Project Description – Project Proposals

Defence response mobilization via interoceptive sensations in children with chronic pain

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Project Description

1 State of the art and preliminary work

Chronic pain conditions in children. Chronic pain disorders are highly disabling disorders in children [49] and constitute a significant health problem with increasing prevalence rates of approximately three to five percent [26]. Contrary to adults who mainly suffer from chronic backpain, children primarily suffer from recurrent/ persistent headache or functional abdominal pain [26] with the core symptoms being severe pain and disability in school functioning, physical activity and social life.

Interoceptive fear and chronic pain. There is accumulating evidence that it is not the pain (intensity) itself accounting for the degree of disability in children with pain disorders but the anxious processing of pain resulting in avoidant behaviours [43,46]. The most prominent model with a focus on the anxious processing of pain is the fear-avoidance model (FAM) for adults with chronic back pain [1,43,45,46]. According to this model, the pain-related disability is acquired and maintained through the development of pain-related fear. The fear itself is perpetuated via conditioned external cues, such as the context in which severe pain might occur, and via context-free conditioned interoceptive sensations. The latter are assumed to play a pivotal role in clinical situations, because of their functional proximity to the pain [46]. However, it is only recently that besides external conditioned stimuli (such as school environment), the (mis)perception and (mis) appraisal of interoceptive sensations as signalling pain is discussed as a core mechanism for the maintenance of pain and fear [46], especially in the context of idiopathic headache in adults [8] and functional abdominal pain, e.g. in adult patients with Irritable Bowel Syndrome [18]. There is a profound lack of research into children with chronic pain disorder, even though chronic headache and functional abdominal pain are the predominant pain problems in children and adolescents [26].

Interoceptive sensations include for example temperature, itch, muscular and visceral sensations [10]. These benign interoceptive sensations occur frequently and naturally together with the pain experience. This co-occurrence enhances associative interoceptive fear conditioning. The chronic pain patient learns that previously benign interoceptive sensations start signalling the occurrence of pain and, hence, elicit anxious apprehension and fear responses (conditioned response), even in the absence of an actual pain experience. According to the Threat Imminence Model, these conditioned interoceptive sensations can be conceptualized as threatening cues evoking defensive motivation or anxious apprehension characterized by freezing and increased selective attention to the body [16] (see **Figure 1**).

Specifically, the anxious apprehension is characterized by a progressive augmentation of selective attention towards any cue signalling threat (e.g. interoceptive sensations related to the pain) and by physiological arousal, i.e., an increase in skin conductance level, heart rate deceleration. With increasing intensity of the interoceptive sensation, the anxious apprehension can switch into the “circa-strike” phase, in which the threat becomes more imminent and the probability of an overt defensive action increases. Massive bursts of autonomic arousal (increase in skin conductance level, cardiac acceleration) and a motor disposition reflected by an increase in potentiated startle are characteristics of this stage. Patients with chronic pain in this stage are assumed to display bursts of autonomic arousal and engage in defensive behaviours to decrease the pain, ranging from resting, visits to the physician or taking pain medication. These behaviours, however, represent dysfunctional pain coping strategies, which maintain chronic pain.

