healthy interoceptive inference and observing only one trial of harmless sensory information, the probability of pain remains relatively low. The slight increase in the beginning stems from the fact that explaining sensory information is "shared" in between the two states of the hidden variable, i.e., there is never a 100% certainty about the cause of sensory information.

Figure 4: Spontaneous development - chronic pain simulation



In chronic pain, $P(\text{pain})$ increases when no information is processed. Upon observation of one trial of harmless sensory information, $P(\text{pain})$ decreases slightly, however, this decrease is not sustained. The spontaneous course of interoceptive inference in this simulation of chronic pain persistently evolves towards a state of increased $P(\text{pain})$.

2 Questionnaire

The following questions were taken from the PI-ANNA ("Pain and interoception: Annahmen von Jugendlichen mit und ohne chronische Schmerzen") questionnaire developed by T. Hechler, A. Thorwart and D. Endres for their project "Heightened Pain Predictions in Chronic Pain". For the present purpose of modeling chronic pain, 10 items were of particular interest. The responses were given by marking an x on a line of 10cm which was measured and transformed into percentages. The original items were as followed:

1. Stell Dir vor, Du wachst morgens auf, für wie wahrscheinlich hältst Du es, dass Du Schmerzen haben wirst?
2. Stell Dir vor, Du bist in der Schule, für wie wahrscheinlich hältst Du es, dass Du Schmerzen haben wirst?
3. Stell Dir vor, es ist Nachmittag, für wie wahrscheinlich hältst Du es, dass Du Schmerzen haben wirst?
4. Stell Dir vor, es ist Abend, für wie wahrscheinlich hältst Du es, dass Du Schmerzen haben wirst?
5. Wenn Du tatsächlich gerade Schmerzen hast, wirst Du dann eine Spannung im Bauch fühlen?
6. Wenn Du tatsächlich gerade Schmerzen hast, wirst Du dann eine Spannung im Nacken fühlen?
7. Wenn Du tatsächlich gerade Schmerzen hast, wirst Du dann eine Spannung in der Hand fühlen?
8. Wenn Du gerade **keine** Schmerzen hast, kannst Du dann trotzdem eine Spannung im Bauch fühlen?
9. Wenn Du gerade **keine** Schmerzen hast, kannst Du dann trotzdem eine Spannung im Nacken fühlen?
10. Wenn Du gerade **keine** Schmerzen hast, kannst Du dann trotzdem eine Spannung in der Hand fühlen?

English translation:

1. Imagine waking up in the morning. How likely will you feel pain?
2. Imagine being in school. How likely will you feel pain?
3. Imagine it is the afternoon. How likely will you feel pain?
4. Imagine it is in the evening. How likely will you feel pain?
5. When you are having pain, are you feeling tension in your belly?
6. When you are having pain, are you feeling tension in your neck?
7. When you are having pain, are you feeling tension in your hand?

8. When you are **not** in pain, are you still feeling tension in your belly?
9. When you are **not** in pain, are you still feeling tension in your neck?
10. When you are **not** in pain, are you still feeling tension in your hand?

3 Descriptive Statistics

Descriptive statistics of the sample and response patterns per group are described in the following tables. Both groups (children and adolescents with chronic abdominal pain or headache versus children and adolescents without chronic pain) did not differ regarding their average age (see table 1). Items 1-4 assessed the expected probability of pain at four different times of the day: in the morning, during school, in the afternoon and in the evening. Participants in the chronic pain group estimated the probability of being in pain at all time-points to be higher than did children in the control group (see tables 2 and 3).

