Topical Review

PAIN®

Altered interoception and its role for the co-occurrence of chronic primary pain and mental health problems in children

Tanja Hechler

1. Introduction

The co-occurrence of chronic primary pain - defined as pain in 1 or more anatomical regions that persists or recurs for longer than 3 months, is associated with significant emotional distress and/or significant functional disability, and symptoms are not better accounted for by another diagnosis[56] -anxiety, and depression in children constitutes a serious health problem, also summarized under the internalizing cluster.[46] (For ease of reading, the word "children" will be used for both children and adolescents throughout the topical review.) Children with chronic pain suffer substantially more from anxiety and depression compared to healthy children,[3] with comorbidity rates ranging between 50%[14] and 82%.[47] This co-occurrence aggravates and leads to severe mental health problems (MHP; the overarching term "MHP" will be used for the presence of psychopathological symptoms or mental health disorders throughout the review[17]) and pain problems in adulthood.[79] Treatment outcome is significantly worse, even in the most intensive form of treatment.[39,71] Today, there are sound conceptual models accounting for the co-occurrence.[40,72,79] Most models suggest predisposing vulnerability factors such as increased anxiety sensitivity (AS),[40] precipitating factors such as instigating stressful life events,[55,72] and perpetuating factors such as child's maladaptive emotion regulation (ER)[72,85] and parental chronic pain and MHP.[73,79]

Thus far, the construct of interoception—defined as body-to-brain afferent signaling, central processing, and neural and mental representations of internal bodily changes[60]—has not been integrated into any existing model (**Table 1** for terminology of key terms related to interoception). There are, however, strong reasons calling for its integration: Altered interoception is considered a prominent feature of a variety of both MHP and chronic pain conditions,[61,76] at least in the adult literature. The assumed factors accounting for the co-occurrence, eg, stressful life events, are closely intertwined with (altered) interoception.[70] Its integration points directly to its therapeutic potential,[9,61,76] which may lead to a decrease in the co-occurrence of MHP and chronic pain. The present topical review therefore aims to establish an initial model on this newly emerging field in paediatric pain with the scope on the role of altered interoception for the co-occurrence of chronic pain and MHP in children. The review presents a developmentally informed examination with the advantage that emergent processes contributing to altered interoception can be identified and studied before they become consolidated in adulthood.

2. (Altered) interoception

Interoception occurs across all major biological systems involved in maintaining bodily homeostasis, including the cardiovascular, gastrointestinal, and autonomic systems.[43] Interoceptive sensations are today regarded as conscious percepts that result from a constructive process, in which the brain interprets information from the body in light of predictions given past experience.[76] Interoception thus interacts with cognition and emotion.[60] Research on the development of interoception is still scarce, but recent evidence suggests that interoceptive ability is already present in infants to regulate hunger and satiety and subsequently develops to more complex interoception in preschool-aged children,[65] school children,[44] and adolescents[48] (for a review, see Ref. 53).

Parents are assumed to play a pivotal role in the development of interoception,[53] although research is still in its infancy. It is hypothesized that parents' capacity to detect and react to the infant's physical needs and emotional states depends on the fine balance between parental interoception and that of the infant.[25] In line with this, Abraham et al.[1] found that greater activation of parent's anterior insula (brain structure belonging to the interoceptive nervous system[34]) during individually tailored videotapes of child–parent interaction when the child was an infant predicted lower child somatic symptoms 6 years later.

Altered interoception may occur at various facets of interoceptive processing (see Ref. 34 for a list of 14 facets of altered interoception). A full depiction of all facets is beyond the scope of the review. Here, I focus on 2 facets with some empirical evidence: (1) altered interoceptive accuracy in the cardiac system, the most common studied channel,[52] and in the gastrointestinal system and (2) altered cognitive processing which is already a key component in existing conceptual models.[40,72,79]

2.1. Altered interoceptive accuracy

Altered interoceptive accuracy is defined as alterations in the process of correctly and precisely monitoring internal sensations.[43,61] The heartbeat tracking task[66] represents one of the most common procedures used today to assess cardiac

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Department of Clinical Psychology and Psychotherapy in Children and Adolescents, University of Trier, Trier, Germany

Corresponding author. Address: University of Trier—FB I/Psychology, Department of Clinical Psychology and Psychotherapy in Children and Adolescents, Universitätsring 15, 54296 Trier, Germany. Tel.: +49 651 201 4351. E-mail address: hechler@uni-trier.de (T. Hechler).

PAIN 162 (2021) 665–671

http://dx.doi.org/10.1097/j.pain.0000000000002099

Table 1

Terminology of key terms related to interoception (in order of appearance).

