Chronic Pain, Enactivism, & the Challenges of Integration

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Abstract

Chronic pain is one of the most disabling conditions globally, yet we are still missing a satisfying theoretical framework to guide research and clinical practice. This is highly relevant as research and practice are not taking place in a vacuum but are always shaped by a particular *philosophy of pain*, that is, a set of implicitly or explicitly prevailing assumptions about what chronic pain is and how it is to be addressed. In looking at recent history, we identify a promising trend from *neuro-centrism* to the application of the *biopsychosocial model*. Unfortunately, due to its limited theoretical foundation, the biopsychosocial model is too often implemented in a reductionist, fragmented, and linear manner. In particular, it remains too vague concerning the relation between involved biological, psychological, and social processes. Sanneke de Haan prominently labeled this the *integration problem*. In this paper, we introduce five different facets of the integration problem that every philosophy of pain needs to address: (i) ontological, (ii) conceptual, (iii) explanatory, (iv) methodological, and (v) therapeutic. We develop an *enactive theory* of chronic pain and outline how far it provides solutions to these different integration challenges.

1 Introduction

Pains are a fundamental part of our everyday life. Many of us know that striking awful feeling when subbing a toe or the slowly increasing pressure of a headache after a day of work in front of a screen. A central characteristic of pains is that they are identified through the first-person perspective. As Klein aptly formulates, "if there's anything that's typical of all pains - I say - it is that they feel like pains. That is how you identify them" (2021, p. 4). Interestingly, pain is a condition characterized *exclusively* in terms of *what it is like* to undergo such experience. This is reflected in the current definition of pain provided by the *International Association for the Study of Pain* (IASP) characterizing pain as a personal experience and giving epistemic authority to the person who regards and reports their experience as pain (Raja et al., 2020). Thus, researchers commonly refer to pain as a group of subjective experiences that feel the same or at least similar enough (Aydede, 2017).

One central goal of pain science is to better understand the generation and maintenance of pain and to develop effective methods of treatment. So far, our knowledge on this matter must be considered insufficient in the face of the current social and personal challenges that persisting and reoccurring pains pose. It still holds that "millions of people – despite all our research – find themselves alone, disabled, and dispossessed by pain" (Morris, 1993). This proves pressing in the light of the high prevalence of *chronic pains* - commonly defined as pains lasting longer than 3 or 6 months - and their impact on quality of life (Breivik et al., 2006; Dahlhamer et al., 2018). As a particularly striking example, musculoskeletal pain is one of the most prevalent and disabling conditions worldwide (Hay et al., 2017; Vos et al., 2012) and one of the main reasons patients seek care (Koleva, 2005; Mäntyselkä et al., 2001). Yet, people living with chronic pain are often unsatisfied with the care they receive and left feeling frustrated, hopeless, and stigmatized (De Ruddere & Craig, 2016; Ojala et al., 2015; Toye et al., 2017).

On that basis, more and more researchers agree that we need a new approach to chronic pain. As a first step, there is a need for a critical examination of the theoretical assumptions that currently prevail, implicitly and explicitly, about pain and its chronification in research and clinical practice. This is a question of which *philosophy of pain* dominates, understood as a consistent or inconsistent set of beliefs about what pain is, how it is caused, how it is to be investigated, and how it could be effectively treated. Realized or not, labeled or not, researchers and practitioners always have a philosophy of pain that influences the way they conceptualize, explain, assess, and treat pain. "Health sciences and healthcare practice are enabled, shaped and

restricted by some tacit philosophical assumptions, of which practitioners should be aware" (Anjum et al., 2020, p. 3). Thus, the decisive question is not whether we have a philosophy of pain, but what this philosophy of pain looks like, especially in the context of understanding and treating chronic pain.

Recently, the *biopsychosocial* (BPS) model (Engel, 1977, 1980) has become more and more popular in its application to chronic pain as it is purported to be a multifactorial approach that overcomes the reductive and dualist shortcomings of alternative pain theories. However, the BPS model is commonly interpreted and applied in *reductionist*, *fragmented*, and *linear* terms; with serious implications for research and clinical practice (Coninx & Stilwell, 2021; Mescouto et al., 2020; Stilwell & Harman, 2019). These misinterpretations and misapplications are unsurprising as the original version of the BPS model was imprecise in its theoretical foundation, in particular with respect to the relation between the involved biological, psychological, and social processes (Coninx & Stilwell, 2021; Stilwell & Harman, 2019). Sanneke de Haan (2020a, 2020b, 2020c) prominently labeled this as the *integration problem*.

In this paper, we develop an *enactive approach* to chronic pain with regard to the question of what a philosophy of pain might look like that addresses the integration problem in a satisfying manner. The paper proceeds as follows: in *section 2*, we outline different manners in which chronic pain has been conceptualized and explained. This leads us to the BPS model as one of the most promising multifactorial approaches. We examine its application, understood as an indicator for the common (and often problematic) philosophy of pain that permeates research and clinical practice. Further, we introduce different facets of the integration problem: (i) ontological, (ii) conceptual, (iii) explanatory, (iv) methodological, and (v) therapeutic challenges. In *section 3*, we develop an enactive approach to chronic pain. We first focus on the ontological assumptions of enactivism concerning the relation of biological, psychological, and social processes and apply them to the particular case of chronic pain. Subsequently, we revisit the remaining challenges of integration and outline the implication of an enactive approach on how we may conceptualize, explain, study, and treat chronic pain. *Section 4* summarizes our results.

2 The Philosophy of Chronic Pain

This section aims to provide the background knowledge concerning the philosophy of (chronic) pain that permeates current clinical research and practice, including its challenges. In *section 2.1*, we provide a brief overview concerning the development of the definition and classification

of chronic pain. In *section 2.2*, we outline the historic development of some of the most central pain theories and their implications. In *section 2.3.*, we discuss the limitations of a neuro-centric perspective on chronic pain which motivates a shift towards more complex multifactorial approaches. In *Section 2.4.*, we discuss the BPS model of pain as one of the most promising philosophies of pain; however, we outline problems that have developed partly due to its vagueness and limited theoretical underpinnings. In *section 2.5*, we analyze the integration problem that lies at the bottom of those problems. In doing so, we introduce five challenges of integration: (i) ontological, (ii) conceptual, (iii) explanatory, (iv) methodological, and (v) therapeutic.

2.1 Chronic Pain: Definition & Classification

In this section, we provide a more in-depth analysis of how chronic pains are commonly defined and classified. This enables us to provide a better understanding of why chronic pain constitutes such a relevant though frustrating subject matter.

In 1979, the *IASP Subcommittee on Taxonomy* sought a classification of chronic pain to make it more visible as a distinct phenomenon in comparison with acute pain, enable consistent use of terminology, and improve communication in clinical research and practice (Merskey & Bogduk, 1994). In reference to Bonica (1953), chronic pain is commonly defined in terms of its *temporal persistence*. Pain is considered chronic if it persists over a certain period of time which is understood as a normal healing phase. In this case, pain turns out to be rather maladaptive than beneficial as it loses its protective biological function. As Melzack and Katz put it: “Pain may be the warning signal that saves the lives of some people, but it destroys the lives of countless others” (2013, p. 1). Usually pain is considered chronic when it persists for about three to six months; however, the exact time span might vary and be flexibly adapted (Merskey & Bogduk, 1994).

While the work of the Subcommittee on Taxonomy constituted a milestone, its definition of chronic pain *solely* in terms of persistence still leaves much to be desired. First, there are in principle multiple time spans that could be chosen. In fact, it might seem that such distinctions are “purely functional and relatively arbitrary time posts that have little relation to underlying mechanisms” (Apkarian et al., 2009, p. 81). Second, chronic pains are not just acute pains that have failed to ease (Hardcastle, 2014). In the process of chronicity, the lived experience of those concerned changes profoundly (Coninx & Stilwell, 2021; Svenaeus, 2015) and their quality of life is strongly affected (Breivik et al., 2006; Rice et al., 2016).

Unfortunately, central aspects of the suffering of patients as well as the resulting social and economic challenges are often neglected (Goldberg & Summer, 2011).

Along similar lines, researchers have argued that chronic pain should be considered a disease in its own right and receive a unified definition in order to facilitate adequate research, diagnosis, and care as well as to acknowledge the impact of chronic pain on patients (Raffaeli & Arnaudo, 2017). In response, an *IASP Task Force* set out to provide a new classification of chronic pain (Treede et al., 2015, 2019). In accordance with this new classification, chronic pain is still characterized in terms of temporal persistence as such criterion allows for a clear and operationalized definition (Treede et al., 2015, p. 1004). What is new is the classification of *chronic primary pain* in contrast to *chronic secondary pain*, such as persisting cancer, visceral, musculoskeletal, or neuropathic pains for which we can identify an underlying pathology (e.g. injury, lesion, disease, inflammation, obstruction):

> Chronic primary pain is pain in 1 or more anatomic regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or significant functional disability (interference with activities of daily life and participation in social roles) and that cannot be better explained by another chronic pain condition. This is a new phenomenological definition, created because the etiology is unknown for many forms of chronic pain. (Treede et al., 2015, p. 1004)

The introduction of chronic primary pain as an independent diagnostic entity beyond a purely temporal and etiological characterization has two decisive advantages. First, it indicates that the best medical approaches to chronic pain do not necessarily rely on the identification and removal of an underlying pathophysiology but might rather focus on the varying factors involved in the causation and maintenance of pains and their disabling consequences for patients (Siddall & Cousins, 2004). Second, the introduction of chronic primary pain may help validate patients' experiences of pain in the absence of clear underlying pathophysiological cause, reduce their stigmatization as psychologically disturbed, and improve their access to and quality of treatment (Melzack & Katz, 2013; Raffaeli & Arnaudo, 2017; Treede et al., 2019). In the next section, we address the question of how pain has been modeled in different pain theories and the extent to which these theories may account for the existence of chronic pains, especially in the absence of definite underlying pathophysiology.