Table 1: Sample characteristics

| Group | N | Age |
|------------------------|----|-------------|
| Chronic pain | 15 | 14.79(2.36) |
| Chronic abdominal pain | 8 | 13.63(2.56) |
| Chronic headache | 6 | 14.00(2.28) |
| Healthy | 20 | 14.20(2.24) |

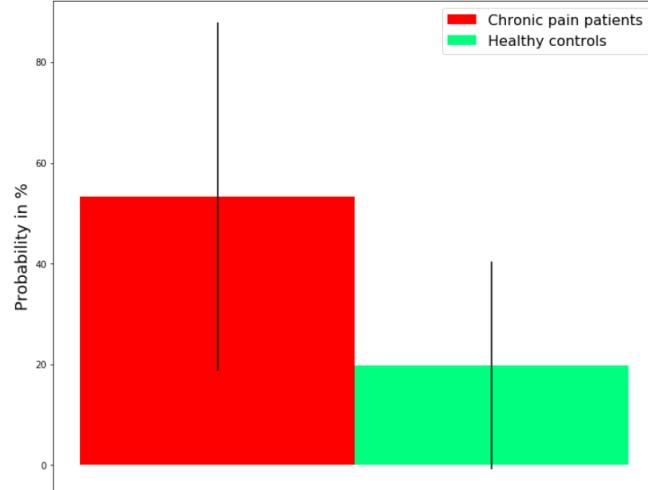
Table 2: Expectation of pain in children with chronic pain

| Pain Group | M | SD | Min | Max |
|---------------------------|-------|--------|-----|-----|
| Item 1: P(Pain—Morning) | 44.07 | 40.634 | 0 | 100 |
| Item 2: P(Pain—School) | 56.64 | 29.354 | 0 | 100 |
| Item 3: P(Pain—Afternoon) | 49.86 | 32.158 | 0 | 100 |
| Item 4: P(Pain—Evening) | 64.00 | 40.679 | 1 | 100 |
| Mean | 53.64 | 35,70 | | |

Table 3: Expectation of pain in healthy control group

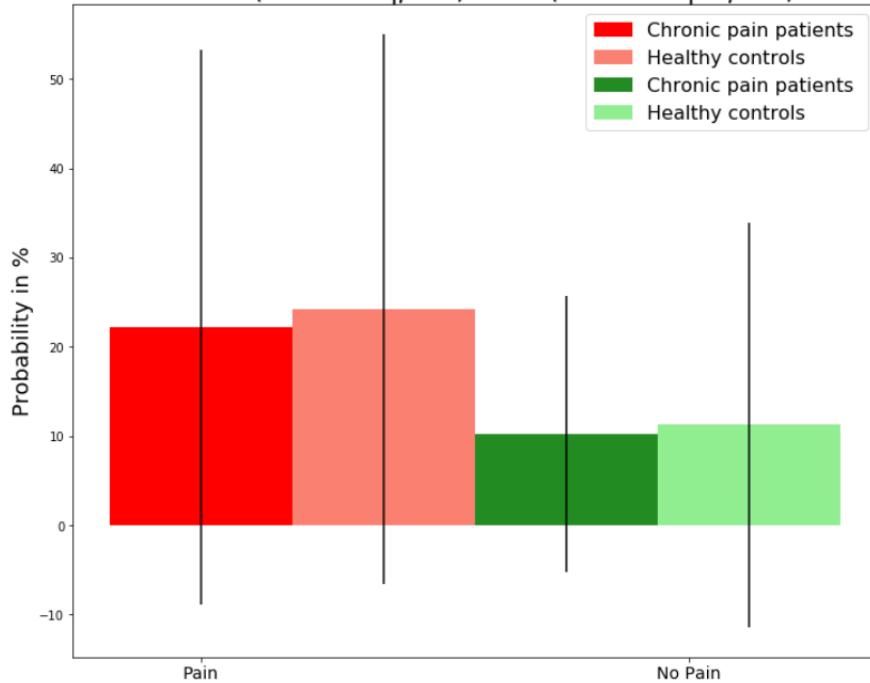
| Healthy group | M | SD | Min | Max |
|---------------------------|-------|--------|-----|-----|
| Item 1: P(Pain—Morning) | 15.15 | 18.34 | 0 | 69 |
| Item 2: P(Pain—School) | 21.70 | 20.946 | 0 | 73 |
| Item 3: P(Pain—Afternoon) | 20.00 | 21.08 | 0 | 70 |
| Item 4: P(Pain—Evening) | 22.40 | 23.17 | 0 | 72 |
| Mean | 19.9 | 20.88 | | |

