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Persistent physical symptoms as perceptual dysregulation: a neuropsychobehavioral model and its clinical implications

Short title: Physical symptoms as perceptual dysregulation

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Abstract

Objective: The mechanisms underlying the perception and experience of persistent physical symptoms are not well understood, and in the models, the specific relevance of peripheral input versus central processing, or of neurobiological versus psychosocial factors in general, is not clear. In this article, we propose a model for this clinical phenomenon that is designed to be coherent with an underlying, relatively new model of the normal brain functions involved in the experience of bodily signals.

Methods: Based on a review of recent literature we describe central elements of this model and its clinical implications.

Results: In the model the brain is seen as an active predictive processing or inferential device rather than one that is passively waiting for sensory input. A central aspect of the model is the attempt of the brain to minimize prediction errors that result from constant comparisons of predictions and sensory input. Two possibilities exist: adaptation of the generative model underlying the predictions or alteration of the sensory input via autonomic nervous activation (in the case of interoception). Following this model, persistent physical symptoms can be described as “failures of inference” and clinically well known factors like expectation are assigned a role, not “only” in the later amplification of bodily signals, but in the very basis of symptom perception.

Conclusions: We discuss therapeutic implications of such a model including new interpretations for established treatments as well as new options like virtual reality techniques combining exteroceptive and interoceptive informations.

Key words: persistent physical symptoms; somatic symptom disorder; predictive processing model; predictive coding; perception

Introduction

Patients with persistent physical symptoms, be it pain, fatigue, dizziness, bowel or sensorimotor dysfunctions or combinations of these, are frequent in medicine. Persistent physical symptoms here are meant to be chronic, burdening physical symptoms that exist for more than 6 months. Traditionally, the symptoms in this field were often termed "medically unexplained", or part of "somatoform disorder" but these concepts have largely been abandoned due to their conceptual and practical problems (1). Indeed, also in well defined organic disease, factors like general negative affect, depressivity and early adverse experiences are associated with elevated somatic symptom reports that are little correlated with physiological disease parameters , and with reduced quality of life (2, 3). Current types of diagnoses used for this clinical problem are, among others, "somatic symptom disorder", "functional somatic syndromes" or "bodily distress syndromes" (see 4, for a discussion). What remains is a challenge to positively explain, in terms of etiology and psychopathophysiology, the suffering of this large group of patients. What is going on in the mind, brain and body of individuals with this condition and what are the etiological factors? These questions are not merely conceptual ones, they are no less clinical ones as they obviously are relevant when determining the diagnostic and therapeutic approaches to these patients – and answers to these questions are also sought by patients themselves in their quest for legitimacy of suffering in a situation without an obvious, classic organic disease.

Historical models for such bodily symptoms assumed purely psychological, i.e. psychogenic, causes and mechanisms that lead from psychological to physiological dysfunctions, while others assumed purely biological causes and mechanisms (e.g. immunological ones for Chronic Fatigue Syndrome). Most current models are more balanced, i.e. they are biopsychosocial in nature. Nevertheless, explaining the mechanisms and the exact nature and interplay of the biological, psychological and social factors is a challenge and many open questions remain, for instance: is specific peripheral input from pain and other receptors in the body that exceeds normal "noise" in the system a necessary component? Is the role of the CNS best captured by a notion of "sensitization"? Where

exactly do psychological factors like attention, catastrophizing, and cognitions, but also social context factors come in in the experience of persistent physical symptoms? And (how) do these psychological and social factors influence, in feedback cycles, the biological factors that underlie the experience of persistent physical symptoms?

In this article, we will present a model of the mechanisms (answering the question "how") involved in the experience of persistent physical symptoms. It is designed to be coherent with an underlying, relatively new model of the normal brain functions involved in the experience of bodily signals; the model is not primarily about the etiology (answering the question "why"). We will concentrate on perception or more precisely interoception, as the conscious experience of persistent physical symptoms is closely related to this normal function, but we will see that perception or interoception cannot really be treated separately from other functions which are also involved, like beliefs and action/ behavior. After presenting some essential elements of the model, we will concentrate on its clinical implications.