2.2 A Brief History of Pain Theories

In this section, we aim to provide a brief, and by no means exhaustive, overview of the history of pain theories. Although it might seem that some of these pain theories should be long outdated, they still influence the current philosophy of pain. We outline two central shifts from

(a) mechanistic and linear approaches that primarily concern neural structures in the *periphery* to (b) an inclusion of multiple mechanisms interacting at the *spinal cord*, and (c) finally more recent approaches that investigate the complexity and plasticity of the *brain*. We respectively indicate the motivation for the further development of these theories.

Descartes (1633/1972) famously conceptualized the human body in analogy to a machine and in contrast to the immaterial mind. Although he had some nuanced ideas about pain and the interaction between the mind and body, researcher primarily latched onto his mechanistic writings that portrayed pain as the result of a sufficiently severe disturbance that is passed along physical tubes to the brain where pain is experienced; similar to a bell that rings in the brain when a string is pulled in the body, indicating the presence of a bodily condition. This view implies that there is a *linear* relation between an originary disturbance and the resulting pain: the stimulation equals the pain. Further, the brain is ascribed only the role of a receiver of signals from a *hardwired* and *specialized* sensory projection system. This Cartesian heritage can be identified in the view of the pain system as a straightforward specialized communication system between body and brain that remained prevalent until the middle of the 20th century (Melzack, 1973; Moayedi & Davis, 2013). As we shall see, the Cartesian heritage in fact still shapes the philosophy of pain today.

The Cartesian view has guided the research on pain with a focus on receptors and fibers involved in peripheral processing of physiological disturbances. *Nociceptors* have been identified as high-threshold sensory receptors of the peripheral somatosensory nervous system that are capable of transducing and encoding noxious stimuli that is damaging or threatens damage to normal tissues. Yet, there is no specialized and directly transmitting pain system with *pain receptors* and *pain fibers*; pain does not equal bodily disturbance (Wall & McMahon, 1986). There is *no* linear relation between the intensity, location, and quality of pain, on the one hand, and the severity, location, and type of affecting stimulation, on the other (Coninx, 2020, 2021a).

In 1965, Melzack and Wall introduced the *Gate Control Theory*. One central element is that *peripheral* input other than nociceptive activity can act upon neurons in the spinal cord and close a ‘gate’ to limit the transmission of nociceptive information via ascending pathways to the brain. This accounts for the pain reducing effects of mechanical stimulation (Hillman & Wall, 1969) or vibration (Melzack et al., 1963). The traffic of nociceptive signals is also controlled by *descending* pathways projecting from the brain back to the spinal cord. That is, the transmission of nociceptive signals is only possible when the integration of all ascending and descending pathways exceeds a critical level in the dorsal horn (Melzack & Wall, 1965).

In that, the Gate Control Theory proves successful to account for the absence of pain in the presence of nociceptive activity or the modulation of nociceptive information by means of diverse sensory and psychological factors such as attention, anxiety, stress, or social context (Melzack & Wall, 1965). Further, it ascribes a more active role to the brain (Melzack & Katz, 2013).

By itself, the Gate Control Theory however fails to account for cases in which pain is experienced in the absence of any nociceptive activity (Melzack, 1989). Complementing the Gate Control Theory, Melzack (1989, 2001) introduced the concept of a *body-self matrix*, i.e. a widely distributed network of dynamically interacting brain structures that receive sensory, affective, and cognitive input and produce a multidimensional pain experience, action patterns, and stress-regulatory reactions. That is, pain is associated with the ongoing dynamic coordination and reconstruction of neural activity across a non-specific brain system (Apkarian, 2017; Garcia-Larrea & Peyron, 2013; Iannetti & Mouraux, 2010). This constitutes a clear rejection of the traditional Cartesian view considering pain as the result of a linear system that simply transmits sensory signals about tissue pathologies (Melzack & Katz, 2013).

With regard to chronic primary pain, the concept of the body-self matrix has created space to better account for the complexity and variability of involved neural processes. Acute and chronic pain may correlate with different activity patterns in the brain (Lee et al., 2021; Ploner et al., 2017; Wager et al., 2013) while alterations of neural anatomy and connectivity appear to play a crucial role in chronification (Hashmi et al., 2013; Mansour et al., 2014; Schmidt-Wilcke, 2015). Further, such approach allows in principle for the influence of a variety factors on the activity and plasticity of the body-self matrix (Melzack & Katz, 2013). This development of pain theories has found its way into various areas of pain research as well as clinical practice and patient education (most prominently see Moseley & Butler, 2017).

2.3 Neuro-Centrism

The historical overview presented leads us to a philosophy of pain in which the brain is considered to play a crucial active role. Without diminishing the great contribution of neuroscientific research in the field of pain research and management, we should remain skeptical about employing on that basis a *neuro-centric perspective* which ascribes an exclusive or at least prioritized role to the brain in understanding and treating chronic pain (Stilwell & Harman, 2019). In this section, we consider five reasons for such skepticism.

First, in focusing solely on the neural activity of the brain, we may overlook other biological factors that significantly contribute to the causation and maintenance of pain. This

involves *genetic* (Denk et al., 2014; Vehof et al., 2014), *epigenetic* (Descalzi et al., 2015; Stenz et al., 2021), as well as *endocrine* and *immunological* processes (Melzack, 1999) which can also function as useful indicators in pain prevention, diagnosis, and treatment (Reckziegel et al., 2019; Vachon-Presseau et al., 2019). All of these processes dynamically interact along brain, spinal cord, and periphery cross-cutting apparently clear boundaries between brain-bound and non-brain-bound systems (Chapman et al., 2009; Melzack & Katz, 2013). Thus, an exclusive study of the brain is too narrow a focus and might lead to a loss of relevant knowledge about the physiology of chronic pain, in particular concerning the intimate relation between neural and non-neural processes that are not as strictly separable as it might seem at first.

Second, we have good reasons to reject a *neuro-reductionist* perspective, which might be encouraged by neuro-centrism, for similar reasons that speak more generally against a *bio-reductionist* perspective. Defenders of reductionism may argue for the type identity of chronic pain with specific pathology, for example, a disease of the brain (Borsook et al., 2010). This perspective is related to the general effort in medicine to reduce clinical conditions to a single underlying abnormality that can be effectively addressed by highly specialized, and at best selective, interventions.[1] While this reductionist agenda might appear attractive due to its coherence and simplicity, it has proven unsuccessful in the application to various conditions (Adam, 2013; Fullana et al., 2020; Kendler, 2005, 2012), including chronic pains (Stegenga, 2018, pp. 61-68; Sullivan, 2014). There are hardly any successful mono-causal explanations for chronic pain conditions and there are no highly specialized interventions that can be effectively applied to them (Melzack & Katz, 2013). That is because pains are quite often not associated with concrete pathophysiological alterations in the body (Kosek et al., 2021) and, to date, researchers are unable to identify a neural correlate of pain that allows for both selective and sensitive measures (Coninx, 2021b; Corns, 2020). Thus, reductionism in terms of a type identity presupposes an oversimplification of how chronic pain is brought about that is incompatible with their multiple realization/causation.

[1] A paradigmatic success story of this approach is the case of neurosyphilis which has been identified with a specific bacterial infection effectively targeted by the administration of arsphenamine. For many conditions, the focus is to identify a corresponding genetic or neurophysiological marker. This constitutes a general shift from the identification of symptom patterns to the search for pathology understood as the common underlying cause or constitutive basis of the phenomenon in question (Goodkind et al., 2015; Insel & Cuthbert, 2015; Kandel, 2018). While neuro-reductionism presupposes the identification abnormalities in the brain, bio-reductionism might also account for deficits in a larger neuro-endocrine-immunological system, for example. The decisive commonality is that a single disease state must be found that is necessary and sufficient for the respective clinical condition to occur.