Figure 5: Expectation of pain
Mean expectation of pain; sick vs. healthy



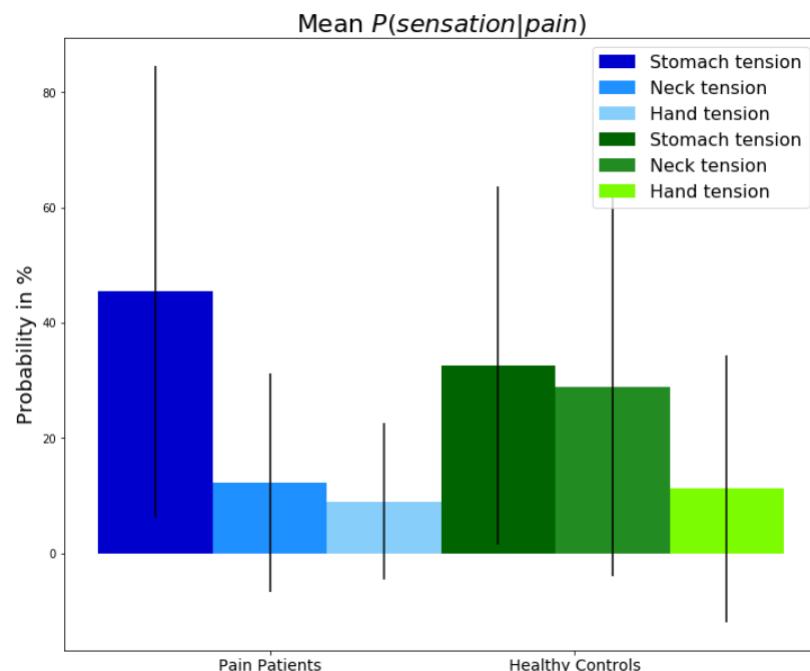
Group differences in the mean expectation of pain ($P(\text{pain})$) across items 1 to 4.

Figure 6: $P(\text{sensation}|\text{pain})$ and $P(\text{sensation}|\text{nopain})$
Mean $P(\text{sensation}|\text{pain})$ and $P(\text{sensation}|\text{nopain})$



Group differences in expecting an interoceptive sensation when in pain versus when pain-free.

Figure 7: Expectation of sensation when in pain



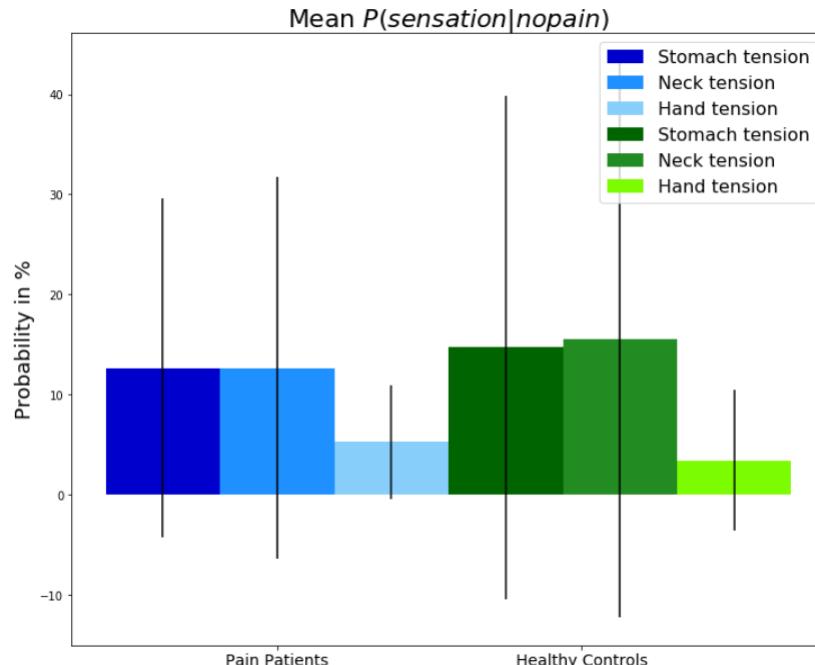
Expectation of the specific type of interoceptive sensation when in a state of pain, contrasted between groups.