Predictive processing, perception and interoception

In recent years, a fundamental shift in the understanding of the basic functions of the brain has evolved. This shift is based on several developments over the last decades such as the discovery of experience-dependent neuroplasticity beyond maturation, the description of the basic principles of interacting neural networks, the perspective of embodiment and enaction (picturing the brain as an "enabler" of successful interactions with the environment rather than as a central controller) and the discovery of the high resting activity of the brain in its default networks (1). An important next step is the perspective of the brain as predictive processing device that uses prediction not only as a strategy to "compress" sensory data but also to regulate physiological systems via action (hence, we prefer predictive *processing* to predictive *coding*). A predictive processing model implies that the

brain is constantly generating, on different levels of abstraction, hypotheses about sensory input which are then compared to the actual input.

This latter step, which has forerunners that go back to von Helmholtz in the 19th and also to cybernetics in the 20th century, will be at the center of this discussion (for more detail see e.g. 5, for an easily accessible introduction see 6, for a discussion from psychology see 2).

In Table 1, we describe 12 important characteristics of the predictive processing (PP) model of perception/interoception and we introduce relevant terms.

---- insert Table 1 approx. here -----

To clarify the condensed set of propositions described in Table 1, a few explanations and figures may help. For example, Figure 1 demonstrates the basic difference between the traditional bottom up- and the new generative model of perception (Table 1, 1, 4 and 11).

---- insert Figure 1 approx. here -----

Figure 1 clearly shows that "prior knowledge" influences perception in both models in different ways. In the traditional model, prior knowledge influences a percept after it has emerged. In the new model expectations, other cognitions and emotions - often summarized as "prior" – are grounded in the underlying generative model of the world/ body where they actively contribute to the very emergence of the percept. In metaphorical terms and related to interoception, this means that one's past viscerosensory experiences resonate in the actual experience of the internal state of the body, but also that the actual experience influences how the body will be experienced in the near future.

Or put otherwise: “It is an elegantly orchestrated self-fulfilling prophecy, embodied within the architecture of the nervous system” (8, p 427).

A vast amount of examples in research on perceptual organization, object recognition, phantom (pain) perceptions and nocebo/placebo phenomena documents that the brain creates meaningful perception by means of unconscious inferential processes that rely on implicit assumptions and experience (9, 2). Symptoms independent of objective physiological dysfunction may emerge in a similar way (see below).

Figure 2 gives an extended and more comprehensive version of this concept. It adds several important aspects.

---- insert Figure 2 approx. here ------

Firstly, it explicitly includes the generative model of body/world that is grounding the prior and hence the predictions; it also explicitly includes the prediction errors that result from comparisons of predictions and sensations. Secondly, it includes a layer of metacognition that is important when discussing clinical implications of the model. This layer refers to the fact that the capacity to pursue the homeostatic goal, i.e. to influence the amount of prediction errors, is constantly evaluating itself. On a conscious level, this is equivalent to self-reflective functions like self-efficacy or learned helplessness (10). Thirdly, the figure includes both ways of interacting with the external state “x” (world or body) – via sensations and via actions (see Table1, 8 and 9). Prior predictions, as embodied forward simulations, may induce changes in physiological variables anticipating sensory events and feeding back to either confirm or modify the priors (11).

This latter aspect is depicted in more detail in Figure 3 which differentiates more clearly between extero- and interoception, extero- and interosensations and extero- and interoactions. Exteroactions, i.e. sensorimotor actions (e.g. moving the eyes and head to change the visual perspective and input to fit the predictions) are an easy to understand alternative in order to minimize prediction errors. Interoactions or the active inference directed at the body is not as intuitive: it means that activations of the autonomic nervous system and, consequently, of neuroendocrine and immune systems involved in the stress axis, could be seen as reactions to prediction errors rather than as a reactions to actual perturbations. This is a form of adaptive prospective control or forward simulation (10). Activating the autonomic nervous system and thereby stimulating the peripheral sensors could be a way to achieve a better fit of the resulting sensations to a prior prediction of "abnormal" bodily perceptions. To give an easy example, the sympathetic smooth-muscle vasodilation experienced in a moment of "blushing with embarrassment" might be induced by descending predictions of such an interoception, i.e., expectation to blush, resulting in prediction errors leading to active inference, i.e. activation of the sympathetic nervous system that generates blushing. Hence, the feeling does not simply follow the peripheral activation, it results from predictions beforehand (example from 12). Similar mechanisms may explain why interoceptive fear conditioning of gastric sensations (establishing prior predictions) increases the sensitivity of visceral perception (13).