Third, a neuro-centric perspective seems to ignore the influence of *psychological* (Martinez-Calderon et al., 2020; Meulders, 2019) and *social* factors (Rossettini et al., 2018; Slade et al., 2009) in the chronification of pain. In principle, neuro-centrism might allow for other factors to be involved and one might even reconcile the impact of non-biological factors with a reductionist perspective, "as long as one maintains that the brain is the real mechanism of change here" (de Haan, 2020a, p. 28). According to this view, chronic pains are primarily grounded in physiological processes while psychological and social factors are considered modulatory factors, distal causes, or the results of pain. While various studies have shown that alterations in brain anatomy and connectivity correlate with chronic pain, these neural correlates could in principle be realizations, causes, or effects of chronic pain and it remains up for debate of why we should privilege the role of brain processes in contrast to psychological or social factors (Borsboom et al., 2018; de Haan, 2020a, pp. 27–30; Varga, 2015, p. 34).[2]

Fourth, Stilwell and Harman (2019) argue that neuro-centrism in pain research and practice commits a *mereological fallacy*: it falsely attributes a property of a whole system to one of its parts. Neuro-centrism seems to suggest that it is the brain that suffers from pain; by contrast, it is a person in a certain context who experiences pain (for a similar argument see Kendler, 2005). We are not treating brains but people that are located in a certain environment. Further, exclusively referring to a neurophysiological process is insufficient to determine that such process constitutes a disorder or pathology (Stegenga, 2018) and to explain why chronic pain often constitutes such a disabling condition for those who suffer from it (Sullivan et al., 2013). That is, even if we could identify a type-identical neurophysiological state, corresponding neuro-centric approaches may still fall short to explain how these states relate to the broader clinical phenomena that chronic pain constitutes and the alterations in patients' experience, self-concept, and agency that come with it (Hoffman & Zachar, 2017).

Fifth, neuro-centrism has serious *pragmatic implications* in clinical practice and research. If we have an overly strong focus on the brain, we may overlook certain treatment options, paradoxically stigmatize patients, and minimize their engagement. Even if we can identify an underlying brain abnormality, the targeting of psychological and social factors does

[2] One might reply that brain processes should prioritized because they are constitutive of pains. We do not aim to defend any position concerning the constitution of pain. However, even if we accept that the minimally sufficient constitutive basis for *singular pain experiences* are brain processes, it still remains up for debate whether changes in brain anatomy, connectivity, and chemistry are realizations, causes, or effects of the *chronification of pain*. It is exactly the relation between biological, psychological, and social aspects in the processes of chronification that we are interested in, and in this regard, there is no principle reason of why brain processes should be privileged.

not lose relevance (Eronen, 2021). The brain is not a particularly useful target for intervention and we lack good reason to believe that more biologically-focused treatment, such as pharmaceuticals, provide us with the best outcomes (Stegenga, 2018), as reflected in clinical practice guidelines for common pain conditions, such as chronic back pain (Qaseem et al., 2017). Further, the trend towards giving neuro-centric explanations for patients' experiences may have unwanted, paradoxical outcomes. There is some evidence that brain- and biologically-focused explanations and beliefs may *increase* rather than decrease stigma and negative beliefs towards health conditions (Berent & Platt, 2021; Larkings & Brown, 2018) and negatively impact patient outcomes (Schroder et al., 2020). Patients might also feel that they are not taken seriously or adequately represented in social dialog (Sullivan et al., 2013) as they are reduced to passive targets of treatment (Rocca & Anjum, 2020). Finally, neuro-centrism as a general heuristic can affect progress in pain research. In assuming that only the brain (or body) plays a decisive role, alternative explanations and targets for intervention are ignored from the outset. For example, this may distract from the consideration of socioeconomic and sociocultural aspects and the critical examination of the health care system itself (Mescouto et al., 2020).

Although defenders of neuro-centrism might surely provide a reply to some of these aspects, we provided arguments for at least a skeptical attitude towards a brain-based focus, in particular, or biologically-focused approaches, in general. The previous considerations indicate the need for an approach to chronic pain that account for the complexity and variability of involved biological, psychological, and social factors. This leads us in the next section to more complex *multifactorial* pain theories, with the BPS model of pain as the most prominent and promising.

2.4 The Biopsychosocial Model & Philosophy of Pain

In this section, we outline basic assumptions of the BPS model and discuss problematic tendencies in its interpretation. Our aim is to highlight general biases in clinical research and practice and show that the potential for corresponding misapplications of the BPS model is grounded in its vagueness and limited theoretical grounding.

Engel (1977, 1980) introduced the BPS model arguing for a more humanistic approach to patient care and that complex health issues cannot be reduced to pathology or disease as they are determined by biological, psychological, and social processes. In reference to *General Systems Theory*, he conceptualized these processes as located at vertically ordered levels, either

considered as ‘layered’ (see Fig. 1 for illustration) or ‘nested’ domains (see Fig. 2 for illustration).[3] Lower levels concern biological processes (e.g. molecular, cellular, or neural activity). Middle levels concern person-related processes (e.g. experiential, cognitive, or behavioral changes). Higher levels concern social processes (e.g. practices in families, subcultures, or nations). Engel viewed this as a ‘vertical stacking’ where larger (higher) units are more complex and superordinate to less complex smaller units (Engel, 1982, p. 803). Systems at higher levels are composed of systems of lower levels while each level requires unique methodological access.

> In scientific work the investigator generally is obliged to select one system level on which to concentrate, or at least at which to begin, his efforts. For the physician that system level is always person, i.e., a patient. (Engel, 1980, p. 537)

Further, Engel suggested that the hierarchical levels are always interconnected by “material and information flow” (Engel, 1980, p. 537) across their boundaries.

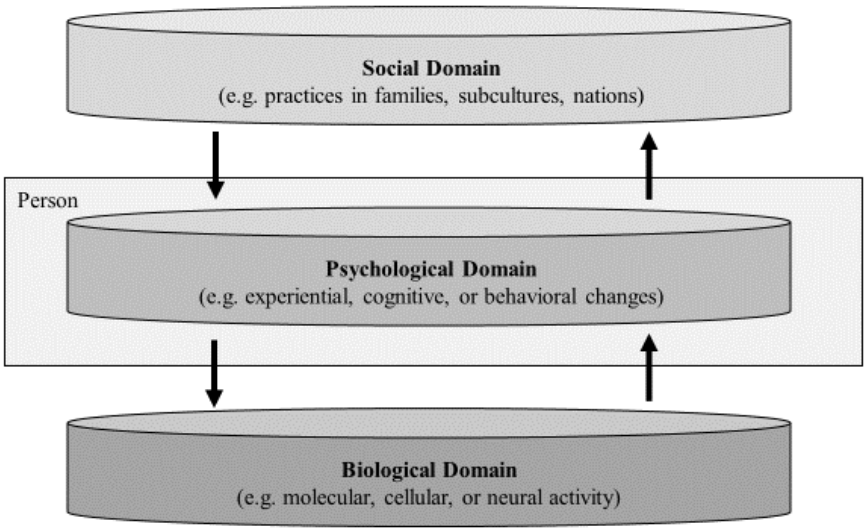

Fig. 1 Vertical hierarchy of layered domains: schematic and simplified illustration of the hierarchy of biological, psychological, and social systems as ‘layered’ domains (inspired by Engel (1980), Fig. 1 ‘Hierarchy of Natural Systems’)

[3] Engel used the term ‘levels’ to relate biological, psychological, and social processes. We prefer to use the term ‘domain’. This is because the notion ‘level’ is more strongly associated with a particular ontological interpretation, that is, of a vertical order as depicted in Fig. 1 and Fig. 2, whereas we aim to employ the term ‘domain’ in a more neutral way.

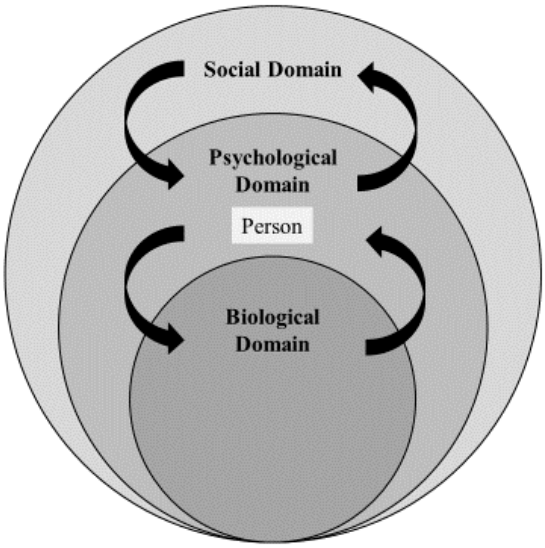

Fig. 2 Vertical hierarchy of nested domains: schematic and simplified illustration of the hierarchy of biological psychological, and social systems as 'nested' domains (inspired by Engel (1980), Fig. 2 'Continuum of Natural Systems')

The BPS model was not developed with particular consideration of chronic pain, but it is now widely applied in this context (Cohen et al., 2021; Foster et al., 2018; Gatchel et al., 2007). In its original version, Engel presented the BPS model as a genuinely humanistic and multifactorial framework. However, many applications in the pain literature do not align with this, as they tend towards a *reductionist*, *fragmented*, and *linear* interpretation (Cormack et al., forthcoming). We take this to characterize a common bias in the current philosophy of pain, once again, understood as the set of beliefs about chronic pain that prevail implicitly or explicitly in research and clinical practice.

First, the BPS model is still too often conflated with a *bio-reductionist* or *neuro-reductionist* model, as evident in prevalent measurement choices, diagnostic focus, and treatment selection (Mescouto et al., 2020; Stilwell & Harman, 2019). In closer examination, the multi-domain approach inherent to the BPS model frequently collapses into a uni-domain approach which, again, prioritizes the search for pathology and corresponding specialized interventions. This implies a reduction of the psychological and social to the biological. The BPS model is thus reinterpreted in that the vertical hierarchy of higher and lower levels is accepted, and that the biological domain is more fundamental – providing the 'real' or 'root' cause of chronic pain. Initial issues of such reductionist approach are indicated in the previous section.