Table 4: Probability of an interoceptive sensation

| Group | $P(\text{sensation} \text{pain})$ | | $P(\text{sensation} \text{nopain})$ | |
|-----------------|-----------------------------------|-----------|-------------------------------------|-----------|
| | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> |
| Chronic pain | 22.2 | 31.037 | 10.2 | 15.477 |
| Healthy Control | 24.23 | 30.772 | 11.25 | 22.685 |

Notes. M=Mean of items 5-7 and 8-10, respectively. SD=standard deviation. See also figure 11.

Figure 8: Expectation of sensation when not in pain



Expectation of the specific types of interoceptive sensation when in a pain-free state

4 Modeling data

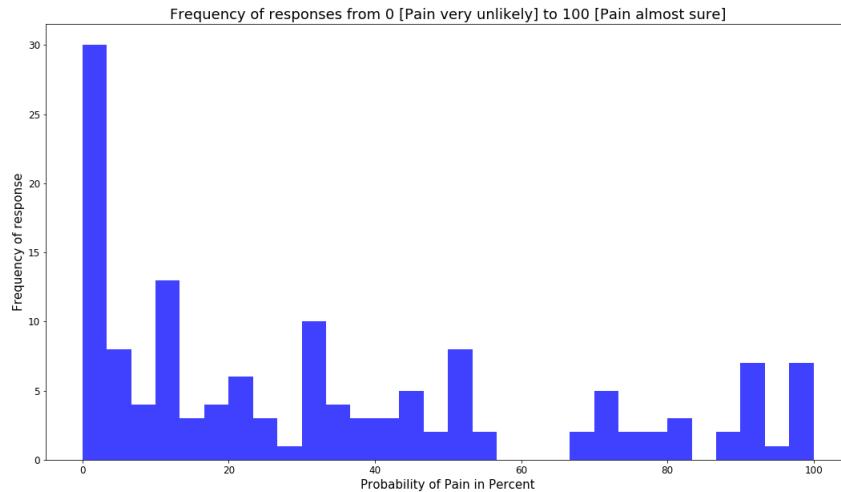
4.1 Prior expectation of pain, $P(\text{pain})$

As described in the main thesis text, all responses to the first four items (e.g., "Imagine waking up in the morning - how likely will you feel pain?") were categorized into three different categories (expectation of pain, moderate pain or no pain). This categorization is based on the frequency of responses in the data, see 9.

4.2 Likelihood model, $P(\text{sensation}|\text{pain})$

As described in the main thesis text, all responses concerning the participants' likelihood model were categorized into three different categories (Participants expects an interoceptive sensation, maybe expects it or does not expect it; given they are

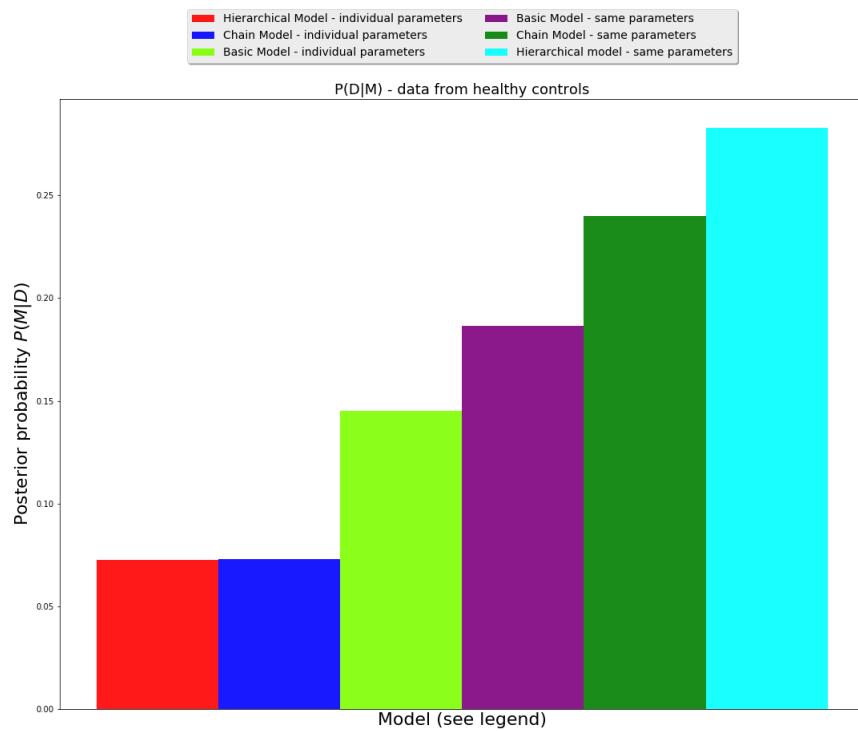
Figure 9: Frequency of responses $P(\text{pain})$