Facet	Definition
Interoception	Body-to-brain afferent signaling, central processing, and neural and mental representations of internal bodily changes[60]
Altered interoception	Alterations in the different facets of interoceptive processing[34]
Interoceptive accuracy or sensitivity	Process of correctly and precisely monitoring the sensations as assessed by comparisons between subjective and self-reported objective indices[43,61]
Cardiac accuracy	Process of correctly and precisely monitoring sensations in the cardiac system[28]
Gastric sensitivity	Process of correctly and precisely monitoring sensations in the gastrointestinal system[38,77]
Water load symptom provocation task (WL-SPT)	Noninvasive paradigm to assess gastric sensitivity[38,77]
Anxious potentially harmful interoceptive schema	Tendency to interpret ambiguous internal sensations as threatening[61]
Interoceptive fear conditioning	Associative learning process where (harmless) interoceptive stimuli are repeatedly paired with an unconditioned stimuli (pain), and thus function as a conditioned stimulus[18,84]
Interoceptive nervous system (INS)	Major brain structures underlying interoception[34]
Autonomic nervous system (ANS)	Collection of nerve cells/fibers consisting of 2 branches, the sympathetic and parasympathetic branch
Autonomic dysregulation	Parasympathetic withdrawal associated with a predominance of sympathetic activity,[30,81] reflected by low heart rate variability (HRV)[13]
Interoceptive predictive coding	Assumption that interoception is largely a construction of beliefs which are based on past experiences and the result of an iterative process of comparing the brain's expectation of an internal sensation with the incoming sensation[4,60,70]

accuracy, defined as the objective accuracy in detecting one's heartbeat.[28] In heartbeat tracking tasks, children are asked to count their heartbeats at rest (for 15-25 seconds).[44] Cardiac accuracy is then based on the comparison between objectively measured and self-reported (ie, counted) number of heartbeats, with higher levels suggesting increased cardiac sensitivity.[34] While decreased cardiac accuracy has been found in adults with chronic pain[19] and in adults with depression,[34] adults with anxiety disorders consistently demonstrate increased cardiac accuracy.[20] Cardiac accuracy has not yet been investigated in children with chronic pain nor in children with depression. The 3 existent studies in children with anxiety[22,23,67] showed inconsistent findings.

The water load symptom provocation task, originally conceptualized as a laboratory analogue for abdominal pain,[7] constitutes a noninvasive paradigm to assess gastric sensitivity.[38,77] During the water load symptom provocation task, children are instructed to drink until they feel completely full (during 3-15 minutes). Immediately after ingestion, the amount of ingested water is recorded and children report pain intensity and gastrointestinal symptoms.[82] Results in children with chronic (abdominal) pain consistently reveal increased gastric sensitivity, indexed by less water ingestion and increased symptom reports compared with healthy children.[2,82] Whether this holds true for children with anxiety and depression is currently an open question.

2.2. Altered cognitive processing of internal bodily sensations

Thoughts and feelings change the internal state of the body and respond to it, and vice versa,[49,60] as has been detailed in the cognitive-perceptual model of anxiety[16] and the fear-avoidance model.[80] Both emphasize the role of cognitive biases such as catastrophic misinterpretations of bodily sensations. Children's cognitive biases (for a review, see Ref. 11) have been integrated into existing conceptual models,[41,72,79] albeit without focusing on interoception. However, children with chronic pain and children with anxiety disorders seem to interpret ambiguous bodily sensations as threatening,[21,35] a cognitive pattern defined as an "anxious potentially harmful interoceptive schema".[62] This pattern leads to subsequent emotional (anxiety), behavioral (avoidance), and somatic responses (increase in heart rate).[49] Whether children with depression also display this cognitive bias is yet unresolved.

Besides cognitive biases, altered memories of painful events are a key construct in pain research.[41,57,58] Children's explicit memories of painful events can be assessed as recalled pain compared with their initial pain report.[58] Noel et al.[58] found that children with increased AS at baseline recalled their pain higher 12 months after surgery. Whether children with chronic pain also display altered memories of nonpainful internal sensations and how this relates to anxiety and depression needs to be investigated in future studies.

3. Initial model on the role of altered interoception

In the previous sections, I summarized some evidence for altered interoception in children. Here, I present an initial model (**Fig. 1**) that postulates that altered interoception constitutes a causal risk factor for the co-occurrence of chronic pain and MHP (for specific research hypotheses, see **Table 2**). The model also addresses the development of altered interoception, integrating top-down and bottom-up processes. Altered interoception is assumed to lead to maladaptive responses[49] and to demonstrate a relationship to symptoms of the internalizing cluster of chronic pain and MHP. Top-down (expectations of harmful sensations) and bottom-up processes (stressed bodily state) fuel altered interoception and subsequent responses, fostering the co-occurrence of chronic pain and MHP.

Altered interoception can be triggered by immediate causes such as (harmless) increased sensory input due to physical activity. Interoceptive fear conditioning describes the associative learning process where (harmless) interoceptive stimuli are repeatedly paired with an unconditioned stimuli (pain) and thus function as a conditioned stimulus.[18,84] Subsequently, the previously harmless sensations entail a threat value and elicit a conditioned fear response such as a potentiated startle

Table 2

Selection of research hypotheses generated by the initial model on the role of altered interoception for the co-occurrence of chronic pain and MHP in children (see also Fig. 1).