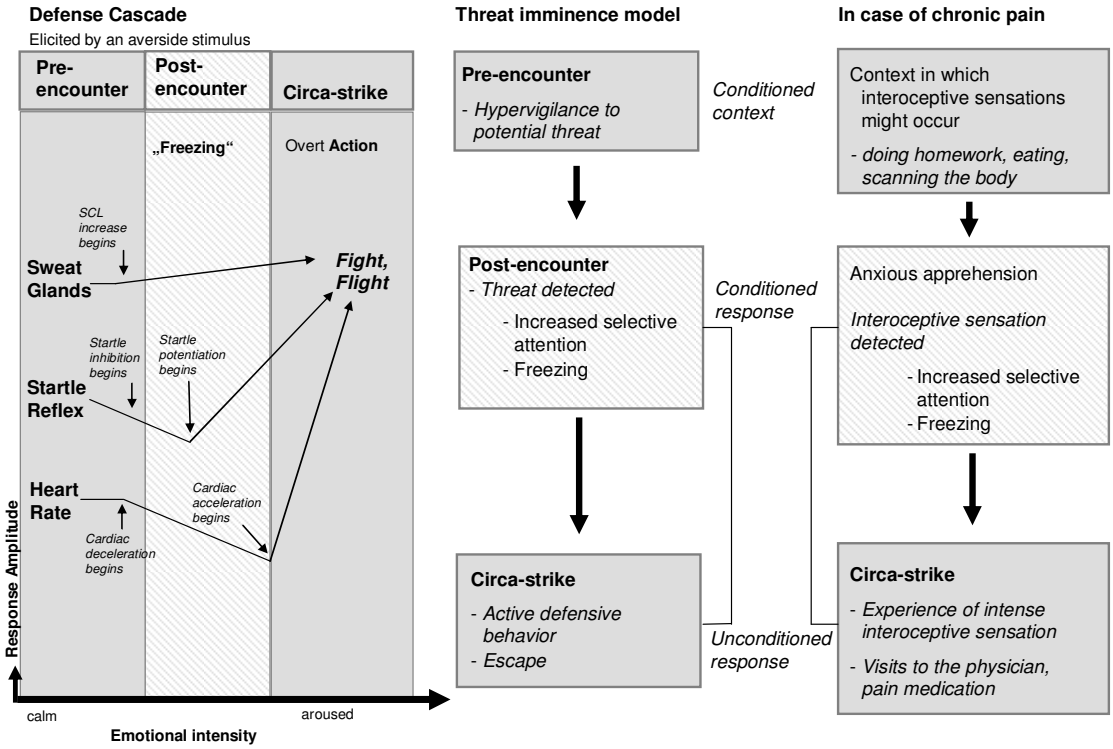

Figure 2: The Threat Imminence Model with defensive behaviour being organized in a cascade of three defensive stages. Defence cascade (left), Threat imminence model (middle), application to chronic pain (right) (adapted from Hamm et al. [20]).

Specificity of interoceptive sensations to elicit fear responses. Not each benign interoceptive sensation that is perceived will be able to elicit fear responses in patients with chronic pain. For treatment conception, it is essential to know which interoceptive sensations elicit defence response mobilization, so that symptom provocation tasks that are able to elicit comprehensive fear responses during interoceptive exposure can be designed [19]. There is, however, a dearth of research on fear responses following benign interoceptive sensations in chronic pain research. From a functional perspective, it has been argued that the conditioned stimulus (interoceptive sensation) must be proximal and related to the unconditioned stimulus (pain) [15]. Interoceptive sensations that evolve from the same body region as the main pain are therefore assumed to more likely become conditioned stimuli and to elicit defence response mobilization than interoceptive sensations more distal to the main pain (e.g., evolving from another body part) [12]. This is in accordance with research looking at panic disorder, which suggests that interoceptive sensations that are especially proximal to the panic may be more likely to evoke anxious apprehension of panic attacks [6]. This assumption, however, has not yet been tested systematically in chronic pain research.

Apart from the proximity to the main pain, the way in which interoceptive sensations are induced is important. Not only direct perception, but also mental imageries of interoceptive sensations have been shown to elicit defence response mobilization [31]. A mental imagery is defined as an experience of perception in the absence of a concurrent sensory input [28]. In adult panic disorder patients, McTeague et al. [31] recently showed that idiographic disorder-specific aversive imagery of panic attacks elicited greater startle potentiation in patients with panic disorder than in healthy adult participants. In chronic pain research, defence response mobilization has been shown for imagining to perform body movements in a group of healthy students who had

previously learned that these body movements were followed by mild pain sensations [33]. The potential of disorder-specific aversive imageries to elicit defence response mobilization has neither been investigated in adults nor in children with chronic pain disorders. Notwithstanding this lack of research, interoceptive imaginal exposure has been proposed to be a useful intervention and implemented in clinical trials with children [21] and adults [11], albeit with mixed results [35]. During such imaginal interoceptive exposure, patients are repeatedly instructed to focus their attention on the sensation of pain to decrease fear responses. This conception, however, differs from the original idea of interoceptive exposure [2], a method to expose individuals suffering from panic disorder to interoceptive sensations experienced shortly before or during a panic attack, rather than to the feared panic attack itself. Translated to chronic pain, interoceptive imaginal exposure may be conceptualized as a method to expose individuals to mental images of interoceptive sensations experienced before or related to the pain experience. This form of interoceptive imaginal exposure, however, has not yet been empirically investigated.

The instructed fear paradigm [39] is a valid paradigm to investigate fear responses in the laboratory when participants are confronted with threats of predictable or unpredictable aversive events such as benign interoceptive sensations. No study, however, has thus far utilized the instructed fear paradigm to study fear responses in chronic pain patients when confronted with interoceptive sensations. Psychophysiological response mobilization assessed via parameters of arousal and the startle reflex (see **Figure 1**) has been extensively and successfully used in children and adults [36], and in isolated studies addressing fear and acute pain [7], but not yet in the context of interoceptive fear in chronic pain patients. This may also account for the mixed results of the few existing clinical studies on the effectiveness of interoceptive exposure in chronic pain patients [11,21,35]. Based on the current literature, the following three assumptions warrant investigation:

1. Anticipation and perception of locally proximal vs. locally distal interoceptive sensations to the main pain will be able to elicit defence response mobilization in children with chronic pain disorders, not in healthy children.
2. Larger fear responses in children with chronic pain disorders are expected when instructed to perceive interoceptive sensations proximal instead of distal to their main pain location.
3. Mental imageries of disorder-specific aversive interoceptive sensations will elicit defence response mobilization in children with chronic pain disorders while neutral imageries won´t.

The empirical testing of these assumptions is particularly relevant to the theoretical placement of interoceptive sensations in aetiology models, to the role of perceptual and cognitive processes to elicit defensive responses and to the conception of interventions.

Summary. Defence response mobilization triggered via benign interoceptive sensations is likely to play a pivotal role in the maintenance of pain and disability, particularly in children suffering from CDH and FAP. Benign interoceptive sensations occur frequently and naturally together with the pain experience. This co-occurrence can result in a constant state of anxious apprehension of pain triggered via conditioned interoceptive sensations and in pronounced avoidance behaviour. To date, there is a dearth of research into fear responses following benign interoceptive sensations in children with chronic pain disorders, into the proximity-hypothesis of these interoceptive sensations, and into fear responses following disorder-specific imageries of aversive interoceptive sensations.