---- insert Figure 3 approx. here -----

The relative influence of predictions and prediction errors on the eventual percept are based (see Table 1, 5 and 6) on probabilistic computations where prior probabilities are taken into account when determining the probability of new inputs (so-called conditional probability according to Bayes' theorem). Fig 4 demonstrates the distributions representing three relevant probabilities, namely the prior expectation, the sensory input (often called "likelihood") and the posterior model. When the

probability distribution of the sensory signal is precise (steep curve, left panel), the resulting posterior is pushed more towards the sensory signal. If the sensory signal is less precise (flat curve, right panel), the posterior is closer to the prior (belief/ expectation). In other words, the belief update representing the posterior is dependent on the prediction error (difference of sensory signal and prior expectation/ belief) weighted by the precision of the signals. In an analogy, if one were driving on a familiar road in thick fog, the reliability of the sensory data is expected to be low, so the weighting of the units processing prediction errors from the sensory data, i.e. their precision, will be low – the driving will largely be determined by top-down expectations of the shape of the road in question (compare right panel). In contrast, driving fast on an unfamiliar mountain road in clear weather, sensory data will largely determine the driving, and prediction errors will be predicted to be of high precision and will be given high weighting (compare right panel, example from 5, p 57).

--- insert Figure 4 approx. here ----

Mapping these computational principles onto neuronal substrates (Table 1, 12) will necessarily be different for the purposes of exteroception, where somatosensory systems are involved, and interoception, where central and peripheral autonomic nervous systems are involved. For interoception, the so-called visceromotor areas (VMAs), such as the anterior insula and cingulate cortex, are at the top of the interoceptive hierarchy. These VMAs receive ascending projections from viscerosensory areas like middle and posterior insula and have descending connections to a wide range of subcortical, brainstem and spinal cord targets involved in visceromotor control (12, compare 15, for a detailed discussion of this hierarchy).

--- insert Figure 5 approx. here -----

Predictive processing and persistent physical symptoms – the "how" question

As stated above, when applying such a model of interoception to describe the mechanisms underlying persistent physical symptoms, it is important to realize that it might answer mechanistic "how", but not necessarily etiological "why" questions. Etiologically, persistent physical symptoms might still be caused by a variety of processes such as: dysfunctions or damage on several levels, in peripheral organs, in sensors, or in brain regions involved in interoception and interoceptive control – and also by failures of inference on several levels, in predictions, in set points for autonomic control and in meta-cognitions (10).

These possibilities are not easily separated from one another in clinical practice, but here we will not concentrate on potential damage to peripheral organs and brain, as this is rare in situations without defined organic disease, but on the mechanistic background for persistent physical symptoms, i.e. failures of inference.

A first failure of inference as mechanism in persistent physical symptoms

Relating back to the model in Figure 2, there are at least three different ways in which "failures of inference" can contribute to the experience of persistent physical symptoms (see the "taxonomy of failure loci", 10). First, a generative model that contains beliefs that, on a high, conscious level amount to contents like "I am in pain, I am dizzy, I cannot move my leg" etc. can generate a highly precise prior in situations with peripheral sensory input close to random fluctuations (low precision). This may lead to the emergence of a posterior percept close to this prior, i.e. the emergence of the respective bodily symptom. Di Lernia et al. (16) call this type of a prior that co-creates symptoms "residual interoceptive ghosts across time". As suggested by Edwards et al. (17, p 3501f.), the difference between somatic amplication and false perceptions is only a matter of degree. However, once a stimulus has been perceived (that is, a posterior model representing the perception of a

stimulus has emerged), the model acts as a generative source of precise priors enhancing the probability for new perceptions close to the reinforced precise prior.

The above argument shows that the more psychological somatosensory amplification model (18) is not in contradiction with the PP model, but appears as a special case of a more comprehensive model that is consistent with current understanding of brain functioning. The same holds true for the neurobiologically informed central sensitization model of persistent pain which posits central nervous system processes that amplify peripheral input (19). A PP account advocates that peripheral physiological dysfunction is neither necessary nor sufficient for bodily symptoms to be experienced. This means that disabling bodily symptoms can develop out of "normal" bodily complaints – without implying any peripheral pathology. This does not mean that all bodily symptoms are seen as "imagined" or "psychogenic", but that the PP perspective blurs the categorical distinction between so-called medically unexplained symptoms and symptoms emerging from physiological dysfunction (see 2). The same inferential processes are involved in both types, with the difference being a matter of degree, namely to what extent priors versus prediction errors dominate the posterior model, with this balance modulated by precision weighting. Also in disease states associated with clear physiological dysfunction symptoms may be poorly related to measurable parameters of the dysfunction (20). Persistent bodily symptoms are considered at the extreme end of the continuum representing the relationship between peripheral input and the experience of a symptom. Typically, prediction errors from actual physiological dysfunction, as processed through a set of hierarchical layers, will be highly precise resulting in the adoption of a posterior model that closely resembles the peripheral input. However, when prediction errors from somatic input have low precision such as when input is less intense, more widespread (systemic) and characterized by poor on/off boundaries, a highly precise prior will shift the experience of a symptom more towards the prior and make it less determined by somatic input. For example, experiments showed that simply inducing negative affect by picture viewing was able to cause elevated somatic symptom reports, but only in functional disorder patients having strong symptom-related priors. Also, in those groups it was shown that