ID	Domain	Research hypotheses
1	Altered interoception	1.1. Children with chronic pain and children with MHP display altered interoception at the different facets of interoceptive processing compared to healthy children. 1.2. Altered interoception constitutes a causal risk factor for the co-occurrence of chronic pain and MHP in children. Using the 4 criteria outlined by Kraemer et al.[45] for determining causal risk, the following research hypotheses can be generated: Altered interoception in children can be identified before the onset of chronic pain and MHP. Altered interoception in children demonstrates a relationship to symptoms of chronic pain and MHP. Altered interoception in children is amenable to treatment. Altered interoception in children produces disparate outcomes in symptoms if intervened before the onset of chronic pain and MHP.
2	Immediate causes for altered interoception	2.1. (Harmless) sensory input triggers altered interoception through cognitive (eg, expectations) and physiological (eg, increased physiological signals) processes in children with chronic pain and MHP compared with healthy children. 2.2. Altered interoception induces altered emotional, cognitive, behavioural, and somatic responses in children with chronic pain and children with MHP. 2.3. These altered (emotional, cognitive, behavioural, and somatic) responses demonstrates a relationship to mutual symptoms of chronic pain and MHP.
3	Distal causes for altered interoception Interpersonal factors Parental MHP Parental chronic pain Altered parental interoception and ER Major stressful life events and early life pain	3.1. Parents with chronic pain and MHP display altered interoception at the different facets of interoceptive processing. 3.2. Altered parental interoception is related to maladaptive parental emotion regulation. 3.3. Altered parental interoception and maladaptive parental emotion regulation modulate their child's interoception and emotion regulation. 3.4. Altered parental interoception and maladaptive emotion regulation demonstrate a relationship to mutual symptoms of chronic pain and MHP, mediated by child's altered interoception. 3.5. Major stressful life events and early life pain trigger altered interoception through increased basal HPA axis activity.
4	Pre-existing physiological traits: Brain alterations and autonomic dysregulation	5.1. Children with chronic pain and children with MHP display brain alterations in the INS. 5.2. These brain alterations correlate with facets of altered interoceptive processing. 5.3. Children with chronic pain and children with MHP display lower HRV compared with healthy children, as an indicator of autonomic dysregulation. 5.4. Low HRV is related to altered interoception in (laboratory) situations where children are faced with immediate causes (eg, [harmless] sensory input).
5	Pre-existing psychological traits: Anxiety sensitivity (AS)	4.1. Increased AS constitutes a causal pre-existing psychological risk factor for altered interoception (for additional research hypotheses for determining causal risk, see Abraham et al.[1] and Kraemer et al.[45]).

HPA, hypothalamus–pituitary–adrenocortical; HRV, heart rate variability; INS, interoceptive nervous system; MHP, mental health problems.

response,[32] even in the absence of the unconditioned stimuli.[27] We recently showed that children with chronic pain report increased fear (emotional response) when confronted with (harmless) internal bodily sensations induced through muscle tension tasks.[27,32]

When vulnerable children are confronted with increased sensory input, they may also exhibit an inability to differentiate between aversive sensory input from constantly ongoing interoceptive afferents.[62,84] As a consequence, they may imbue interoceptive sensations with motivational significance in line with the motivational perspective in chronic pain,[78] and react upon them, although they may not be threatening.[62] The internal sensation will be associated with negative valence and linked to beliefs, eg, illness beliefs ("There is something wrong in my body."). [62] Bodily symptoms are then amplified, resulting in a vicious cycle of bodily sensations and responses.[49]

Interpersonal factors, major stressful life events, and early life pain constitute distal causes, ie, antecedent conditions with long-term consequences.[24] Although parental chronic pain is a key aspect in existing conceptual models,[40,72,73] parental (altered) interoception has not yet been included. Recent studies showed that half of the parents of children with chronic pain suffer from chronic pain and MHP themselves,[5] placing these parents at risk of both altered interoception and maladaptive ER.[19,59] As parents are assumed to play a pivotal role in the development of interoception[53] and ER,[64] I postulate that altered parental interoception and maladaptive ER demonstrate a relationship to their child's symptoms, mediated by child's altered interoception. Parents with altered interoception may face difficulties in supporting their child when dealing with intense bodily sensations.[53] They may be faced with difficulties in their own ER,[60] affecting their child's ER.[73] This may lead children to develop maladaptive ER, such as expressive suppression,[31] which has been frequently observed in adults with chronic pain[59] and is associated with depressive and anxiety symptoms.[31]

The role of major stressful life events (eg, sexual abuse) and the associated dysregulation of the stress axes have already been outlined in the existing models.[29,55,75,79] Altered interoception, however, has not yet been integrated. Research suggests that early life pain can also be conceived as an early environmental stressor[12] that place children at risk of increased basal hypothalamus–pituitary–adrenocortical axis activity.[12] Schulz and Vogele[69] postulate that the dysregulation of the stress axes