Second, even if the biological, psychological, and social domain are considered equally relevant, their examination is often *fragmentated*. That is, a trichotomization arises between

apparently separate domains that become the subject of independent research, diagnosis, and treatment while it remains largely unclear how they are connected. Engels characterization of 'material and information flow' proves hardly informative (de Haan, 2020b; Svenaeus, 2021). This can lead to an artificially splitting of patients into their physiological, psychological, and social characteristics, a plurality of potentially contradictory diagnoses, and thus a patchwork of independent approaches in pain research and health care (Anjum et al., 2020; Cabaniss et al., 2015; Stilwell & Harman, 2019). What would be needed is an approach that is not only *complex*, in that it rejects reductionist assumptions concerning the prioritization of biological processes, but also *integrative*, in that it seeks to examine the relation between biological, psychological, and social aspects rather than aiming for multiple parallel approaches (Bolton & Gillett, 2019).

Third, the BPS model is often implemented in a *linear* manner. That is, uni-directional causal pathways are assumed between involved factors, which themselves are considered as insensitive to context or temporal unfolding and, thus, strictly decomposable (Rocca & Anjum, 2020; Stilwell & Harman, 2019). This implies that we can understand a complex phenomenon, such as chronic pain, by analyzing the involved factors in isolation. This picture seems empirically inadequate concerning the relation of processes within and across domains as they are dynamically intertwined along different time spans (Kendler, 2012). As a consequence, the involved processes themselves cannot be easily differentiated and there are limitations to their decomposability (Boer et al., 2021). Further, it seems misguided to start from a static picture of 'layered' or 'nested' domains that at best interact in a sequential order. Instead, we need a more dynamic model that creates space for time- and context-sensitive interaction along multiple feedback-loops (Bolton & Gillett, 2019; Lehman et al., 2017).

Taken together, the recent and widespread philosophy of pain in research and practice reveals reductionistic, fragmented, and/or linear tendencies. Engel's work on its own does not offer strict principles that prevent such interpretations and applications, as central aspects concerning the relation between biological, psychological, and social factors are kept too vague or do not offer sufficiently detailed and coherent theoretical orientation (Benning, 2015; Bolton & Gillett, 2019; Ghaemi, 2009; Kendler, 2010). Instead, we need a truly complex, integrative, and dynamic model. In the following section, we discuss these findings in the context of the *integration problem*. Before doing so, a few words shall be said about multifactorial alternatives to the BPS model, in particular, network models.

Network models aim to account, among others, for the complex web of interconnected processes involved in psychopathologies (Borsboom, 2017; Borsboom et al., 2018; Cramer et al., 2016). Mental disorders are conceptualized as arising from the dynamic interaction between

a network of symptoms causally connected through biological, psychological, and social processes. Network models rely on already existing lists of symptoms provided by diagnostic frameworks and also allow non-symptoms, such as environmental factors, to become part of the relevant network architecture (Borsboom et al., 2018). To suffer from disorder means to be trapped in a relatively stable, self-sustaining network of causally interacting factors. For present purposes, it might be sufficient to note that, despites their advantages, network models are, by themselves, insufficient to provide a complex, integrative, and dynamic approach to chronic pain. However, network models only describe correlations. As such, they fall short to show how the symptoms and non-symptoms that are considered part of a network architecture are precisely related (e.g. common cause vs. uni-directional causation vs. bi-directional causation vs. (partial) realization) (Boer et al., 2021; de Haan, 2020a, pp. 41–43, Kästner, forthcoming). That is, they fail to adequately address the integration problem.

2.5 Five Facets of Integration

In this section, we take a closer look at the *integration problem*. Sanneke de Haan (2020a, pp. 36–43, 2020b, 2020c) introduces the integration problem as one of the most central challenges that multifactorial approaches in clinical medicine and psychiatry face. In a nutshell, to address the integration problem we need to characterize the relation between those factors involved in the generation and maintenance of a clinical condition, assuming that there is a variety of relevant factors of different kinds – biological, psychological, and social. Given the previous investigations, it is obvious that such integration problem equally applies to chronic pain. What we aim to highlight is that there are different *interrelated facets* to the integration problem that require a more fine-grained examination.

> *(i) Ontological Challenge*: At its core, the integration problem is an ontological matter raising the question of how processes of different kinds relate to each other. Can biological, psychological, and social factors be reduced to each other? Are these factors connected in linear ways or do they reciprocally affect each other? Are they sensitive to contexts and temporally unfolding dynamics? Do the investigated factors partially overlap or can they be modelled as perfectly mapping layers? Do the biological, psychological, and social domain characterize independent ontological spaces or are they perspectives on one and the same process?
>
> *(ii) Conceptual Challenge*: This challenge raises the question of how to conceptualize chronic pain in the light of the integration problem. Is chronic pain a brain disease or a

psychological disorder? And what role is attributed to the social context in the definition of chronic pain? What is chronic pain assuming that temporal persistence does not provide on its own an informative and exhaustive understanding?

(iii) Explanatory Challenge: This challenge addresses how we explain the occurrence of chronic pain, given the plurality of biological, psychological, and social factors involved. Do we need to rely on multiple independent explanations for different scientific purposes? Or, can we reach a single coherent explanation of chronic pain that unifies insights from all disciplines at once? Or, should we rather aim for more 'local' integrative efforts bringing together particular aspects of biological, psychological, and social explanations concerning particular phenomena?

(iv) Methodological Challenge: This challenge addresses the constraints of how we should study chronic pains. Which methods are best suited to invest chronic pain? Is there any method to be prioritized? How can we integrate insights from multiple research areas which employ different methods while targeting the same phenomenon? And, how could a resulting complex set of data be of practical value?

(v) Therapeutic Challenge: The therapeutic challenge concerns how we can best treat chronic pain. What is the best target for intervention? What role does the relationship between patients and practitioners or institutional structures play for the success of treatment? How do we account for the uniqueness of each patient and still do justice to the ideal of science where clinicians base assessment and treatment decisions on commonalities and statistical averages?

The integration challenge is typically formulated in terms of the ontological issues, targeting the BPS model as originally developed by Engel. Aftab and Nielson (2021) argue that Engel's main concern was not to establish an ontology, but to prove psychological and social aspects as worthy of integration into the scientific realm, that is, as relevant for our understanding and explanation of health and disease, selection of methodological tools, and choice of treatment. They further argue that addressing the ontologically challenge does not provide an answer to the question of how biological, psychological, and social factors are to be integrated, for example, in coherent explanations or therapeutic practice. Even if Engel did not explicitly focus on ontological issues in the development of the BPS model, they play a crucial role in the background (Bolton, 2021) and we surely need to address them to solve the integration problem. That is, we need an approach that *"defines the foundational theoretical*

constructs - the ontology of the biological, the psychological and the social - and especially the causal relations within and between these domains" (Bolton & Gillett, 2019).

In our view, the ontological, explanatory, conceptual, methodological, and therapeutic facets of the integration problem are not independent. An answer to the ontological challenge does not immediately provide an answer to the others, as this might require to also consider epistemic, normative, or pragmatic aspects. Nonetheless, the ontological assumptions that define our philosophy of pain clearly shape how we conceptualize, explain, study, and treat pain. Thus, a central step in initiating far-reaching and stable change in different areas of research and clinical practice is to change the manner in which we think about how biological, psychological, and social processes relate from an ontological perspective (de Haan, 2020b; Rocca & Anjum, 2020). Again, clinical research and practice do not taken place in a vacuum, but they are shaped by theoretical assumptions and ideals.

3 An Enactive Approach to Chronic Pain: Revisiting the Five Challenges of Integration

Our aim in the following is to introduce an enactive approach to chronic pain and indicate how it might fruitfully contribute to a change in the philosophy of pain that permeates all facets of the integration problem. In *section 3.1,* we provide a brief introduction to enactivism. In *section 3.2,* we outline what we consider the minimal assumptions of an enactive ontology. In *section 3.3,* we apply these assumptions to chronic pain and explore their implications for addressing the ontological challenge. We argue that an enactive ontology can provide the needed theoretical foundation for a complex, integrative, and dynamic approach. In *section 3.4*., we revisit on that basis the remaining four challenges of integration – explanatory, conceptual, methodological, and therapeutic.

3.1 Main Pillars of Enactivism

In this section, we briefly outline the main pillars of enactivism. To provide a universal definition of enactivism that does justice to all the nuances of those accounts that are members of this theory family is hardly possible. Enactivism is a rapidly evolving movement with many strands, such as autopoietic enactivism (Di Paolo et al., 2018; Di Paolo & Thompson, 2014; Thompson, 2007; Varela et al., 1991), sensorimotor enactivism (Noë, 2004; O'Regan & Noë, 2001; O'Regan, 2011), and radical enactivism (Hutto & Myin, 2013, 2017). We do not aim to provide a systematic historical overview or detailed analysis of the various strands of

enactivism and other related traditions (see Baggs & Chemero, 2021; Käufer & Chemero, 2021; Popova & Rączaszek-Leonardi, 2020; Ward et al., 2017; Ward & Stapleton, 2012).