The existing validated threat procedures to study fear responses [39] and assessments of the defence cascade, particularly the startle potentiation, have already been successfully utilized in children [25,36] and can be used in children with chronic pain disorders. Hence, there are three aims of the present project: First, we aim to investigate whether children with CDH and FAP display greater defence response mobilization following benign interoceptive sensations proximal to their main pain than healthy children. Second, it will be tested in children with CDH and FAP if stimuli from the same body region (proximal) will elicit greater defence response mobilization than stimuli from distal body regions. Third, we aim to investigate defence response mobilization

following disorder-specific aversive imagery of interoceptive sensations vs. neutral imagery in children with chronic pain.
This research project has the potential to make substantial contributions regarding the

1. understanding of interoceptive fear responses in children with chronic pain disorders,
2. extension of existing theoretical models of chronic pain such as the fear-avoidance model with regards to the role of interoceptive fear,
3. comprehensive assessment of fear in the context of chronic pain,
4. development of interoceptive exposure and interoceptive imaginal exposure for different groups of children with chronic pain disorders.

Preliminary work. Priv.-Doz. Dr. Tanja **Hechler** as the principal investigator has extensive experience in the evaluation of interdisciplinary pain treatment of affected children and adolescents. Recent projects are the first randomized-controlled trial on the efficacy of intensive interdisciplinary pain treatment funded by the Robert Bosch Foundation [22] and the development of the German Pain Questionnaire for Children and Adolescents [42] awarded by the German Pain Society. Priv.-Doz. Dr. **Hechler** also conducted one of the first case-control trials on the effectiveness of an interoceptive exposure in children with chronic pain [21]. A case study on the interoceptive exposure [13] was awarded by the German Psychological Pain Society. Priv.-Doz. Dr. **Hechler** set up a research group (see **Composition of project group**) with expertise in the field of chronic pain in children, anxiety in children, experimental paradigms for interoception and anxiety in adults. Preliminary results on research into maldaptive interoception and chronic pain were presented at the 8th Workshop-Congress of the DGP Section Clinical Psychology and Psychotherapy, Trier, the German Pain Congress 2013, Hamburg, and the 9th International Symposium on Pediatric Pain, Stockholm, for which Priv.-Doz.Dr. **Hechler** obtained funding from the DAAD. For the present project, two pilot studies with children with CDH and FAP are currently in progress (see **Pilot studies**). A topical review on "A new perspective on interoception and chronic pain: Defence response mobilization via interoceptive sensations in patients with chronic pain" to be submitted to a peer-reviewed journal is in preparation.

Prof. Dr. **Schneider** as the co-operating investigator has considerable experience in research on the etiology and treatment of anxiety disorders in childhood, adolescence and adulthood, which has been at the core of her scientific work over several years. Beside of prospective longitudinal studies and clinical randomized controlled trials, she conducted studies on the psychophysiological reactivity and cognitive biases in children with anxiety disorders using experimental designs and multi-modal assessment approaches that are of direct impact for the present proposal. In several ongoing studies at the psychophysiological labs of Prof. Schneider's group at the Ruhr-Universität Bochum, more than 40 children and adolescents underwent extinction-learning paradigms with the same self-report and psychophysiological measures to be applied in the present proposal.

Pilot studies. The hypothesis that stimuli from the same body region (proximal) are more likely to evoke defence response mobilization than stimuli from distal body regions was piloted by Dr. **Hechler**. Using self-reported fear as an indicator of defence response mobilization, we found first evidence of higher fear report in children with CDH and FAP when exposed to proximal vs. distal stimuli (see **Table 3**). The imagery scripts for Study 2 have already been developed and tested in a second pilot study. Results of this pilot study show that for both pain groups the self-reported fear for aversive scripts was higher than for the neutral script (see **Table 3**). In several ongoing studies at the psychophysiological labs of Prof. **Schneider's** group, more than 40 children and adolescents underwent extinction-learning paradigms with the same self-report and psychophysiological measures to be applied in the present proposal, showing the feasibility of the planned psychophysiological assessments. Finally, ethical approval from the Vestische Kinder- und Jugendklinik Datteln has been obtained (see Attachment).

Table 3: Self-reported fear (VAS 0-100) in the PERCEPTION and IMAGERY conditions

PERCEPTION	Frown (proximal for CDH)	Clinch fists	Tighten stomach (proximal for FAP)	Clinch fists
CDH (n=3)	20.3 (*SD*=35.2)	0	0	0
FAP (n=5)	18.6 (*SD*=30.1)	11.4 (*SD*=25.5)	52.8 (*SD*=36.2)	13.6 (*SD*=30.4)
IMAGERY	**Aversive script**	**Neutral script**		
CDH (n=3)	15.3 (*SD*=17.2)	0		
FAP (n=5)	37.6 (*SD*=32.0)	18.2 (*SD*=22.9)		

1.1 Project-related publications

1.1.1 Articles published by outlets with scientific quality assurance, book publications, and works accepted for publication but not yet published.