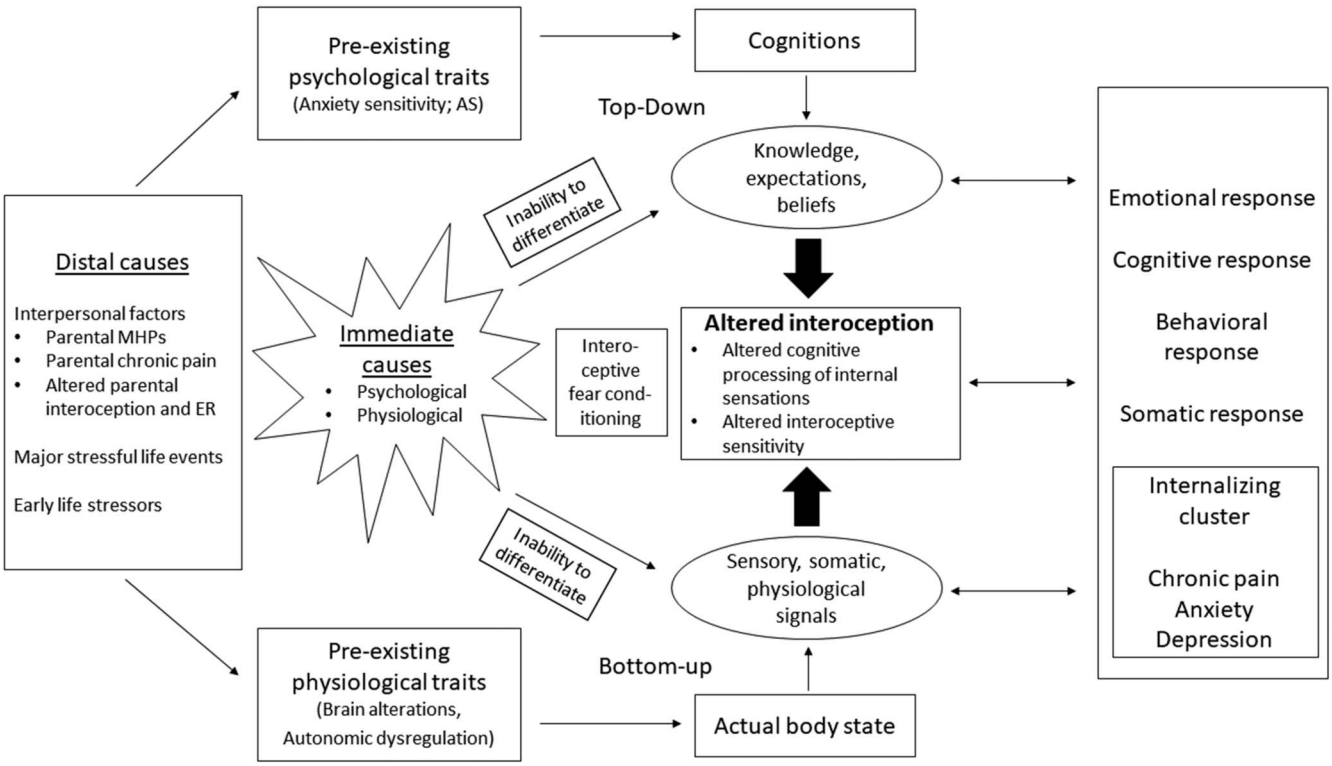

Figure 1. Initial model on the role of altered interoception for the co-occurrence of chronic pain and MHP in children (adapted from Ref. 49). The initial model, aimed to initiate research in this newly emerging field in paediatric pain, postulates that altered interoception constitutes a causal risk factor for the co-occurrence of chronic pain and MHP. Altered interoception can be triggered in daily life by immediate causes, eg, internal sensations during physical activity. These immediate causes trigger afferent interoceptive input and cognitions about the sensations, that both result in altered interoception (ie, altered cognitive processing and interoceptive sensitivity). Altered interoception then interacts with emotional, cognitive, behavioral, and somatic responses, leading to mutual symptoms of chronic pain, anxiety, and depression. Altered interoception may be fueled by both pre-existing psychological traits (AS) and physiological traits such as brain alterations. Distal causes, ie, antecedent conditions with long-term consequences, may account for the development of these traits. These entail interpersonal factors, major stressful life events, or early life pain. ER, emotion regulation, AS, anxiety sensitivity; MHP, mental health problems.

will permanently induce altered interoception. Individuals with major stressful life events experience allostatic load,[55,63] ie, a significant wear and tear on the body's sympathetic and parasympathetic response system caused by mobilization of multiple response systems. The overactivation of the hypothalamus–pituitary–adrenocortical axis, an element of the allostatic load, results in a state of hyperarousal that can dysregulate the brain–body communication and, hence, alter interoception. This altered interoception contributes to the manifestation of (physical) symptoms.[69]

Brain alterations and autonomic dysregulation constitute pre-existing physiological traits. The major brain structures underlying interoception are summarized under the interoceptive nervous system and include (1) the insula, the interoceptive center of the brain[61,62]; (2) the hippocampus, responsible for the use of interoceptive signals as contextual cues for memory storage and retrieval[34]; (3) the anterior cingulate cortex, responsible for responses to experience or expectation of internal bodily sensations[50]; and (4) the ventromedial prefrontal cortex, responsible for the integration of interoceptive and exteroceptive information.[34] Recent evidence consistently suggests altered interoception at the brain level in children and adults with chronic pain,[6,50] with anxiety,[33,62] and with depressive disorders.[8,34]

Autonomic dysregulation has been integrated into existent models,[32] albeit without addressing the role of interoception. The autonomic nervous system (ANS) is a collection of nerve cells/fibers consisting of 2 branches, the sympathetic and parasympathetic branch. Each ANS branch has afferent fibers that carry internal bodily information to the brain and efferent fibers that regulate the viscera based on brain activity.[60] The ANS is assumed to be important for interoception and ER.[60] Adults with chronic pain show low heart rate variability,[13] reflecting parasympathetic withdrawal associated with a predominance of sympathetic activity.[30,81] This autonomic dysregulation is assumed to be associated with a reduced capacity to downregulate autonomic reactivity,[59] resulting in increased internal bodily sensations. Research is still scarce in children, but 2 recent studies confirmed that pain-persistent young women[81] and children with chronic pain[51] also displayed low heart rate variability. Autonomic dysregulation can be substantial in postural tachycardia, a clinical syndrome comorbid with chronic pain in children, characterized by tachycardia upon standing.[83] Its association with altered interoception warrants future research.[49]