What we consider most central for present purposes is that enactivism rejects neuro-centrism and motivates to employ a broader perspective taking into account the entire person, including brain and body, in interaction with their environment (Di Paolo & Thompson, 2014; Fuchs, 2017; Varela et al., 1991). With respect to our target phenomenon this means that (chronic) pain is (a) enabled and constrained by the dynamic coupling of the neural and non-neural body (*embodiment*), (b) crucially dependent on the bi-directional relation between person and environment (*embeddedness*), and (c) bound and brought forward by a person's activity and actions in the environment (*enactment*) (Coninx & Stilwell, 2021; Miyahara, 2019; Stilwell & Harman, 2019; Tabor et al., 2017).[4]

Enactive approaches typically focus on the first-person perspective in investigating how chronic pain affects the manner in which patients attune to their environment, including changes in the perception of themselves and their environment (Coninx & Stilwell, 2021). That is not only because enactivism is deeply intertwined with the phenomenological tradition, but first and foremost because there is a vital need to better understand the lived experiences of patients and their transformative potential (Stilwell & Harman, 2021). In this paper, we consider experiential aspects as defining our target phenomenon and as contributing to chronic pain. The primary aim is to address the relation between the biological, psychological, and social factors in the processes of pain chronification, rather than to characterize in detail the changes in experience that paradigmatically occur in the course of such process and profoundly affect the lives of those concerned (for more detail see Coninx & Stilwell, 2021).

3.2 Minimal Ontological Assumptions

In the following, we outline five closely related aspects that we consider the minimal assumptions of enactive ontology: *naturalism*, *emergence*, *asymmetric determination*, *dynamic organization*, and *spatio-temporal scaling*. We discuss these concepts here in the broader context of the relation between biological, psychological, and social processes to be translated into the more specific context of chronic pain in the subsequent section. We focus the discussion mainly on the work of de Haan (2020a, 2020b, 2020c, 2020d) as "a genuinely novel and

[4] We do not consider extendedness as a main pillar of enactivism, although some authors in the enactive debate commit to the extendedness of certain phenomena, with partly deviating definitions of extendedness.

outstanding branch on the enactivist tree" (Bruineberg, 2021, p. 1). Further connections are made to the work of Aftab and Nielsen (2021), Fuchs (2020), and Thompson and Varela (2001).

Naturalism: Enactivism is a naturalistic theory in that it is compatible with the assumption that everything is made out of natural components. All properties, behaviors, and structures that can be found in our world are instantiated by systems composed of the same matter. There are no supernatural entities, mystic powers, or vital forces involved. There is no tripartite structure of ontology as biological, psychological, and social processes are all located in the same ontological realm (Aftab & Nielsen, 2021). Thus, enactivism rejects the dualistic assumption of a further substance over and above matter. It is compatible with monistic versions of naturalism, but at the same time incompatible with certain reductionist versions of monism as it entails a commitment to emergence (de Haan, 2020a, pp. 65–66).

Emergence: Enactivism entails emergence in that new properties, behaviors, and structures may occur in complex systems given the particular organization and interactions of their components. This kind of novelty presupposes 'qualitative emergence': a system instantiates characteristics that are not present in any of its parts and, thus, may count as qualitatively new (Gillett, 2016, p. 176). In general, the notion 'emergence' is highly debated and a full exploration of its diverse meanings would exceed the scope of this paper (Gillett, 2002, 2016; O'Connor & Hong Yu, 2020; Stephan, 2006). Our provided characterisation of emergence merely implies that the constellations and interactions of components can bring forth properties, behaviors, and structures in a complex system that do not exist in its parts. This is compatible, but does not necessarily imply further ontological commitments of 'stronger' variants of emergence theories (e.g., de Haan, 2020a, pp. 113–121).

This idea is implemented in the enactive tradition in different ways (e.g., Di Paolo & Thompson, 2014; Froese & Di Paolo, 2009; Thompson, 2007; Varela et al., 1991). Most prominently, organisms are considered self-organizing units which interact with their environment to maintain themselves and show characteristics that their physiological components, such as neurons, genes, and hormones, do not instantiate. Only the arrangements of and relations between these components bring about the emergent characteristics of the organism as a whole. Similarly, we may consider the emergence of new properties, behaviors, and structures in social systems that involve the interaction of multiple organisms, although they are not present in the individual organisms themselves.

The biological, psychological, and social domain characterize systems of growing complexity, such as brains, organism, or societies, with properties, behaviors, and structures emerging in the specific constellation of matter. These systems can be described in more *local*

or *global* manners as we can zoom in or out, employing a more or less spatially and temporally extended perspective (de Haan, 2020a, pp. 97–104). Thus, we may address characteristics of more local systems (e.g. neural activity patterns), the person (e.g. expectations about the future), and more global systems (e.g. socio-cultural practices). At the same time, these systems cannot be reduced in the sense that they implement properties, behaviors, and structures that are not found in more local systems. This entails a rejection of what we might label as *naïve reductionism*, i.e. the assumption that all things just differ in terms of the number, arrangement, and movement of the natural components they are made of. In contrast, we may assume in accordance with an enactive framework that although there is nothing *over and above matter*, this does not imply that everything is *nothing but matter* (de Haan, 2020a, p. 106).[5]

Asymmetric Determination: As a naturalistic approach, enactivism needs to assume that the emergent properties, behaviors, and structures of global systems depend or at least supervene on the characteristics of the simpler components of which the system is composed (Stephan, 2002). All other things being equal, a system with the exact same organization of components will reveal the exact same emergent characteristics. There can be no difference in the system without corresponding differences in the involved parts, their arrangements, and interactions. Further, it is not excluded that different components can bring about systems with the same emergent characteristics. The same characteristics of a global system can be realized by different constellations of more local systems.

The characteristics of the components can in turn be determined by the emergent characteristics of the system as a whole. Local systems may derive their properties and configuration, and in parts their existence, from being part of more global systems (de Haan, 2020a, p. 95). The brain functions the way it does because it is part of a more complex organism. Psychological processes are bound to being instantiated by a person engaging with their environment. This implies that the components of a system are not the same when they occur in isolation or when they are part of a larger system that differs in terms of the involved components, their constellations, and interactions. This is a rejection of an *atomistic view* assuming that the parts of a system could be individuated solely in terms of their intrinsic properties, independent of the context in which they are embedded (Burnston, 2021). By

[5] Two terminological remarks are needed. First, we use de Haan's distinction of 'global' and 'local' systems, in contrast to 'higher-level' and 'lower-level' systems. This because we want to draw a clear distinction with respect to the vertically stacked levels, understood as universal layers (Fig. 1) or perfectly mapping parts and wholes (Fig. 2), as originally introduced by Engel. Second, we often refer to 'more global' and 'more local' systems, instead of simply 'global' and 'local' systems, to emphasize that the distinction of what counts as the global or local system depends on our epistemic perspective and scientific interest.

contrast, the components of a system do not remain unchanged when being part of such system. They are distinct but not separate and as such not strictly composable and decomposable.

It follows that there are two directions of determination: *local-to-global* and *global-to-local* (Thompson & Varela, 2001). The properties, behaviors, and structures of a more global system are determined by the properties and organizations of the more local systems that it is composed of. The global properties, behaviors, and structures govern, constrain, or enslave local characteristics and interactions. Interestingly, there exist an *asymmetry* in the determination between local and global systems (de Haan, 2020a, pp. 101–102). Global changes necessarily involve changes in local systems while not all local changes 'add up' to global effects. Physiological processes necessarily change with psychological processes as the former are part of a global system that instantiates the latter. At the same time, not every change in physiological activity leads to a qualitative change in what a person thinks or feels. Similarly, social changes necessarily rely on changes in the members of the respective group and their relations while not every change on the side of individual group members adds up to a social upheaval. That is, asymmetric determination is to be understood in that global and local systems determine each other, however, changes in more global systems necessarily imply changes in more local systems while this relation does not hold the other way around.

***Dynamic Organization*:** The emergent properties, behaviors, and structures of global systems substantially rely on the dynamic interaction between the involved components. It is the positive and negative feedback loops between more local systems that give rise to the emergent characteristics of more global systems in the absence of an external control mechanism (Thompson & Varela, 2001). As such, the considered systems cannot be understood in reference to components interacting in a sequential manner, like gears in a clockwork (de Haan, 2020d). A machinal apparatus has pre-fixed rules along which the components interact while the components typically do not change in terms of their intrinsic properties. In a rigid sequence, one gear moves the next and we can replace a single gear (e.g., because of structural damage) without affecting other gears or the overall functioning of the clockwork. In contrast, in a *dynamic system*, the components interact and influence each other over more or less extended time spans, and the components themselves thereby often change. Suitable comparisons that illustrate the context-sensitivity and temporal unfolding of complex systems in the interaction of their components are rather found in chemistry than in relation to classical mechanics and the interaction of macroscopic objects (Varela et al., 1991).

We should also keep in mind that the interaction between the components of a system does not necessarily lead to a change in that system as a whole. Only in a trivial sense, a change

in local components implies a change in the global system. However, when certain negative and positive feedback loops add up in a certain manner, they can lead to a shift, "tipping the system over from one stable state into another" (de Haan, 2020a, p. 101). When the respective threshold is reached might depend on the connections between the involved components as well as the constraining properties, behaviors, and structures of the global system. That is, the effect of a single component is always to be considered against the background of the dynamic interaction with other components in the overall organization of the system. At the same time, the manner in which the rather local components and their organization are affected by the system as a whole also depends on the broader context in which the system itself is embedded.