Notes. Illustrated is the frequency of responses to the first four items in the PI-ANNA questionnaire over all participants. This pattern suggested a categorization of pain expectancies into three different categories: 'pain' (pain is expected), 'medium pain' and 'no pain' which the modeling of the participants' responses was based on.

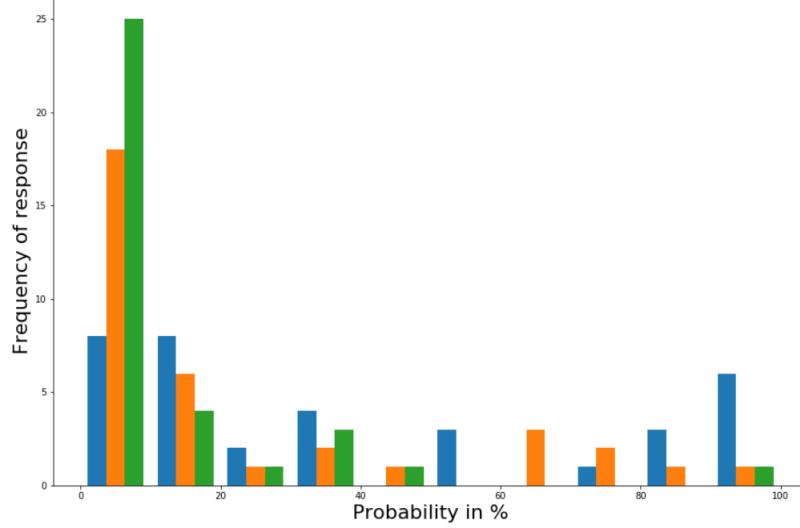
currently in pain or not in pain). This categorization was based on the frequency of responses in the data, see figures 11 and 12.

Figure 10: Model evidence for $P(\text{pain})$ in healthy participants



When modeling the data of healthy participants, a picture similar to modeling chronic pain patients emerges. Again, all models where each participant is modeled individually do not achieve a higher posterior probability. The hierarchical model achieves the highest posterior probability, followed by the chain- and the basic model.

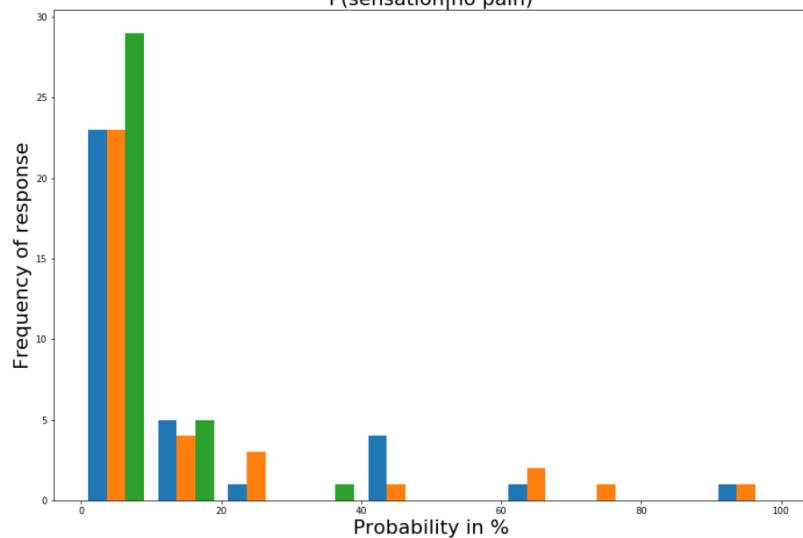
Figure 11: Response frequency: $P(\text{sensation}|\text{pain})$
 $P(\text{sensation}|\text{pain})$