symptom reports reflected priors rather than somatic input, but only when the somatic input became weak (21, 22). Importantly, determinants of symptom experiences may dynamically change over time, as is experimentally shown by conditioning experiments (23, 2, 24, 25) at an early stage, symptoms may closely reflect peripheral input like in a physiological challenge induced by CO_2-inhalation, but after a number of episodes associated but harmless cues may act as strong priors and induce symptom experiences by themselves. Clinically, the same is evident in the many cases where an organically explained deficit is followed by a dysfunction like in irritable bowel syndrome after inflammatory bowel or in functional dizziness after vestibular neuritis (26).

A second failure of inference

It should be noted that in a PP account, the inferential process leading to persistent physical symptoms represents in itself a form of belief that is encoded in the neural probability distributions used to construct interoceptive reality. Also attention is, as a gain mechanism influencing the neural distributions, intrinsically involved in the construction of the percept. All symptoms are therefore characterized by an equally compelling experience of being “real” or “true”, regardless whether there is a strong, weak or absent relationship with peripheral dysfunction. The unconscious automatic character of the inferential process and the compelling quality of reality/trueness makes the experience of physical symptoms relatively impermeable for deliberate conscious argumentation and reasoning. In addition, it leads to a secondary failure of inference, namely to the conscious belief that the interocept indeed is a symptom, i.e. an expression of abnormal bodily function.

A study where this secondary failure is combined with the first one in a tendency to “jump to conclusions”, not from symptom to cause but from experienced to reported symptom, concerns one of the rare directly observable functional symptoms, so-called psychogenic tremor. Parées et al. (27) recorded actual and diary-based self-reported tremor and found a wide discrepancy between the two (4% vs 84% of the waking day, respectively). Such a discrepancy was also present in organic

tremor, but much less so (25% vs 58%). The authors interpret this finding as a failure of inference induced by an all too precise prior of having tremor: a failure to perceive that they do not have tremor for most of the day (hence the title of the paper: Believing is perceiving). Other research that can also be interpreted in the PP frame of reference concerns the repeated finding of symptom inductions through conditioning, poorer interoceptive accuracy, smaller correspondence between induced physiological dysfunction and symptom reports in patients with persistent physical symptoms and of the large discrepancies between actual symptom reports and symptom recall (see (28, 29), and work by the group of Van den Bergh). Related to the belief that an interocept is a symptom is the metacognitive belief that an individual holds that s/he has no means to influence this state of bodily dysregulation, a situation with low self-efficacy or possibly learned helplessness (10).

A third failure of inference

A third type of failure refers to active inference, when maladaptive priors with high precision create large prediction errors given rather "harmless" peripheral input. This may not lead to a shift of the posterior closer to the prior but to a shift of the set point for homoeostatic or allostatic responses to dyshomoeostatic states such as elevated blood pressure that could entrain into hypertension. As stated above, this results in activations of the autonomic nervous and related systems in order to create sensory input that more closely conforms to the predictions (12). Currently, it is not clear to what extent this type of psychophysiological "inference-control-loop" with its activations of biological systems contributes to the pathophysiological findings that are often but inconsistently observed in patients with persistent physical symptoms. This "failure of inference" as included in the model presented here could potentially explain both facts: that pathophysiological changes especially in "stress axis systems" are found in many patients with persistent physical symptoms and that their relation to experienced symptoms and disability are far from consistent.

It should be noted that “failures of inference” can also explain diagnostic mistakes in an opposite direction: priors with high precision for interpreting a bodily symptom as functional may lead to misinterpretation of relatively imprecise sensory input as white noise where in fact significant organ pathology is at the origin of this sensory input.