Spatio-Temporal Scaling: It follows that the relation between the biological, psychological, and social domains is to be considered in terms of their complex, dynamic organization (de Haan, 2020a, pp. 114-116), rather than in terms of their reciprocal determination (e.g., Thompson & Varela, 2001). Speaking of reciprocal relations between biological, psychological, and social processes might suggest that they are instantiated by ontologically distinct systems that are related to each other in terms of a two-way dependence. This might still foster a false trichotomy of opposed systems that apparently interact in a sequential manner, reciprocally switching processes in the other systems on and off. This is problematic as it is incompatible with what is actually happening. The biological, psychological, and social aspects characterize aspects of the same matter with a narrower or wider spatio-temporal focus, showing distinct emergent properties, behaviors, and structures in their increasing constitutional complexity (Aftab & Nielsen, 2021; Fuchs, 2020).

It follows that when speaking about biological, psychological, and social processes we can do so in an insightful manner, but we are not referring to three separate ontological buckets along which natural things can be strictly categorized. What we do when referring to biological, psychological, or social aspects, we zoom in or out on the same process. This allows for the same target system to be investigated from different spatio-temporal perspectives while the respective distinctions of biological, psychological, and social are potentially fuzzy (Eronen, 2021). Furthermore, we should not expect that the biological, psychological, and social processes that we typically address from different perspectives perfectly map in that they are spatio-temporally cross-cutting and overlapping (Potochnik & Sanches de Oliveira, 2019).

Based on these minimal ontological assumptions, it follows that the enactive view rejects the idea that we can *uniformly* cut all nature into horizontal layers across which material and information flows back and forth (Fig. 1). While such approach of 'layered' domains might account for the emergence of new characteristics at higher levels, it facilitates a fragmented and

linear reading. The view of ‘nested’ domains (Fig. 2) might do better in so far as it emphasizes that biological, psychological, and social processes do not exist in independent ontological realms but relate as parts and wholes with increasing complexity. Still, this view is misleading as it fails to account for the dynamic entanglement of involved processes within and across domains which unfolds over time and allows for their partial overlap and crosscutting. An enactive view demands to embrace *complexity* in terms of the emergence of qualitatively new characteristics in more global systems, *integration* in terms of the asymmetric determination of global and local aspects as spatio-temporally crosscutting and overlapping, and *dynamics* in terms of the looping relations between the local parts of a system and the coupling between the global system and its environment. That is, biological, psychological, and social processes cannot be reduced to each other and stand in asymmetric local-to-global and global-to-local relations as more or less spatio-temporally extended excerpts of the same natural process (Aftab & Nielsen, 2021; de Haan, 2020a; Fuchs, 2020).

The previous considerations focused primarily on the general relation between biological, psychological, and social processes as instantiated by more local and global systems. What we chose to be our *target system* might depend on our scientific interests as there is no universally valid division of what counts as parts and wholes as these distinctions are best understood as useful heuristic idealizations (Eronen, 2021). From an enactive perspective, the central unit of analysis is the embodied person in dynamic interaction with their environment. Considering the person as the central unit of analysis does not mean to address only psychological aspects. We also need to *look down* and consider the dynamic interaction of more local physiological systems, *look around* and consider the organization of the involved parts in their co-determining relation to the person as a whole, and *look up* and consider the broader (social) context in which the person is located in and dynamically coupled to (Bechtel, 2009).

Taken together, this provides a picture of a hierarchy best characterized as ‘organizational’ (de Haan, 2020a, 2020b, 2020c) or ‘enmeshed’ (Thompson & Varela, 2001) (for an illustration see Fig. 3). According to this ontological architecture, biological, psychological, or social aspects are located in the same material realm: they are the more or less spatio-temporally extended aspects of the dynamic development of the same person-environment-system, or brain-body-environment-system, relating as partially overlapping and cross-cutting parts and wholes (Aftab & Nielsen, 2021; de Haan, 2020a, 2020b, 2020c).

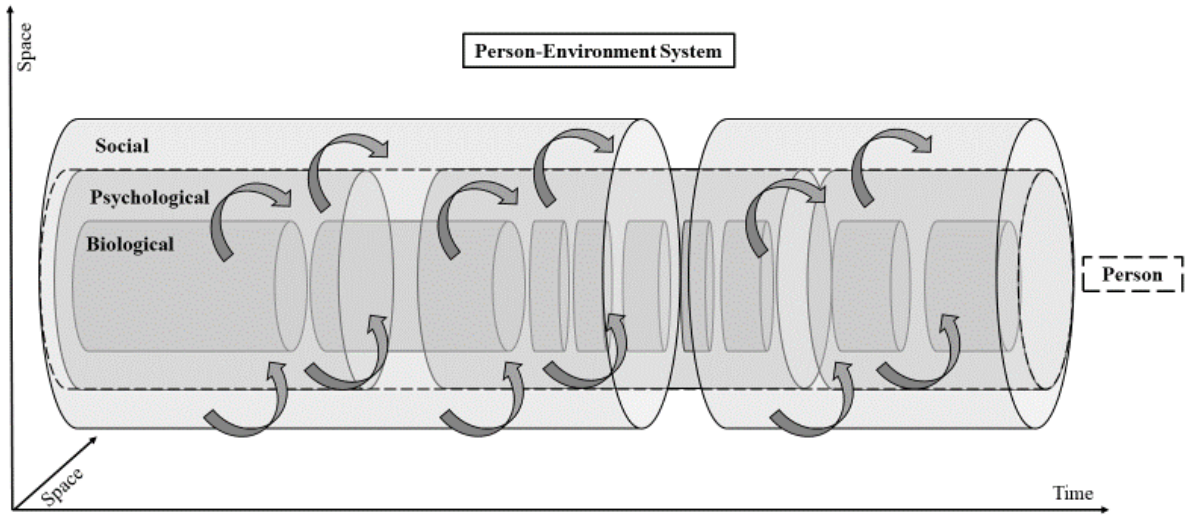

Fig. 3 Organizational or enmeshed hierarchy (inspired by Krickel (2018), Figure 7.2): the figure illustrates the relation of biological, psychological, and social processes as more or less spatio-temporally extended aspects of the same person-environment-system. The research target is the individual person and their unfolding dynamics over time whose understanding requires not only the consideration of the psychological aspects, but also of more local biological and more global social aspects. The *arrows* indicate that biological, psychological, and social processes co-determine each other which behave asymmetrically in their global-to-local and local-to-global relation. The *breaks* between sections are not meant to indicate that the biological, psychological, or social domain temporally cease to exist, but that specific biological, psychological, and social processes can start or stop and spatiotemporally intersect

3.3 Application to Chronic Pain

In this section, we further unpack the minimal assumptions of an enactive ontology in the context of chronic pain. We implement the previously introduced approach of an organizational or enmeshed hierarchy by highlighting five central implications for our understanding of the relation between biological, psychological, and social factors in the process of pain chronification.[6] We do so with the help of an illustrative analogy. The enactive view rejects misleading comparisons of complex systems with clockworks involving neatly separable parts that are linearly connected. Instead, we find in the literature different references to the process of baking. Feldmann-Barrett (2017) uses the analogy of baking bread to exemplify how different brain systems contribute to psychological phenomenon. de Haan (2020a, pp. 97–104, 2020b, 2020c, 2020d) applies the analogy of baking cakes to the interaction of physiological and psychological aspects in psychopathologies. This analogy has clear limitations as we are about to outline in the following. Nonetheless, it may help to illustrate in particular the relation between physiological and psychological processes in chronic pain and it provides a more

[6] For a more detailed analysis of empirical data concerning the relation of biological, psychological, and social factors in the process of pain chronification see Coninx and Stilwell (2021), Stilwell and Harman (2019), and Cormack et al. (forthcoming).

compelling picture of the complex, integrative, and dynamic approach of an enactive philosophy of pain.

First, consider the process of baking a bread or cake. The baking product (e.g. banana bread or chocolate cake) represents a more global system, in our case, the person suffering from chronic pain. The ingredients of the baking product, such as flour, water, sugar, or salt, are the more local components of which it is made, standing in for physiological processes, including (epi)genetic, immunological, endocrine, or neural aspects. What such analogy illustrates is that we cannot reduce chronic pain to a single physiological factor in the sense that it is the person suffering from pain, not their brain, hormones, or genes. Chronic pain is an emergent characteristic of the person; just as being crusty or fluffy are not properties present in any of the ingredients, but in the baking product. At the same time, the more global experiential, behavioral, or cognitive alterations instantiated by a person in chronic pain are determined by the processes of more local physiological systems. Persisting pain as experienced by a person is nothing over and above the physiological (re)organization of their brain and body without being reducible to it; just like a bread or cake is nothing over and above flour, water, salt, or sugar without being reducible to such ingredients.