Hechler

Dobe, M., **Hechler**, T., & Zernikow, B. (2009a). The pain provocation technique as an adjunctive treatment module for children and adolescents with chronic disabling pain: a case report. *Journal of Child & Adolescent Trauma, 2,* 297-307.

Hechler, T., Dobe, M., Kosfelder, J., Damschen, U., Hübner, B., Blankenburg, M. et al. (2009b). Effectiveness of a three-week multimodal inpatient pain treatment for adolescents suffering from chronic pain: Statistical and clinical significance. *The Clinical Journal of Pain, 25,* 156-166

Hechler, T., Dobe, M., Damschen, U., Schroeder, S., Kosfelder, J., & Zernikow, B. (2010a). The pain provocation technique for adolescents with chronic pain: Preliminary evidence for its effectiveness. *Pain Medicine, 11,* 897-910.

Hechler, T., Blankenburg, M., Dobe, M., Kosfelder, J., Hübner, B., & Zernikow, B. (2010b). Effectiveness of a multimodal inpatient treatment for pediatric chronic pain: A comparison between children and adolescents. *European Journal of Pain, 14,* 97.e1-97.e9

Hechler, T., Ruhe, A., Schmidt, P., Hirsch, J., Wager, J., Dobe, M. et al. (2013). Inpatient-based intensive interdisciplinary pain treatment for highly impaired children with severe chronic pain: Randomized controlled trial of efficacy and economic effects. *Pain, 155,* 118-128.

Schneider:

In-Albon, T., Kossowsky, J., & **Schneider, S**. (2010). Vigilance and avoidance of threat in the eye movements of children with separation anxiety disorder. Journal of Abnormal Child Psychology, 38, 225-235.

Kossowsky, J., Wilhelm, F., Roth, W., **Schneider S.** (2012). Separation anxiety disorder in children: disorder-specific responses to experimental separation from the mother. Journal of Child Psychology and Psychiatry, 53: 2, 178-187.

Kossowsky, J., Wilhelm, F., **Schneider, S.,** (2013). Responses to voluntary hyperventilation in children with separation anxiety disorder: implications for the link to panic disorder. *Journal of Anxiety Disorders, 27, 627-634.*

Schneider, S., Unnewehr, S., Florin, I., & Margraf, J. (2002). Priming panic interpretations in children of patients with panic disorder. *Journal of Anxiety Disorders, 16,* 605-624.

Wilhelm, F., **Schneider, S.**, & Friedman, B. (2005). Psychophysiological Assessment. In M. Hersen (Ed.), Comprehensive Handbook of Behavioral Assessment (CHOBA). Child Assessment (Vol. II) (1. edition) (pp. 200-231). New York: Wiley.

1.1.2 Other publications

Not applicable.

1.1.3 Patents

1.1.3.1 Pending

Not applicable.

1.1.3.2 Issued

Not applicable.

2 Objectives and work programme

2.1 Anticipated total duration of the project

36 months

2.2 Objectives

In the present project, we aim to explore whether benign perceived or imagined benign interoceptive sensations elicit defence response mobilization in children with chronic pain disorders. Results from Study 1 will provide information on fear responses following the perception of locally proximal vs. distal interoceptive sensations to the main pain in children with CDH, FAP and HC. If the hypothesis of greater defence response mobilization following proximal vs. distal sensations is confirmed, this will provide evidence for a functional perspective that the conditioned stimulus (interoceptive sensation) is proximal and related to the unconditioned stimulus (pain) [15].

Results from Study 2 can answer the question of whether a disorder-specific imagined interoceptive sensation in the absence of a direct percept can also trigger the fear response. If the results confirm an increased fear response following imagination, this will confirm the potential of imageries to elicit fear responses [29,31] and will provide knowledge into the conception of interoceptive imaginal exposure.

The long-term aim of the present project is to provide empirical evidence for the implementation of interoceptive (imaginal) exposure in children with chronic pain. If children with chronic pain display defence response mobilization triggered via interoceptive sensations, a subsequent project can be composed to investigate the efficacy of interoceptive (imaginal) exposure to reduce such fear responses.

2.3 Work programme incl. proposed research methods

Research group. The research group is composed of two applicants: Priv.-Doz. Dr. Tanja **Hechler** (Dipl.-Psych.) as the principal investigator will be responsible for the design and methods, general management of the project, pilot testing of the experimental paradigms, supervision of the recruitment and diagnostic assessments of the children with chronic pain disorders at the German Paediatric Pain Centre, and conception of papers and conference proceedings. Prof. Dr. Silvia **Schneider** (Dipl.-Psych.) as the co-operating investigator will be responsible for pilot testing of the experimental paradigms, the conduction of the experimental paradigms and psychophysiological assessments of the children with chronic pain disorders and the healthy children at the psychophysiological laboratory (http://www.kli.psy.ruhr-uni-bochum.de/labor/labor.html), the recruitment of the healthy children, and conception of papers and conference proceedings.

Two experimental studies. The research questions will be investigated in two distinct experimental studies (see **Figure 2**). In Study 1, children and adolescents with CDH and FAP will be compared to a healthy control group (HC). In Study 2 only children with CDH or FAP will be assessed. The investigation of a HC in Study 2 is not feasible because the imagination of interoceptive sensations in the main pain region may not be possible for healthy children. Based on the results of the first study, a second sample of children with chronic pain disorders will be selected dependent on the magnitude and specificity of fear responses in Study 1. This is done to maximize the likelihood of potential effects of the imagery condition. In both studies it is ensured that the length of experimental blocks will meet the age appropriate attention span of the children and adolescents.