Predictive processing and persistent physical symptoms – the “why” questions

Where does the tendency for these failures of inference come from? As stated before, these etiological “why” questions are not answered by the description of such psychophysiological mechanisms. However, substantial epidemiological knowledge about risk factors for the development of persistent physical symptoms is available – how does this relate to a predictive processing model of this phenomenon? In this article, we only mention a few examples.

First, chronic stress, being typically associated with anticipated threat, activates priors representing increased metabolic needs. Through active inference, autonomic activity will be prompted feeding back to the brain as a way of error minimization. Autonomic activity is typically of low intensity that is spread across the body and is characterized by poor on/off boundaries creating low precise prediction errors for somatic input. In addition, it is typically prompted in close spatiotemporal association with threatening contextual cues, creating the learning conditions for strong (cue-induced) priors to eventually dominate the posterior model of the body. This means that learning mechanisms may gradually loosen the connection between physiological dysfunction and self-reported symptoms. Interestingly, there is also evidence that chronic activation of the stress axes compromises interoceptive sensitivity (30). Chronically inadequate processing of visceral-afferent signals is often associated with in increased interoceptive focus, creating the conditions for persistent physical symptoms to emerge: little precise somatic input combined with precise predictive priors about the bodily state.

Second, persons prone to develop persistent physical symptoms are characterized by elevated threat sensitivity as shown by high scores on trait negative affectivity (NA;5). High NA is associated with an overreactive evaluative system and less efficient inhibitory systems to counteract negative affect (31, 32). When experimentally inducing symptoms, high trait NA persons with health-related concerns and patients with functional syndromes typically show enhanced symptom reports for the same level of induced physiological dysfunction compared with controls. Because visceral-afferent information is relayed to the brain through a sensory-perceptual branch representing intensity, location, temporal aspects, etc. and an affective-motivational branch underlying a drive to act that is integrated into a unified symptom experience at the level of the anterior insula (33), a stronger relative contribution of the evaluative component to this integrative proces is likely responsible for these elevated symptom reports in high NA (34). However, enhanced affective-motivational responding to somatic experiences may go at the expense of detailed sensory-perceptual processing, resulting in augmented but imprecise prediction errors that largely overlap with prediction errors representing an emotional state. This view is consistent with findings showing that the induction of brief states of negative affect through picture viewing results in elevated symptom reports, but more pronounced in persons with high NA and high habitual symptoms and in patients with functional somatic syndromes, despite absent differences in arousal-related physiology. Interestingly, the difficulty to identify feelings, a factor characterizing alexithymia, moderated this effect suggesting that especially persons who cannot correctly identify their negative affect are particularly vulnerable to this kind of “failure of inference” (35, 36, 21).

Third, attachment patterns form a link between childhood adversity and somatization, with maternal insensitivity at 18 months predicting somatization in children aged 5 years and attachment insecurity in adults predicting somatization, with strongest links existing between attachment anxiety and health anxiety (37). A PP perspective introduces new ways at understanding such a developmentally grounded link as it is the nourishing, soothing or other actions of the caregiver that co-determine the developing generative model and the perception of bodily distress or satisfaction in the child.

Growing up with caregivers who consistently fail to recognize and differentiate types of negative emotions and bodily distress, consistently catastrophize or fail to soothe and generally fail to relate safely with the baby in distress will form a developmental basis for later experiences of persistent bodily distress (38).

Seen from this angle, the gradual development of interoception during development is not confined to a baby/ child alone, it is a deeply social process taking place in close bodily interactions. Later higher level “mental” constructs like attachment anxiety and behavior are likely to be the “mental surface” of such a bodily-grounded interpersonal process serving the maintenance of homeostasis – hence the term “embodied mentalization”. This means that, also later in adulthood, the generative models co-determining the perception of persistent physical symptoms are constituted not only by prior individual bodily experiences but also by the interpersonal context in which they took place, This hypothesis is supported experimentally, for instance, by earlier findings on the effect of social context on the subjective experience of pain and pain behaviors (39).