Second, we may understand how physiological processes contribute to pain chronification only in their interaction and as being part of a more complex organism. “To understand how salt transforms a recipe of bread, you must watch it work in context.”(Feldman Barrett, 2017). The physiological processes involved in the generation and maintenance of pain cannot be individuated according to what they do intrinsically and chronic pain cannot be analyzed as the mere collection of what these physiological systems do in isolation or in other systems. Individual brain-bound processes depend on their broader neural contexts and their interaction with non-brain-bound processes while these biological processes themselves are constrained by psychological and social aspects. That is, not all physiological events, such as an injury, necessarily result in pain. Further, a shift in a more global system may take place and persist, even if the local components that were initially involved have changed. That is, the inciting issue linked to the onset of pain may not be the sustaining factor.

Third, psychological characteristics are instantiated by global systems and equal in our analogy to properties of the bread or cake as a whole. At this point, first limitations of the baking analogy become evident, as these psychological processes themselves interact in looping manners which can hardly be illustrated by the relation between ‘crustiness’ or ‘fluffiness’. For example, positive expectations about treatment outcome, negative thoughts about one’s body, and increasing pain may reveal ongoing faciliatory and inhibitory effects on each other. Further,

psychological processes constrain physiological processes in terms of global-to-local determination. Most importantly, psychological processes do not affect physiological processes in a sequential manner, but to intervene on the former is to intervene on the latter. It is not that a subject holds negative thought about their body which in turn causes certain physiological alterations that may further contribute to pain chronification. Psychological changes always involve physiological changes; just like changes to a cake always involve changes to its ingredients. At the same time, changes in the whole might mold changes in the involved components in varying manners. For example, psychological processes (e.g. negative expectations) might influence some physiological systems faster than others (e.g. neural vs endocrine system) (de Haan, 2020a, pp. 101-102).

Fourth, in the processes of chronification, organism and environment continuously determine and constrain each other. In our analogy, the oven that provides heat or the baker that continuously moistures a bread with water might stand in for the relevant social factors in the process of chronification, such as stigmatization, social support, or messages of rest and avoidance. This is where the introduced analogy reveals further limitations (Bruineberg, 2021): oven and baker only have a uni-directional relation to the baking product which is typically finished at some point while a person interacts with their environment in an ongoing dynamic manner. However, what the enactive view emphasizes is that the processes contributing to pain are not restricted to the patient, as chronic pain is partly a social and iatrogenic phenomenon. Further, none of the domains function as a uni-directional switch, in that social factors only trigger psychological or physiological changes, rather social factors permeate the person and their experiences, beliefs, and behavior and in that their physiological constitution.

Fifth, it follows that chronic pain does not emerge only because of certain physiological, psychological, or social processes, as they are not static and fragmented elements in a collection of heterogenous factors. It is not simply relevant which factors are involved but how they relate and unfold over time. We can hardly find any ‘root causes’ for chronic pain as the involved biological, psychological, and social processes continuously co-determine each other as more or less local or global excerpts of the same process. We cannot say that the persistence of pain is the result of a single factor; just like we cannot say that bread or cake is the *sole* result of any particular ingredient or the heat of the oven. Further, we cannot decompose a person in pain into clear-cut biological, psychological, and social elements. In our analogy, we might study bread and determine that a certain ingredient or external condition has been involved, for example, because it tastes salty or is fully baked. However, we cannot open the bread and neatly dissect it into the different ingredients and procedural steps to unravel their contribution in

isolation of all other factors involved. In that, enactivism guarantees the rejection of naïve reductionism, fragmentation, and linearity in relation to the generation and maintenance of chronic pain and provides at the same time a complex, integrative, and dynamic alternative.

As a crucial final note, it should be highlighted that even if the outlined assumptions might seem hardly controversial or radical to some philosophers, their acceptance might have a significant influence on how we conceptualize, explain, assess, and treat pain; especially as these assumptions are not yet fully embraced in pain research and clinical practice. That is, even if the minimal assumptions of an enactive ontology reflect common sense in certain philosophical debates, they do not characterize the implicit or explicit philosophy of pain implemented in clinical research and practice. As such, enactivism offers a theoretical foundation for a complex, integrative, and dynamic view on chronic pain. It provides conceptual tools and illustrations that might prove useful the cascading interaction of philosophers, researchers, clinicians, and patients, especially in order to avoid misguided interpretations and applications of the BPS model.

We are aware that enactive frameworks often entail stronger ontological assumptions than so far presented while some aspects are, in our view, still up for debate. First, it seems necessary to further investigate how an enactive ontology relates to strong and weak emergence and different epistemic or ontological interpretations of the global-to-local determination (e.g., Gillett, 2016; O'Connor & Hong Yu, 2020; Stephan, 2006). Second, while an enactive framework is not compatible with the idea of a vertical hierarchy, it remains questionable whether this entails a commitment to a horizontal hierarchy (e.g., de Haan, 2020a, p. 119). Third, it remains to be seen whether enactivism implies a certain interpretation of (synchronic or diachronic) constitution (e.g., Gallagher, 2017). In our view, the outlined minimal assumptions themselves do not commit to a particular position regarding these more controversial issues. While further investigation is needed, it might be the case that at least some of those assumptions going beyond the outlined minimal commitments make no difference to the outstanding conceptual, explanatory, methodological, and therapeutic challenges in the context of chronic pain.

3.4 Conceptual, Explanatory, Methodological, & Therapeutic Challenges

In the following, we revisit the remaining challenges of integration and outline which implications the previous considerations may have on how we conceptualize, explain, study, and treat chronic pain. We are aware that these facets of the integration problem require an in-depth analysis as they connect to extensive ongoing debates in the philosophical literature. We

aim to primarily indicate ways in which an enactive approach to chronic pain may potentially contribute to discussions on conceptual, explanatory, methodological, and therapeutic issues and explore in how far it is compatible with existing positions in corresponding debates.

Conceptual Challenge: This challenge raises the question of how to conceptualize chronic pain in the light of the integration problem. It follows from the previously introduced framework that chronic pain cannot be conceptualized as a disease of the body or brain, at least not exclusively. Chronic pain is not identical or primarily grounded in physiological abnormalities. However, it is neither adequate to conceptualize chronic pain only as a psychological or social disorder. In fact, it seems misguided from the beginning to discuss the conceptual challenge in terms of such trichotomy. From an enactive perspective, chronic pain is best understood as a disruption of the interactive embodied relation between patient and environment that permeates all domains in their dynamic interplay as more local or global excerpts of the same process (Coninx & Stilwell, 2021; Cormack et al., forthcoming).

Pain is identified in reference to the first-person perspective. Analyzing the lived experience of patients shows that they are often unable to flexibly attune to the requirements of different situations as they are stuck in a particular pattern of perceiving themselves and their interactive relation to the environment (Coninx & Stilwell, 2021). This is not to say that the transition to chronicity is somehow the individual's fault or that they can simply think away their pain or act differently. It is the interplay of biological, psychological, and social processes over time that brings forth chronic pain and the corresponding changes in lived experience. Thus, we need to conceptualize chronic pain as a condition of the person as a whole that we can fully understand only when considering the ongoing interaction of brain, body, and environment (Cormack et al., forthcoming). In the conceptualization of chronic pain, references to temporal persistence are useful only in as much as the dynamics of chronification typically unfold over a certain time span in the co-determination of biological, psychological, and social processes.

Explanatory Challenge: This challenge addresses the question of how we can explain chronic pain given the variety and heterogeneity of involved factors and their dynamic entanglement. An enactive approach clearly suggests the rejection of *explanatory reductionism*, according to which only biological explanations are 'real' explanations (Bickle, 2003), or at least to be preferred (Insel & Cuthbert, 2015; Kandel, 2018). In contrast, enactivism favors *explanatory pluralism* in that none of the three domains are considered more fundamental (Borsboom et al., 2018). Biological, psychological, and social explanations rely on different perspectives on one and the same process, while there is no principle reason for why any of them should be considered more 'real' or superior (Kästner, 2018).

While accepting explanatory pluralism, it remains challenging to determine how biological, psychological, and social explanations can be brought together (Kästner, 2018; Potochnik & Sanches de Oliveira, 2019). Within and across disciplines, there are different approaches to what the relevant global and local systems under investigation might be and the corresponding explanatory approaches might frame chronic pain in terms of varying spatio-temporal complexity. Further, the processes they refer to prove partially overlapping and crosscutting, connected through multiple more or less extended feedback-loops. That is, we receive a complex picture of different explanatory perspectives on chronic pain suited for varying scientific purposes which come with a different focus.

In principle, explanatory pluralism allows for multiple interpretations (Eronen, 2021; Miłkowski & Hohol, 2021). First, we may argue that researchers need to rely on a set of incompatible explanations concerning more local or global aspects of pain chronification. This provides a non-reductionist, although fragmented picture. Second, we may aim for a single unifying explanation of chronic pain that bring together all scientific perspectives at once. This however seems to neglect that our explanations may indeed vary with our scientific interests. A third option emerges when thinking about the previous two interpretations as two extremes with moderate versions of explanatory pluralism in-between. For example, *integrative pluralism* considers biological, psychological, and social explanations as complementary and mutually informative. Still, its aim is not necessarily to provide a single unified explanation but to integrate 'bit-by-bit' in different contexts different aspects of explaining the emergence of chronic pain (Kendler, 2005, 2008).