Methods of Study 1: PERCEPTION

In Study 1, we aim to investigate differences in the elicited fear responses in three groups (CDH, FAP, HC) dependent on the local proximity of the interoceptive sensation to the main pain. Startle modulation will constitute the core outcome measure as a direct index of defensive mobilization during the anticipation of the threat. The following hypotheses will be tested:

- Children with CDH and FAP will display greater defence response mobilization than healthy children following directly perceived benign interoceptive sensations proximal to the main pain.
- In children with CDH and FAP, stimuli from the same body region (proximal) will elicit greater defence response mobilization than stimuli from distal body regions.

Induction of locally proximal vs. distal interoceptive sensations. Two different threatening interoceptive conditions and one safe condition will be used:

1. Tensing the musculus corrugator supercilii ("frown"). This condition represents the locally proximal interoceptive sensations to CDH and the locally distal sensations to FAP.
2. Tensing the abdominal muscles ("tightening stomach"). This condition represents the locally proximal interoceptive sensations to FAP and the locally distal sensation to CDH.
3. Clinching the fists. This condition represents the safe condition.

We chose these two threatening tasks based on the following criteria: First, there is initial empirical evidence in the literature that the induced interoceptive sensations are associated with fear responses in FAP and CDH patients [11,27]. Second, the children should be able to elicit the interoceptive sensations without any external stimulation. This is done to model the induction of interoceptive sensations in the natural environment. Third, the respective tasks should produce benign interoceptive sensations proximal to the main pain.

Children will be trained to tense the respective muscle groups without tensing the other in a trial prior to the experiment. Their ability to follow the instructions will be assessed by surface EMG activity of the respective muscle groups (see **Table 1**). The anticipation conditions will be established by instructing the children that after the presentation of an orange or yellow coloured cue (presented for 3 min) a muscle tensing task will follow in which they are either asked to frown or to tighten their belly. After presentation of a green cue (for 3 min), the children will be asked to clench their fists. We decided to compose a safe condition, which requires some attentional processes to physical sensations. This is done to control for potential attentional processes recently shown in studies of the startle response following interoceptive stimuli [9]. Children will be informed that these tasks will produce mild transient sensations in the respective body region such as feelings of tension or pressure.

The order of the three conditions will be balanced across children. Children are instructed to hold the respective muscle tension for as long as possible. The maximum time will be 3 min. We will thus realize a 3 (groups [CDH, FAP, HC]) *3 (conditions [frown, tighten belly, clench fists]) paired experimental design. Methods are summarized in **Table 1**.

A priori calculated sample size. Our analysis is based on our primary hypothesis that proximal interoceptive stimuli will elicit greater defence response mobilization than distal stimuli in children with chronic pain compared to healthy children, using startle potentiation as primary outcome. Previous studies in adults comparing startle magnitude during interoceptive threat between healthy adults high and low in anxiety sensitivity found small to medium effect sizes (e.g., [32] (eta squared=0.106)). The stability of the emotion-modulated startle response has been shown to be high with correlations between measures of r=.50 [30]. We based our sample size calculation on study results from adults. Given that increased startle overall magnitude has previously been reported during adolescence [37], this results in a conservative estimate of the requested sample size. At an alpha level of 0.05, the sample size of 33 per group (total sample size=99) is suitable to detect the within-between interaction effect (moderate size, f=0.25) with a power of .80 [17]. Taking a dropout of 20% (although we observed a smaller dropout of 10% in previous studies [21]), results in a sample size of 40 per group (total sample size=120).