In sum, typical risk factors for persistent physical symptoms and somatic symptom disorder are associated with mechanisms relaying interoceptive information to the brain with very low precision, allowing that highly precise priors come to dominate the generative posterior model about the health status of the body. All kinds of factors that contribute to increasing the precision of prior predictions about the presence of symptoms will enhance this process. Factors that promote a lowered threshold to perceive physical symptoms include growing up with illness in the family and own childhood illness (40), but also health anxiety and illness concerns that more easily arise in threat-sensitive persons may act as a chronic source of symptom-related prior expectations. Several exacerbating factors in the doctor-patient relationship such as repeated medical examinations, discussing diagnostic hypotheses and poor reassurance may further increase the gain on symptom-related predictions resulting in persistent physical symptoms.

Clinical implications

Traditional models of medically unexplained symptoms implicitly assume some kind of direct perception of physiological dysfunction, which is subsequently modified by attention and beliefs (see Fig 1, A). The present model considers attention and beliefs as intrinsic elements of the inferential processes themselves rather than the post-hoc elaborations of the symptoms after they emerged (see Fig 1, B). Consequently, modifying the posterior generative model should rely on techniques that impact these inferential processes. In that respect, the model surpasses strict distinctions between psychosocial and pharmacological therapies, because all therapy may have effects on multiple levels of description. For example, neurostimulatory or pharmacological therapies may change peripheral input or central processing and impact precisions, the balance between priors and prediction errors, and the "failures of inference" involved in the experience of persistent physical symptoms in a similar way as psychosocial therapies. Another implication is that the therapeutic focus should shift from trying to modify a "wrong" model to trying to understand and modify its adaptiveness. This prompts different questions: why and how did persistent physical symptoms become an adaptive way to construe interoceptive reality? For example, the chronic presence of large prediction errors resulting from mismatch between high precision priors/illness beliefs and noisy sensory input may be reduced by experiencing pain or dizziness as a way of "making sense" of the internal world (a form of a "better the devil you know"strategy, see 2). And how can we modify the conditions for a person prompting an adaptive update of the posterior model and, as a consequence, remove the persistent physical symptoms? Obviously, the present model includes a challenge to develop new therapeutic techniques in the future, but it does not imply that current approaches are necessarily wrong as they may fit into the model to some extent.

In general, there are two major strategies, one targeting the precision of the prediction errors, the other focusing on highly precise symptom-related priors. First, the analysis of the risk factors above converges on the conclusion that interoceptive prediction errors are conveyed to the brain with very low precision. This suggests that "interoceptive differentiation training" might be an important target

for treatment in order to promote more fine-grained differentiation within and between somatic and emotional states (2; see 41, for an example). This idea is already implicitly present in several current treatment approaches. For example, it is part of interoceptive exposure as a treatment technique for interoceptive fears, but rather than mainly targeting habituation/extinction of the anxiety response, we suggest to train particularly perceptual differentiation of interoceptive sensations. Biofeedback is traditionally used for self-regulation of physiological processes, but it implicitly involves learning to differentiate interoceptive sensation. It could further be explicitly targeted to train interoceptive differentiation. Also mindfulness-based stress reduction involving body-scan techniques may implicitly train patients to improve sensory-perceptual processing of interoceptive information. Treatments focusing on emotion regulation (42) as well as several forms of body-oriented treatment techniques may also implicitly promote interoceptive differentiation. However, the benefit of making this strategy explicitly as a result of a theoretical analysis within the present account may lead to more focused, elaborated and powerful treatment components.

Second, the other important strategic component relevant to clinical interventions is to include techniques that help the patient to give up all kinds of strategies to predict and control the symptoms, including worrying and ruminating about them. Excessive checking and scanning the body for signs of symptoms and chronic concerns about the potential future course, as typically enacted through a large variety cognitions and behaviors, serve as a continuous source of highly precise priors determining the somatic state. In fact, this strategy comes down to training the patient in exposure to the risks involved in feeling symptoms, and to adopting a “let go” or an acceptance attitude when processing bodily information rather than mobilizing the defensive response system trying to keep control on the symptoms. Doing so, it may be expected that high-level priors representing illness will loose precision, and thus, impact on the somatic state. However, according to the present model priors are represented in the neural distributions associated across multiple hierarchical levels. This suggests that changing priors is more likely when mobilizing the whole “machinery” across all levels of processing by training this in the context of actual experiences with bodily sensations rather than

targeting the metacognitive level only. This suggests that behavioral exercises may be particularly critical to repeatedly induce symptoms and facilitate the adoption of alternative causal models to construe interoceptive sensations. Such behavioral excercises may include hyperventilation provocation, turning quickly around to induce dizziness, stress induction tasks while visualizing bodily responses through psychophysiological measurements, etc. but also the different types of body-oriented psychotherapies.