Anxiety sensitivity is conceptualized as a pre-existing psychological trait feeding into the altered cognitive processing of internal sensations described above. Anxiety sensitivity is defined as a constitutional trait characterized by hypersensitivity to anxious-related sensations based on the beliefs that these sensations have harmful somatic, psychological, and social consequences.[68] There is emerging evidence that children with chronic pain display increased levels of AS and that this is associated with symptom severity.[15,26,40] Heightened AS is also found in a range of emotional disorders (for a review, see Ref. 10).

4. Research agenda

There is a profound lack of research on altered interoception in children with chronic pain. I here propose a research agenda

focusing on an in-depth investigation of interoception profiles and an empirical investigation of the initial model. Testable hypotheses for future research studies are summarized in **Table 2**.

4.1. Limitations

Interoception may quickly become an important topic in paediatric pain, comparable with the adult literature.[61,76] The presented initial model might be helpful to guide research in this newly emerging field. Although the scope of the review was on the role of altered interoception for the co-occurrence of chronic pain and MHP in children, there are many ways how interoception may be approached, eg, focusing on the role of interoceptive predictive coding in children.[36,76] In this initial model, a broad perspective was taken to stimulate research in a wide range of fields, at the expense of depth in some parts. The profound lack of research on altered interoception in children also means that the initial model will develop and be specified as more research emerges.

4.2. Clinical implications

There is an increasing need for mind–body therapeutic approaches to treat chronic pain in children,[51] and this topical review clearly follows calls to do so. With a deepened understanding of altered interoception in children with chronic pain, appropriately tailored treatment strategies can be implemented. These might range from biofeedback to refine interoceptive sensitivity[52] to interoceptive exposure to decrease fearful responses to internal sensations (for a review, see Ref. 37). A clearly important future research line should examine whether these therapeutic strategies are capable of changing altered interoception and subsequently decreasing the co-occurrence of chronic pain and MHP.[43]

Conflict of interest statement

The author has no conflicts of interest to declare.

Acknowledgements

The author thanks the anonymous reviewers for their thoughtful comments on the topical review.

Article history:
Received 8 January 2020
Received in revised form 4 September 2020
Accepted 23 September 2020
Available online 30 September 2020