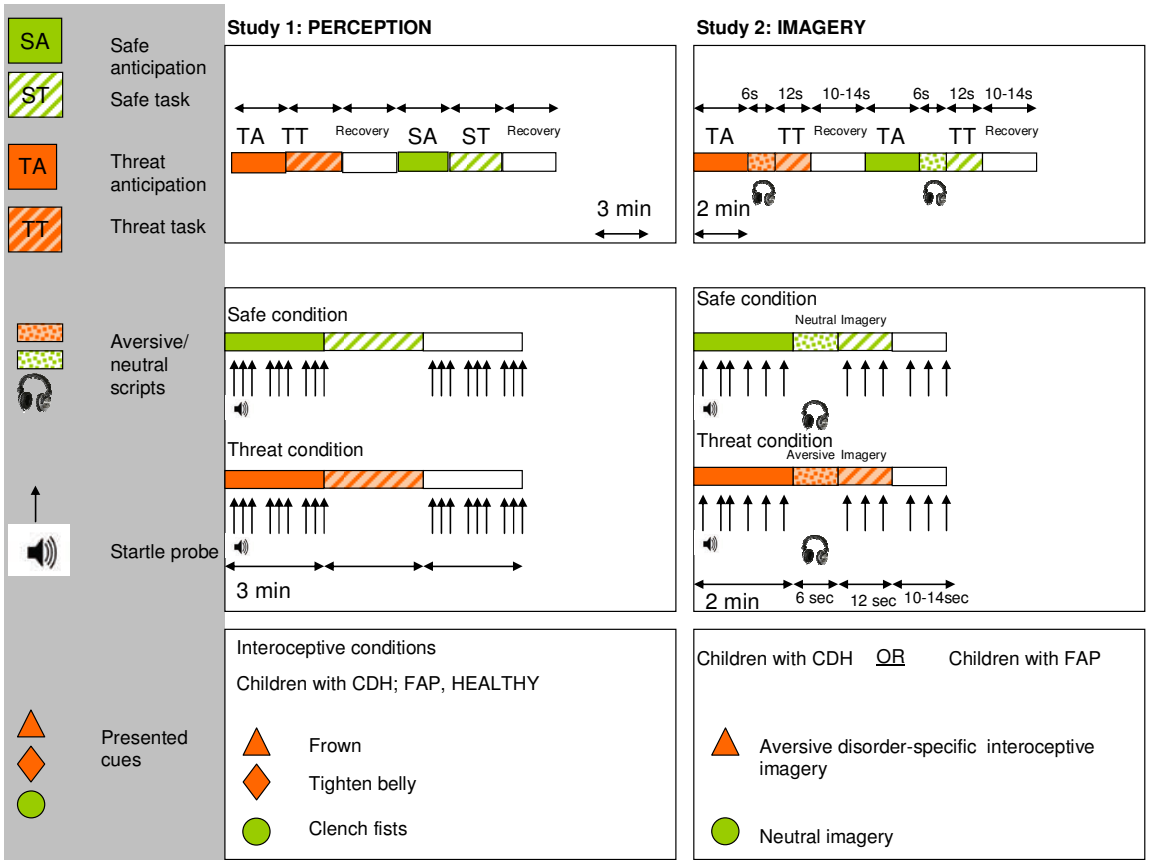

Figure 2: Schematic representation of the experimental paradigms of the two studies. The upper part represents a complete experimental block. The middle part shows the anticipation, task and recovery, including startle probes. The lowest part shows the interoceptive threats and safe conditions (adapted from [39]).

Table 1: **Methods of Study 1 (PERCEPTION) (anticipated duration: 20 months)**

Sample	3 study groups CDH: Children with chronic pain disorder diagnosed according to ICD-10 [38], and primary headache diagnosis of a CDH according to state of the art classification of headache by use of the criteria of the International Headache Society (IHS)) FAP: Children with chronic pain disorder diagnosed according to ICD-10 [38], and functional abdominal pain according to state of the art classification of functional abdominal pain by use of Rome-III-criteria; including a diagnosis of Irritable Bowel Syndrome, Functional Abdominal Pain Syndrome and Functional Dyspepsia HC: Healthy children (HC) without pain disorder
Inclusion criteria	For children with chronic pain disorder: Children will fulfil criteria for admission to intensive interdisciplinary pain treatment at the German Paediatric Pain Centre [22]. For all children and adolescents: Age: 11 to 18 years; Comprehension of German language; No impairment of hearing assessed via parental report
Exclusion criteria	For children with chronic pain disorder:

	Comorbidity of headache and functional abdominal pain Existent post-traumatic stress disorder (PTSD) assessed via the diagnostic interview for mental disorders in children and adolescents (Kinder-DIPS) [40] Childhood obesity: Body mass index (BMI) > 95th percentile. BMI will be assessed by age- and sex-specific percentiles (http://www.mybmi.de/main.php). For healthy children: Existent chronic pain disorder assessed via the validated German Pain Questionnaire [42]. Childhood obesity (see above)
Place of recruitment	Children with CDH & FAP: at the German Paediatric Pain Centre Healthy children: Via contacting children from an already existing data base of interested school age participants and via local schools in Bochum
Primary measure	
Startle potentiation	Recorded eyeblink component of the startle response via electromyographic activity (EMG) over the orbicularis oculi muscle beneath the left eye using two electrolyte-filled Ag/AgCI miniature surface electrodes.
Secondary measures	
Self-report	Iconic Self-Assessment of Anxiety in Children (ISAAC) [41] with ratings on a numeric rating scale (NRS): 0 (not at all) to 10 (extremely).
Fear	NRS: 0 (not at all) to 10 (extremely).
Interoceptive sensations	List with symptoms of a panic attack (DSM-IV) and three pain-specific sensations: feelings of tension, mild pain head, mild pain abdomen. Ratings of intensity and unpleasantness on a NRS
Pain	NRS: 0 (no pain), 10 (maximal pain). Children's ratings of the probability that they might experience pain on a NRS: 0 (not likely) -10 (definitely)
Escape/avoidance behaviours	Ratings of the desire to leave the present situation on a NRS [&]
Psychophysiological measures	
Skin conductance level (SCL)	Recorded with Ag/AgCI standard electrodes placed 15mm apart on the hypothenar eminence of the children's palmar surface of the non-dominant hand
Heart rate	EEG, Einthoven lead II setup with two standard, electrolyte-filled Ag/AgCI electrodes
Electromyographic activity	To control if children will follow the instruction to tension the respective muscle group For tensing the musculus corrugator supercilii: Surface EMG activity electrodes will be placed at the musculus corrugator supercilii. For tensing the abdominal muscles: Surface EMG electrodes will be placed over left lower rectus abdominis (2cm lateral and caudal to the umbiculus, and left obliquus externus (over the tip of the eighth rib and angled diagonally in the direction of the muscle fibers) [34]
Startle probe	50ms burst of white noise with an intensity of 95dB (A) (rise (fall time <1ms),

	generated with a soundcard and a HiFi amplifier. Presented binaurally over in-ear headphones (Shure SE 215)

[&] The self-report of avoidance behaviour constitutes an approach to assess the behavioural component of avoidance and has been frequently implemented in previous studies (e.g., [24]).