Recently, new concepts have been launched to capture how interoceptive signals become integrated into a holistic representation of the body and how to modify the latter in clinical conditions. For example, the notion of a *simulation map* has been suggested to describe an abstraction of the fluctuating sensory input providing relatively stable body representation (43). The authors consider contemplative practices generating as-if representations of the state of the body as means to update maladaptive interoceptive priors and reduce prediction errors. Another concept is *interoceptive modeling* (16). It relies on the idea that interoceptive representations are multimodal and multisensory, as is shown by the rubber hand illusion (44). The authors suggest that by gradual and strategic use of exteroceptive input in augmented or virtual reality set ups, interoceptive representations of the body state could possibly be (re)modeled to treat chronic pain conditions. For example, in one study a full body illusion similar to the rubber hand illusion was induced in patients with chronic pain. This was done by having them watching a body via a head-mounted display that was apparently stroked with a wooden stick, while they were themselves either simultaneously or asynchronously stroked with a stick. This created an “out-of-body” illusion in the simultaneous stroking condition that resulted in a substantial decrease in pain ratings (45).

Embedding these strategies into an interpersonal context to modify the social influence on interoception sketched above may be of particular importance. Having, in a sufficiently well-functioning therapeutic relationship, a corrective emotional experience of being supported and understood may, on its own or together with “interoceptive differentiation training” e.g. also in

different varieties of body psychotherapy, change priors of feeling pain or other persistent physical symptoms constantly.

In general, the model presented here can serve as a point of reference that allows to conceptually integrate the effect of different “verbal” and “non-verbal” treatment modalities on bodily distress. With its emphasis on active involvement of the patient in both strategies outlined above it helps to understand the empirically grounded notion that treatments that actively involve the patient (like psychotherapy or graded activation) are more effective than treatments that involve the patient only passively (like massage or medication directed at peripheral physiology) (46). However, we are only starting to think about the potential implications of the present model for persistent physical symptoms. Some suggestions to test hypotheses presented in this article have been made by Van den Bergh et al. (2). The clinical benefit at this moment is that it provides a theory-based rationale in accordance with current understanding of how the brain works to make more informed choices among the wide variety of existing treatment approaches, to understanding which treatment components work and why, and to advance more specific hypotheses and guidelines for new treatment approaches. Finally, a major challenge remains to develop metaphors and motivational techniques to convince patients to go along with these strategies and modify the patient’s illness beliefs. In addition to optimizing the therapeutic relationship, a patient-centered approach to finding the optimal solution to reduce and preferably eradicate persistent physical symptoms is likely to result in long-term benefits.

Conclusion

The recent fundamental shift in the conceptualization of the brain as a prediction generating system has prompted new ways to understand how bodily symptoms relate to physiological dysfunction. Just like in exteroception, the brain’s task is to develop an adaptive model about the sources and meaning of interoceptive stimulation using informed predictions and prediction errors resulting from

somatic input. Symptoms come about as a result of an unconscious inferential process about interoceptive sensations, representing implicit beliefs and actions and compellingly inducing a sense of being real, regardless of the actual somatic input. This means that the relationship between symptoms and bodily dysfunction can be highly variable and may be completely absent in conditions that are typically characterized by highly precise prior expectations and low precise prediction errors from somatic input. Because the unconscious inferential processes are relatively impermeable for conscious metacognitions, this new model implies a challenge to develop new treatment approaches that more explicitly target unconscious inferential processes.

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Legends to Table and Figures

Table 1: Basic assumptions and characteristics of the predictive processing (PP) model of perception/interoception.

Fig. 1 Schema representing a traditional bottom-up (A) and the new generative model of perception that is based on predictive processing (B) (from 7).

Fig. 2 Overview of a predictive processing model of perception - see text (from 10).

Fig. 3 Extero- and Interoception - see text (from 10).

Fig. 4 Probability distributions of sensory signal (red), prior (blue) and posterior (green). (from 14).

Fig. 5 Superficial pyramidal cells (red triangles) compare sensory input with predictions from higher level deep pyramidal cells (black triangles) and send up prediction errors to the next higher level. The synaptic gain of the pyramidal cells (blue, plus or minus) determines the precision and is thought to be achieved through neuromodulatory mechanisms (from 12).

Abbreviations

CNS	Central Nervous System
NA	Negative Affectivity
PP	Predictive Processing
VMA	Visceromotor Area