Enactivism fits well with integrative pluralism. First, enactivism takes a particular perspective on chronic pain, focusing on patients in their environment, which requires the combination of multiple explanatory perspectives. This seems most suitable for the aims of clinical research and practice while enactivism might accept that these are not the only purposes of pain science (Coninx, 2021). Second, even if a full multi-domain integration could never be reached, this might still function as a useful heuristic ideal. That is, integration is to be understood as a process rather than a goal, promoting local integrative efforts in terms of interdisciplinary exchange (Eronen, 2021; Kendler, 2005). Third, integrative pluralism aligns with the enactive claim that the targets of many research projects are only excerpts of a more complex process. This should result in more modest interpretations in that a single discipline might hardly provide *the* explanation of chronic pain. For example, an explanation of chronic pain in terms of neural reorganization can be most useful in certain scientific circumstances but is not a 'full' explanation as it provides only one piece of the puzzle.

Methodological Challenge: Concerning the methodological challenge, an enactive approach faces similar issues as with respect to the previous explanatory challenge. In a nutshell, there is no particular instrument of investigation that is to be prioritized for principle reasons over others, as they provide access to different aspects of dynamically developing processes.[7] At the same time, we should also not expect to identify a single unifying methodology for all pain science. Aspects of varying spatio-temporal complexity require different methodological approaches to be studied. No method is superior but it may only prove more or less suited for certain scientific purposes. As such, an enactive approach allows for a flexible choice of methods depending on the more local or global focus of a particular investigation while fostering overall an integrative multi-domain perspective (Stilwell & Harman, 2021).

Physiological investigations are on their own inadequate to assess the generation and maintenance of chronic pain. We also need to consider methods addressing the lived experience of patients and the ways in which social processes co-determine psychological and physiological aspects (Mescouto et al., 2020). One might argue that certain 'objective' methods are to be preferred. By contrast, all methods are to some degree dependent on the scientific context in which they are employed, coming with their own constraints and idealizations. For example, interpretations of neural data always depend on research context as these are sensitive to interest-driven decisions of which groups and features are respectively selected for study and comparison (e.g., Viola, 2021; Ward, 2019). At the same time, the study of how chronic pain affects and is affected by psychological and social processes is in principle not more 'subjective'. For example, we should be careful not to conflate a subjective approach to studying pain with an approach to studying the subjective experience of pain (Gallagher & Zahavi, 2012).

One might still critically ask how can we make a multi-domain approach pragmatically manageable. As an initial reply, it might be said that also with regard to the variety of methodological perspectives, integration is not a goal that needs to be actively pursued at all times, but it might rather provide the overarching framework within which research studies and clinical efforts are to be conducted and interpreted. As a strand of future research, it might also prove fruitful to investigate the complementarity of the enactive framework with *multiplexes*,

[7] While multiple instruments might be of relevance for the *study* of the process of chronification of pain, with none of them being in principle more valuable than others, there are differences when it comes to the *identification* of pain cases. Not least for ethical, legal, and methodological reasons, first-person pain reports are to be considered the best available way to identify whether a person is experiencing pain or not and how it feels.

that is, complex multi-layered network models that have the potential to account for the dynamic interaction between multiple factors of varying spatio-temporal complexity (Boer et al., 2021; Kästner, forthcoming). Multiplexes could provide a statistically grounded model to make an integrative approach to chronic pain manageable while enactivism offers a theoretical foundation of how biological, psychological, and social processes relate, making ontological and conceptual assumptions that are not inherent to network models themselves (de Haan, 2020a, p. 43).

Therapeutic Challenge: This challenge concerns the question of how we can best treat chronic pain. Once again, an enactive approach indicates some kind of *integrative pluralism*. There are many routes to change and no target or method of intervention is to be prioritized *only* because they address biological, psychological, or social processes (Coninx & Stilwell, 2021; Stilwell & Harman, 2019; Cormack et al., forthcoming). This means that treatment should not limit patients to passive targets of physiological interventions. By contrast, a central element of pain management can be to reinforce the patient's self-efficacy by training problem-solving skills and providing support in the re-assessment of goals (Kongsted et al., 2021). Improving self-management strategies and active self-care can be an effective measure to increase the patient's autonomy and sense of agency, as well as to increase their ability to flexibly adapt to the requirements of a situation in and outside of clinical contexts (Coninx & Stilwell, 2021). We often do not find 'magic bullets' that allow us to cure medical conditions or fully eliminate pain; instead, we might rather focus on improving quality of life and addressing social conditions, such as reducing stigmatization and facilitating access to healthcare (Stegenga, 2018). Further, we need to reflect on the role that clinical practitioners themselves play in this process by transmitting to patients a particular philosophy of pain that may not be helpful or aligned with current pain science (Setchell et al., 2017; Stilwell & Harman, 2017).

Enactivism emphasizes that it is the dynamic interaction between biological, psychological, and social aspects that is most relevant. A pluralistic approach is misguided if it results in fragmented health care neglecting the connections and interactions across domains, including inhibitory and excitatory effects. By contrast, an enactive approach considers multidisciplinary approaches most promising that take into account the interplay of interventions dynamically unfolding over time (Coninx & Stilwell, 2021; Kamper et al., 2014; Low, 2017). There are no purely psychological or purely physiological interventions, for example, as they asymmetrically co-determine each other. More global or local interventions address aspects of varying spatio-temporal complexity, but they all concern the person living with chronic pain in their environmental context. They only offer different points of

intervention and trajectories of the same target system (de Haan, 2020b, 2020c). This implies that the effects of treatment are non-linear and can be difficult to predict. Treatments that are effective with respect to one patient might not work for another. Even interventions that have been effective for the same patient before might no longer prove helpful, indicting the need for care that is sensitive to the patient and their context.

Acknowledging the complexities and dynamics of chronification poses a serious challenge. Each patient in their particular situation reveals idiosyncratic characteristics which means that we cannot make - with certainty - any assumptions concerning the effectiveness of future interventions (Coninx, 2021; Corns, 2020). This raises the question of how we could ever make informed therapeutic choices. Even if there are no strict regularities, it remains possible to make probabilistic assumptions about the success of certain interventions based on the similarities between patients and their contexts (Coninx, 2021). What we need to identify are the most relevant comparative classes for the respective cases. For example, with respect to multiple groups of patients it might show that changing more local aspects is less effective than intervening on more global aspects. The enactive framework indicates that subgrouping of patients can be most useful when not only one but multiple factors are considered and respectively addressed in prediction and treatment (Cholewicki et al., 2019). Furthermore, it is not necessarily the static set of involved factors but their dynamic interplay that might prove most relevant in this consideration. At the same time, it does not follow that ‘everything goes’. In the study of similarities and dissimilarities, an evidence-based approach is needed to identify the most promising intervention targets and methods for the relevant comparison classes, while also being aware of the respective limitations of sub-grouping (Saragiotto et al., 2017). For example, so far, there is no clear answer to the question of which sub-groupings are most predictive of therapeutic success given the idiosyncrasies of chronic pains.

Finally, it is an empirical question which comparison classes prove most useful for certain scientific purposes and which are the most useful intervention targets and methods for these comparison classes. An enactive framework indicates that team-based approaches, involving different disciplines intervening on different aspects of the person-environment system at (potentially) different times during the development of pain conditions, are most promising. Further, independent of our scientific progress, we should always expect individual and situational differences to impact therapeutic outcomes. Thus, a certain degree of uncertainty might be inevitable. It should therefore be part of clinical practice to address such uncertainties and potentially explore them in communication with patients, instead of searching for simple solutions to ‘fix’ the patient (Coninx & Stilwell, 2021; Cormack et al., forthcoming).

4. Conclusion

In studying the recent development in pain sciences, we have good reason to take a critical view on neuro-reductionist and bio-reductionist tendencies in research and clinical practice. Instead, in order to meet the challenge of chronic pain, multifactorial approaches prove more promising. While the enactive approach is considered a further development of the BPS model, it provides a framework avoiding reductionist, fragmented, or linear misinterpretations and misapplications due to its more comprehensive theoretical foundation. At the same time, the enactive philosophy of pain enables us to address the different challenges of integration.

Following enactive theory, the biological, psychological, and social processes involved in the chronification of pain are located in the same ontological realm without being reducible. They relate to each other as spatio-temporally overlapping and cross-cutting excerpts which characterize the same matter with a narrower or wider focus, showing qualitatively new properties, behaviors, and structures in their increasing complexity. Thus, chronic pain is understood as an emergent property of the person in their context that cannot be fully understood in the consideration of isolated factors, but only when their asymmetric co-determination and unfolding dynamic is taking into account. Chronic pain is best understood as a disruption of the relation between person and environment that permeates all domains in their ongoing interplay as more local or global processes. This motivates an integrative pluralism in terms of the explanation of chronic pain as well as the selection of methodological instruments or therapeutic interventions.

Finally, one might criticize the outlined approach as too abstract as it does not make concrete hypotheses to be directly tested. It also remains vague in that it does not prioritize or exclude particular research approaches and allows for the application of different tools and treatments. In reply, the enactive philosophy of pain should not be understood as a specific research program within a specific scientific discipline. On the contrary, we see it as a ‘philosophy of nature’, that is, a philosophical stance which connects the results from multiple research strands, provides an overarching framework for their interpretation, and motivates new scientific endeavors (Käufer & Chemero, 2021, pp. 181–182). We hope to have shown how fruitful this philosophical stance can be in relation to chronic pain and the challenges of integration.

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