Experimental Procedure. Upon the child's arrival at the Bochum Mental Health Research and Treatment Center (MHRTC), the doctoral candidate andresearch assistant of the Bochum site will briefly repeat the study information to the child and parents and place the electrodes. The research assistant is responsible for the application of the physiological assessments. He/she and the parents will leave the laboratory after all electrodes are placed and the child feels comfortable to stay alone in the laboratory. Following this, an *adaptation phase* of 1.5 min with six startle probes will take place to habituate startle response magnitudes. This phase will be immediately followed by the *threat condition*. Each condition is subdivided into three parts (see **Figure 2**):

1. Threat or safe *anticipation* indicated by coloured cue presented for 3 min and nine startle probes (average of 20 s mean inter-probe interval),
2. Threat or safe *task* indicated by a slide with instruction to tension the respective muscle group (3 min maximal time) and no startle probe to reduce interferences,
3. *Recovery* with 3 min duration and nine startle probes (average of 20 s mean inter-probe interval).

Children are asked to report fear, interoceptive sensations, pain and avoidance behaviours following each of the three conditions. After the recovery phase (3 min), the second trial will follow consisting of a threat and safe condition. The experiment will be finished with the safe condition to ensure a decrease of potential fear. Total duration of one block will sum up to approximately 36 min.

Methods of Study 2: IMAGERY

In Study 2, children with CDH or FAP (dependent on which patient group displays greater and more specific fear responses in Study 1) will be studied with regards to their defence response mobilization following an aversive imagery script of interoceptive sensations (see **Figure 2**). Startle modulation will constitute the core outcome measure. The following hypothesis will be tested:

- Children with chronic pain disorder will display greater defence response mobilization during aversive vs. neutral imagery.

Aversive vs. neutral interoceptive imagery. The following two interoceptive imagery conditions will be presented:

1. Three disorder-specific aversive imagery scripts with detailed descriptions of interoceptive sensations at the main pain location
2. Three neutral imagery scripts with instruction to imagine neutral scenes (e.g., going for a walk on a calm street).

For both imagery scripts, children are asked to listen to an auditory script with eyes closed, vividly imagining the events described, as if actively involved. The scripts have already been developed and pilot-tested (see **Pilot studies** for details). Participants will be instructed to engage in the imagery tasks for 12 seconds [31]. We will thus realize a single group design with 2 conditions (aversive vs. neutral imagery). Methods are summarized in **Table 2**.

Table 2: **Methods of Study 2 (IMAGERY) (anticipated duration: 16 months)**

Sample	Single study group Either children with CDH (see **Table 1** for details) or children with FAP (dependent on fear responses in study 1)
Inclusion and exclusion criteria	Identical to inclusion and exclusion criteria in Study 1, see **Table 1** for details.
Place of recruitment	Children with CDH or FAP: At the German Paediatric Pain Centre

Primary measures	The startle potentiation constitutes the primary measure (see **Table 1** for details).
Secondary measures	Identical to Measures in Study 1, see **Table 1** for details.
Vividness of mental imagery	Children's ratings on the clarity of the mental imagery on a NRS: 0 (no image at all, I only know that I was thinking the perception) to 10 (perfectly clear and as vivid as normal perception) (adapted from [4]).

A priori sample size calculation. Our analysis is based on our primary hypothesis that aversive imagery scripts will elicit greater defence response mobilization than neutral imagery scripts using startle potentiation as primary outcome. A priori sample size calculation was based on the expected difference in startle potentiation between the aversive vs. neutral imagery in a single clinical group of children with chronic pain (either CDH or FAP). Previous studies in adults comparing startle magnitude following aversive vs. neutral imagery scripts found medium effect sizes (e.g. [31], d=0.56). We based our sample size calculation on study results from adults although increased startle overall magnitude has previously been reported during adolescence [37]. This results in a conservative estimate of the sample size. At an alpha level of 0.05, the sample size of 22 children is suitable to detect the interaction effect with a power of .80 [17]. Expecting a dropout of 20%, results in a total sample size of 26 children.

Experimental Procedure. Upon the child's arrival at the MHRTC and similar to Study 1, the doctoral candidate and the research assistant of the Bochum site will repeat the study information to the child and place the electrodes. Following the *adaptation phase* of 1.5 min with six startle probes, each block will start with an anticipation phase of 2 min with 6 startle probes. Two different coloured cues will be presented to signal either the aversive or the neutral imagery script. Then the script will be presented for 6 s. After this, a tone will be presented signalling the children to imagine the previously read scene for 12 s [31]. Another tone will terminate the imagery. Startle probes will be presented during imagery (at 6.5, 7.5 or 8.5 s), and during the recovery phase (at 6, 7 or 8 s) [3]. The aversive and neutral scripts will be presented in random order. After each imagery phase, children will be asked to self-report fear, interoceptive sensations, pain, escape/avoidance behaviours (see **Table 1**) and vividness of the mental imagery (**Table 2**). Total duration of one block will sum up to approximately 15 min.