References

[1] Abraham E, Hendler T, Zagoory-Sharon O, Feldman R. Interoception sensitivity in the parental brain during the first months of parenting modulates children's somatic symptoms six years later: the role of oxytocin. Int J Psychophysiol 2019;136:39–48.
[2] Anderson JL, Acra S, Bruehl S, Walker LS. Relation between clinical symptoms and experimental visceral hypersensitivity in pediatric patients with functional abdominal pain. J Pediatr Gastroenterol Nutr 2008;47:309–15.
[3] Balottin U, Fusar Poli P, Termine C, Molteni S, Galli F. Psychopathological symptoms in child and adolescent migraine and tension-type headache: a meta-analysis. Cephalalgia 2013;33:112–22.
[4] Barrett LF, Simmons WK. Interoceptive predictions in the brain. Nat Rev Neurosci 2015;16:419–29.
[5] Beveridge JK, Neville A, Wilson AC, Noel M. Intergenerational examination of pain and posttraumatic stress disorder symptoms among youth with chronic pain and their parents. Pain Rep 2018;3(suppl 1):e667.
[6] Bhatt RR, Gupta A, Mayer EA, Zeltzer LK. Chronic pain in children: structural and resting-state functional brain imaging within a developmental perspective. Pediatr Res 2019:1–12. doi: 10.1038/s41390-019-0689-9 [Epub ahead of print].
[7] Birnie KA, Caes L, Wilson AC, Williams SE, Chambers CT. A practical guide and perspectives on the use of experimental pain modalities with children and adolescents. PAIN 2014;4:97–111.
[8] Blom EH, Connolly CG, Ho TC, LeWinn KZ, Mobayed N, Han L, Paulus MP, Wu J, Simmons AN, Yang TT. Altered insular activation and increased insular functional connectivity during sad and happy face processing in adolescent major depressive disorder. J Affect Disord 2015;178:215–23.
[9] Boettcher H, Barlow DH. The unique and conditional effects of interoceptive exposure in the treatment of anxiety: a functional analysis. Behav Res Ther 2019;117:65–78.
[10] Boettcher H, Brake CA, Barlow DH. Origins and outlook of interoceptive exposure. J Behav Ther Exp Psychiatry 2016;53:41–51.
[11] Brookes M, Sharpe L, Kozlowska K. Attentional and interpretational biases toward pain-related stimuli in children and adolescents: a systematic review of the evidence. J Pain 2018;19:1091–101.
[12] Brummelte S, Chau CMY, Cepeda IL, Degenhardt A, Weinberg J, Synnes AR, Grunau RE. Cortisol levels in former preterm children at school age are predicted by neonatal procedural pain-related stress. Psychoneuroendocrinology 2015;51:151–63.
[13] Burr RL, Heitkemper M, Jarrett M, Cain KC. Comparison of autonomic nervous system indices based on abdominal pain reports in women with irritable bowel syndrome. Biol Res Nurs 2000;2:97–106.
[14] Campo JV, Jansen-McWilliams L, Comer DM, Kelleher KJ. Somatization in pediatric primary care: association with psychopathology, functional impairment, and use of services. J Am Acad Child Adolesc Psychiatry 1999;38:1093–101.
[15] Cappucci S, Simons LE. Anxiety sensitivity and fear of pain in paediatric headache patients. Eur J Pain 2015;19:246–52.
[16] Clark DM, Salkovskis PM, Ost LG, Breitholtz E, Koehler KA, Westling BE, Jeavons A, Gelder M. Misinterpretation of body sensations in panic disorder. J Consult Clin Psychol 1997;65:203–13.
[17] Costello H, Bouras N. Assessment of mental health problems in people with intellectual disabilities. Isr J Psychiatry Relat Sci 2006;43:241–51.
[18] De Peuter S, Van Diest I, Vansteenwegen D, Van den Bergh O, Vlaeyen JW. Understanding fear of pain in chronic pain: interoceptive fear conditioning as a novel approach. Eur J Pain 2011;15:889–94.
[19] Di Lernia D, Serino S, Riva G. Pain in the body. Altered interoception in chronic pain conditions: a systematic review. Neurosci Biobehav Rev 2016;71:328–41.
[20] Domschke K, Stevens S, Pfleiderer B, Gerlach AL. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. Clin Psychol Rev 2010;30:1–11.
[21] Dudeney J, Sharpe L, Hunt C. Attentional bias towards threatening stimuli in children with anxiety: a meta-analysis. Clin Psychol Rev 2015;40:66–75.
[22] Eley TC, Gregory AM, Clark DM, Ehlers A. Feeling anxious: a twin study of panic/somatic ratings, anxiety sensitivity and heartbeat perception in children. J Child Psychol Psychiatry 2007;48:1184–91.
[23] Eley TC, Stirling L, Ehlers A, Gregory AM, Clark DM. Heart-beat perception, panic/somatic symptoms and anxiety sensitivity in children. Behav Res Ther 2004;42:439–48.
[24] Fava L, Morton J. Causal modeling of panic disorder theories. Clin Psychol Rev 2009;29:623–37.
[25] Feldman R. The adaptive human parental brain: implications for children's social development. Trends Neurosci 2015;38:387–99.
[26] Flack F, Gerlach AL, Simons LE, Zernikow B, Hechler T. Validation of the German fear of pain questionnaire in a sample of children with mixed chronic pain conditions. Eur J Pain 2017;21:1224–33.
[27] Flack F, Pané-Farré CA, Zernikow B, Schaan L, Hechler T. Do interoceptive sensations provoke fearful responses in adolescents with chronic headache or chronic abdominal pain? A preliminary experimental study. J Pediatr Psychol 2017;42:667–78.
[28] Garfinkel SN, Seth AK, Barrett AB, Suzuki K, Critchley HD. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. Biol Psychol 2015;104:65–74.
[29] Gatchel RJ. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. Am Psychol 2004;59:795–805.
[30] Groh AM, Narayan AJ. Infant attachment insecurity and baseline physiological activity and physiological reactivity to interpersonal stress: a meta-analytic review. Child Dev 2019;90:679–93.