Notes. The frequency of responses to items 5-7 in the PI-ANNA questionnaire, assessing the probability of a sensation (stomach, neck- or hand-tension) given being in pain. This pattern suggested a categorization into three categories: 'yes', a sensation is expected (Probability of $\geq 65\%$), 'maybe', there might be a sensation given pain is experienced (Probability between 40-65%), and 'no', no sensation is expected given being in pain ($\leq 40\%$).

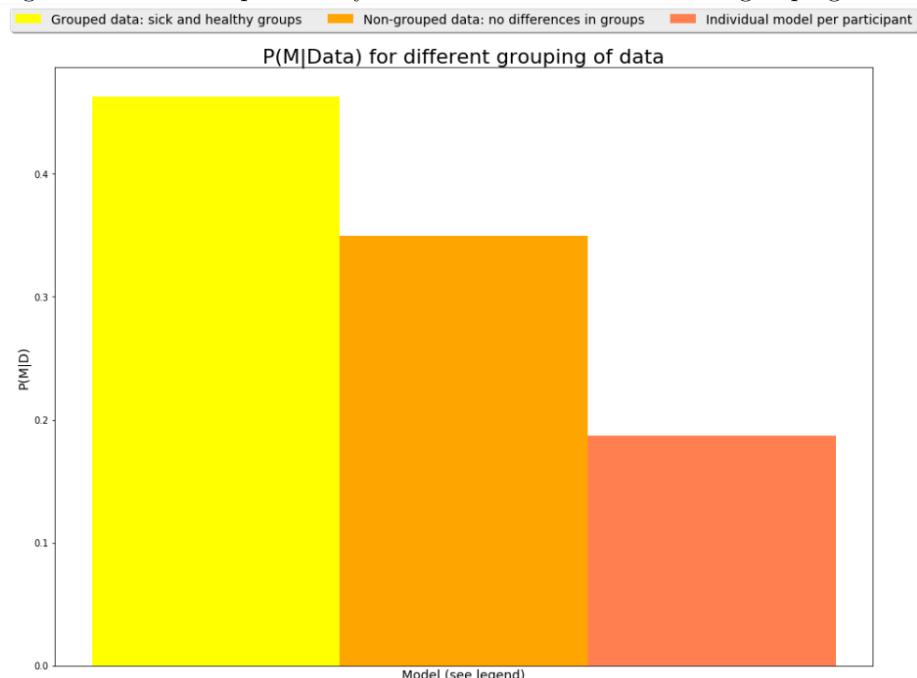
When modeling the likelihood responses of all participants, modeling participants group-wise is preferred over models that do not account for group differences or modeling each participant individually, see figure 13. The figure shows the combined probabilities of $\sum P(M_{groupeddata}|D)$, $\sum P(M_{non-groupeddata}|D)$ and $\sum P(M_{individual}|D)$.

Figure 12: Response frequency: $P(\text{sensation}|\text{nopain})$
 $P(\text{sensation}|\text{no pain})$



Notes. The frequency of responses to items 8-10 in the PI-ANNA questionnaire, assessing the probability of a sensation (stomach, neck- or hand-tension) when pain is not experienced. The same categorization as before (figure 11) is used.

Figure 13: Posterior probability of likelihood models - different grouping of data



Modeling the participants group-wise (that is, distinguishing between healthy control participants and patients with chronic pain) leads to the highest posterior probabilities. This approach is followed by a non-grouped modeling approach. Lastly, modeling each participant individually achieves the smallest posterior probability.