[31] Gross JT, Cassidy J. Expressive suppression of negative emotions in children and adolescents: theory, data, and a guide for future research. Dev Psychol 2019;55:1938–50.
[32] Gruszka P, Schaan L, Adolph D, Pane-Farre CA, Benke C, Schneider S, Hechler T. Defence response mobilization in response to provocation or imagery of interoceptive sensations in adolescents with chronic pain: a study protocol. Pain Rep 2018;3(suppl 1):e680.
[33] Hamm LL, Jacobs RH, Johnson MW, Fitzgerald DA, Fitzgerald KD, Langenecker SA, Monk CS, Phan KL. Aberrant amygdala functional connectivity at rest in pediatric anxiety disorders. Biol Mood Anxiety Disord 2014;4:15.
[34] Harshaw C. Interoceptive dysfunction: toward an integrated framework for understanding somatic and affective disturbance in depression. Psychol Bull 2015;141:311–63.
[35] Heathcote LC, Jacobs K, Eccleston C, Fox E, Lau JY. Biased interpretations of ambiguous bodily threat information in adolescents with chronic pain. PAIN 2017;158:471–8.
[36] Hechler T, Endres D, Thowart A. Why harmless sensations might hurt in individuals with chronic pain: about heightened prediction and perception of pain in the mind. Front Psychol 2016;7:1638.
[37] Hechler T. Interoceptive exposure for children and adolescents with chronic pain: on the way, but not yet there. Pediatr Pain SIG Newsl 2019. Available at: https://www.smore.com/k7wtj-pediatric-pain-sig-newsletter.
[38] Herbert BM, Muth ER, Pollatos O, Herbert C. Interoception across modalities: on the relationship between cardiac awareness and the sensitivity for gastric functions. PLoS One 2012;7:e36646.
[39] Hirschfeld G, Hechler T, Dobe M, Wager J, von Lutzau P, Blankenburg M, Kosfelder J, Zernikow B. Maintaining lasting improvements: one-year follow-up of children with severe chronic pain undergoing multimodal inpatient treatment. J Pediatr Psychol 2013;38:224–36.
[40] Jastrowski Mano KE, O'Bryan EM, Gibler RC, Beckmann E. The co-occurrence of pediatric chronic pain and anxiety: a theoretical review of a developmentally informed shared vulnerability model. Clin J Pain 2019;35:989–1002.
[41] Katz J, Melzack R. Pain "memories" in phantom limbs: review and clinical observations. PAIN 1990;43:319–36.
[42] Khalsa SS, Lapidus RC. Can interoception improve the pragmatic search for biomarkers in psychiatry? Front Psych 2016;7:121.
[43] Khalsa SS, Adolphs R, Cameron OG, Critchley HD, Davenport PW, Feinstein JS, Feusner JD, Garfinkel SN, Lane RD, Mehling WE, Meuret AE, Nemeroff CB, Oppenheimer S, Petzschner FH, Pollatos O, Rhudy JL, Schramm LP, Simmons WK, Stein MB, Stephan KE, Van den Bergh O, Van Diest I, von Leupoldt A, Paulus MP, Interoception Summit p. Interoception and mental health: a roadmap. Biol Psychiatry Cogn Neurosci Neuroimaging 2018;3:501–13.
[44] Koch A, Pollatos O. Cardiac sensitivity in children: sex differences and its relationship to parameters of emotional processing. Psychophysiology 2014;51:932–41.
[45] Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. Coming to terms with the terms of risk. Arch Gen Psychiatry 1997;54:337–43.
[46] Lee KS, Vaillancourt T. The role of childhood generalized anxiety in the internalizing cluster. Psychol Med 2019:1–11.
[47] Liakopoulou-Kairis M, Alifieraki T, Protagora D, Korpa T, Kondyli K, Dimosthenous E, Christopoulos G, Kovanis T. Recurrent abdominal pain and headache—psychopathology, life events and family functioning. Eur Child Adolesc Psychiatry 2002;11:115–22.
[48] Mai S, Wong CK, Georgiou E, Pollatos O. Interoception is associated with heartbeat-evoked brain potentials (HEPs) in adolescents. Biol Psychol 2018;137:24–33.
[49] Mallorqui-Bague N, Bulbena A, Pailhez G, Garfinkel SN, Critchley HD. Mind-body interactions in anxiety and somatic symptoms. Harv Rev Psychiatry 2016;24:53–60.
[50] Mayer EA, Labus J, Aziz Q, Tracey I, Kilpatrick L, Elsenbruch S, Schweinhardt P, Van Oudenhove L, Borsook D. Role of brain imaging in disorders of brain–gut interaction: a Rome Working Team Report. Gut 2019;68:1701–15.
[51] McInnis PM, Braund TA, Chua ZK, Kozlowska K. Stress-system activation in children with chronic pain: a focus for clinical intervention. Clin Child Psychol Psychiatry 2020;25:78–97.
[52] Meyerholz L, Irzinger J, Witthoft M, Gerlach AL, Pohl A. Contingent biofeedback outperforms other methods to enhance the accuracy of cardiac interoception: a comparison of short interventions. J Behav Ther Exp Psychiatry 2019;63:12–20.
[53] Murphy J, Brewer R, Catmur C, Bird G. Interoception and psychopathology: a developmental neuroscience perspective. Dev Cogn Neurosci 2017;23:45–56.
[54] Murphy J, Catmur C, Bird G. Classifying individual differences in interoception: implications for the measurement of interoceptive awareness. Psychon Bull Rev 2019;26:1467–71.
[55] Nelson SM, Cunningham NR, Kashikar-Zuck S. A conceptual framework for understanding the role of adverse childhood experiences in pediatric chronic pain. Clin J Pain 2017;33:264–70.
[56] Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, Cohen M, Evers S, Giamberardino MA, Goebel A, Korwisi B, Perrot S, Svensson P, Wang SJ, Treede RD, Pain ITftCoC. The IASP classification of chronic pain for ICD-11: chronic primary pain. PAIN 2019;160:28–37.
[57] Noel M, Chambers CT, Petter M, McGrath PJ, Klein RM, Stewart SH. Pain is not over when the needle ends: a review and preliminary model of acute pain memory development in childhood. Pain Manag 2012;2:487–97.
[58] Noel M, Rosenbloom B, Pavlova M, Campbell F, Isaac L, Page G, Stinson J, Katz J. Remembering the pain of surgery 1 year later: a longitudinal examination of anxiety in children's pain memory development. PAIN 2019;160:1729–39.
[59] Okur Guney ZE, Sattel H, Witthoft M, Henningsen P. Emotion regulation in patients with somatic symptom and related disorders: a systematic review. PLoS One 2019;14:e0217277.
[60] Pace-Schott EF, Amole MC, Aue T, Balconi M, Bylsma LM, Critchley H, Demaree HA, Friedman BH, Gooding AEK, Gosseries O, Jovanovic T, Kirby LAJ, Kozlowska K, Laureys S, Lowe L, Magee K, Marin MF, Merner AR, Robinson JL, Smith RC, Spangler DP, Van Overveld M, VanElzakker MB. Physiological feelings. Neurosci Biobehav Rev 2019;103:267–304.
[61] Paulus MP, Feinstein JS, Khalsa SS. An active inference approach to interoceptive psychopathology. Annu Rev Clin Psychol 2019;15:97–122.
[62] Paulus MP, Stein MB. Interoception in anxiety and depression. Brain Struct Funct 2010;214:451–63.
[63] Peters A, McEwen BS, Friston K. Uncertainty and stress: why it causes diseases and how it is mastered by the brain. Prog Neurobiol 2017;156:164–88.
[64] Rutherford HJ, Wallace NS, Laurent HK, Mayes LC. Emotion regulation in parenthood. Dev Rev 2015;36:1–14.
[65] Schaan L, Schulz A, Nuraydin S, Bergert C, Hilger A, Rach H, Hechler T. Interoceptive accuracy, emotion recognition, and emotion regulation in preschool children. Int J Psychophysiol 2019;138:47–56.
[66] Schandry R. Heart beat perception and emotional experience. Psychophysiology 1981;18:483–8.
[67] Schmitz J, Blechert J, Kramer M, Asbrand J, Tuschen-Caffier B. Biased perception and interpretation of bodily anxiety symptoms in childhood social anxiety. J Clin Child Adolesc Psychol 2012;41:92–102.
[68] Schneider S, Adornetto C, In-Albon T, Federer M, Hensdiek M. Psychometrische Eigenschaften und Normierung der deutschen Version des childhood anxiety sensitivity index (CASI). Z Klin Psychol Psychother 2009;38:175–80.
[69] Schulz A, Vogele C. Interoception and stress. Front Psychol 2015;6:993.
[70] Seth AK. Interoceptive inference, emotion, and the embodied self. Trends Neurosci 2013;17:565–73.
[71] Simons LE, Sieberg CB, Conroy C, Randall ET, Shulman J, Borsook D, Berde C, Sethna NF, Logan DE. Children with chronic pain: response trajectories after intensive pain rehabilitation treatment. J Pain 2018;19:207–18.
[72] Soltani S, Kopala-Sibley DC, Noel M. The co-occurrence of pediatric chronic pain and depression: a narrative review and conceptualization of mutual maintenance. Clin J Pain 2019;35:633–43.
[73] Stone AL, Wilson AC. Transmission of risk from parents with chronic pain to offspring: an integrative conceptual model. PAIN 2016;157:2628–39.
[74] Thompson RA. Emotion dysregulation: a theme in search of definition. Dev Psychopathol 2019;31:805–15.
[75] Timmers I, Quaedflieg CW, Hsu C, Heathcote LC, Rovnaghi CR, Simons LE. The interaction between stress and chronic pain through the lens of threat learning. Neurosci Biobehav Rev 2019;107:641–55.
[76] Van den Bergh O, Witthoft M, Petersen S, Brown RJ. Symptoms and the body: taking the inferential leap. Neurosci Biobehav Rev 2017;74:185–203.
[77] Van Dyck Z, Vögele C, Blechert J, Lutz AP, Schulz A, Herbert BM. The Water Load Test as a measure of gastric interoception: development of a two-stage protocol and application to a healthy female population. PLoS One 2016;11:e0163574.
[78] Van Ryckeghem D, Crombez G. Pain and attention: towards a motivational account. In: Karoly P, Crombez G, editors. Motivational perspectives on chronic pain: theory, research, and practice: Oxford University Press, 2018. pp. 211–45.
[79] Vinall J, Pavlova M, Asmundson GJ, Rasic N, Noel M. Mental health comorbidities in pediatric chronic pain: a narrative review of epidemiology, models, neurobiological mechanisms and treatment. Children (Basel) 2016;3:40.

[80] Vlaeyen JW, Crombez G, Linton SJ. The fear-avoidance model of pain. PAIN 2016;157:1588–9.
[81] Walker LS, Stone AL, Smith CA, Bruehl S, Garber J, Puzanovova M, Diedrich A. Interacting influences of gender and chronic pain status on parasympathetically mediated heart rate variability in adolescents and young adults. PAIN 2017;158:1509–16.
[82] Walker LS, Williams SE, Smith CA, Garber J, Van Slyke DA, Lipani T, Greene JW, Mertz H, Naliboff BD. Validation of a symptom provocation test for laboratory studies of abdominal pain and discomfort in children and adolescents. J Pediatr Psychol 2005;31:703–13.
[83] Wang Y, Zhang C, Chen S, Li X, Jin H, Du J. Frequency domain indices of heart rate variability are useful for differentiating vasovagal syncope and postural tachycardia syndrome in children. J Pediatr 2019;207:59–63.
[84] Zaman J, Vlaeyen JW, Van Oudenhove L, Wiech K, Van Diest I. Associative fear learning and perceptual discrimination: a perceptual pathway in the development of chronic pain. Neurosci Biobehav Rev 2015;51:118–25.
[85] Zvolensky M, Jardin C, Farris SG, Kauffman B, Bakhshaie J, Garey L, Manning K, Rogers AH, Mayorga NA. Gut interpretations: how difficulties in emotion regulation may help explain the relation of visceral sensitivity with depression and anxiety among young adults with gastrointestinal symptoms. Psychol Health Med 2018;23:840–5.