Feasibility of recruitment

Children with chronic pain disorder. The proposed research project will be embedded in an ideal working environment. The German Paediatric Pain Centre (www.deutsches-kinderschmerzzentrum.de) is the largest tertiary pain centre in Germany and worldwide, with up to 500 new referrals of children with persistent pain per year [49]. Of these, approximately 240 children are admitted to intensive interdisciplinary pain treatment [14,22]. The centre has provided firm evidence to reach the required sample size, confirmed by the fact that we have actually exceeded such target numbers in previous studies [22]. Previous studies consistently showed that approximately 50% of the children (n=120) suffer from CDH and 25% (n=60) suffer from FAP [14,22]. For the present **pilot studies**, we were able to recruit eight children per month (n=3 with CDH, n=5 with FAP, see **Table 3**). Hence, we consider a time frame of 12 months as feasible for the recruitment of 40 children with CDH and 40 children with FAP for Study 1, and a time frame of six months for the recruitment of 26 children with CDH or 26 children with FAP for Study 2.
Healthy children. The MHRTC at the Ruhr-Universität Bochum with its state of the art equipped psychophysiological labs (http://www.kli.psy.ruhr-uni-bochum.de/labor/labor.html) allows the parallel investigation of 2 to 4 children and offers the ideal environment for the conduction of the present study. The MHRTC has the appropriate formal infrastructure and maintains a collaborating network between schools and psychosocial services that will assure referrals of participants. An already existing database of children and adolescents interested in participating in psychological

studies in Bochum, advertisements in schools, newspapers, online-communities and news-websites will help to increase recruitment. Our goal is to enrol at least 3-4 participants per month and, thus, consider a recruitment period of 12 months for the intended sample size of 40 healthy children as feasible.

General Procedure

The implementation of the experiments and the psychophysiological assessments will take place at the MHRTC. For children with chronic pain, external assessments outside the German Paediatric Pain Centre are required. This has been successfully conducted previously with high compliance of the children and their families [48].

Children with chronic pain disorder and their parents will be informed about the study at treatment commencement by the doctoral candidate and the research assistant. Study information will include that physiological reactions during different kinds of tasks will be assessed. To increase study compliance, relevant study data will be made available for the children for possible integration into their treatment. They will then read and sign the informed consent. A trained doctoral candidate will conduct the diagnostic interviews on the ward. An appointment will be scheduled together with the head nurse of the ward for the assessment at the Ruhr-Universität so that it will fit in the therapeutic schedule. The research assistant will drive the children back and forth to the laboratory.

Healthy children will be informed via a mailed letter or a letter distributed by school principals with a short description of the study, an invitation to participate and informed consent. Healthy children will receive a 10 Euro reimbursement for participation. For children who agree to participate and who fulfil inclusion criteria (see **Table 1**), the research assistant at the Bochum site will obtain informed consent as well as the contact details to schedule an appointment for the assessment at the Ruhr-Universität. Parents will accompany their children to the assessment.

2.3.1 Statistical analysis

Data reduction. Data reduction and editing of artifacts for startle response, SCL and HR will be performed using ANSLAB software [47]. Mean startle response magnitude will be calculated according to the experimental conditions. SCL will be calculated by averaging for each experimental condition across blocks of 10 s excluding the 10-s blocks in which acoustic startle probes will be administered. HR will be calculated accordingly.

Experimental design. Both studies entail a repeated-measure design (repeated-measure factor: interoceptive conditions, see **Figure 2**). In Study 1, group (CDH, FAP, HC) constitutes the second independent variable.

Statistical analysis. For the statistical analyses of **Study 1 (PERCEPTION)**, we will first compute a global mixed-model analysis of variance (ANOVA) for the startle response with the three interoceptive conditions ([frown] vs. [tighten belly] vs. [clinch fists]) as within-factor and group (CDH, FAP, HC) as between-factor. Post-hoc *t*-Tests will be computed to explore the expected differences between CDH and FAP in startle response magnitude dependent on proximal ([frown for CDH], [tighten belly for FAP]) vs. distal ([tighten belly for CDH], [frown for FAP]) interoceptive conditions.

The analyses of **Study 2 (IMAGERY)** are based on a single-group design with the two different imagery scripts ([aversive] vs. [neutral]) as repeated-measure factor. Paired-samples *t*-Tests will be applied to investigate differences in startle response magnitude between the two conditions.

In both studies, statistical analyses will also be computed for the secondary outcomes (SCL, HR, self-report of fear, interoceptive sensations, pain and escape/avoidance behaviours) by use of ANOVAs. For the SCL and HR, an additional factor time will be included to explore SCL and HR over the course of the experiment. This will be defined as (18-9)*10 s for Study 1, and (15,2-9)*10 s for Study 2.

All statistical tests will use a significance level of $p<.05$. For all *F*-tests effect sizes (partial eta squared) will be reported.

Working steps during the anticipated funding period of 36 months

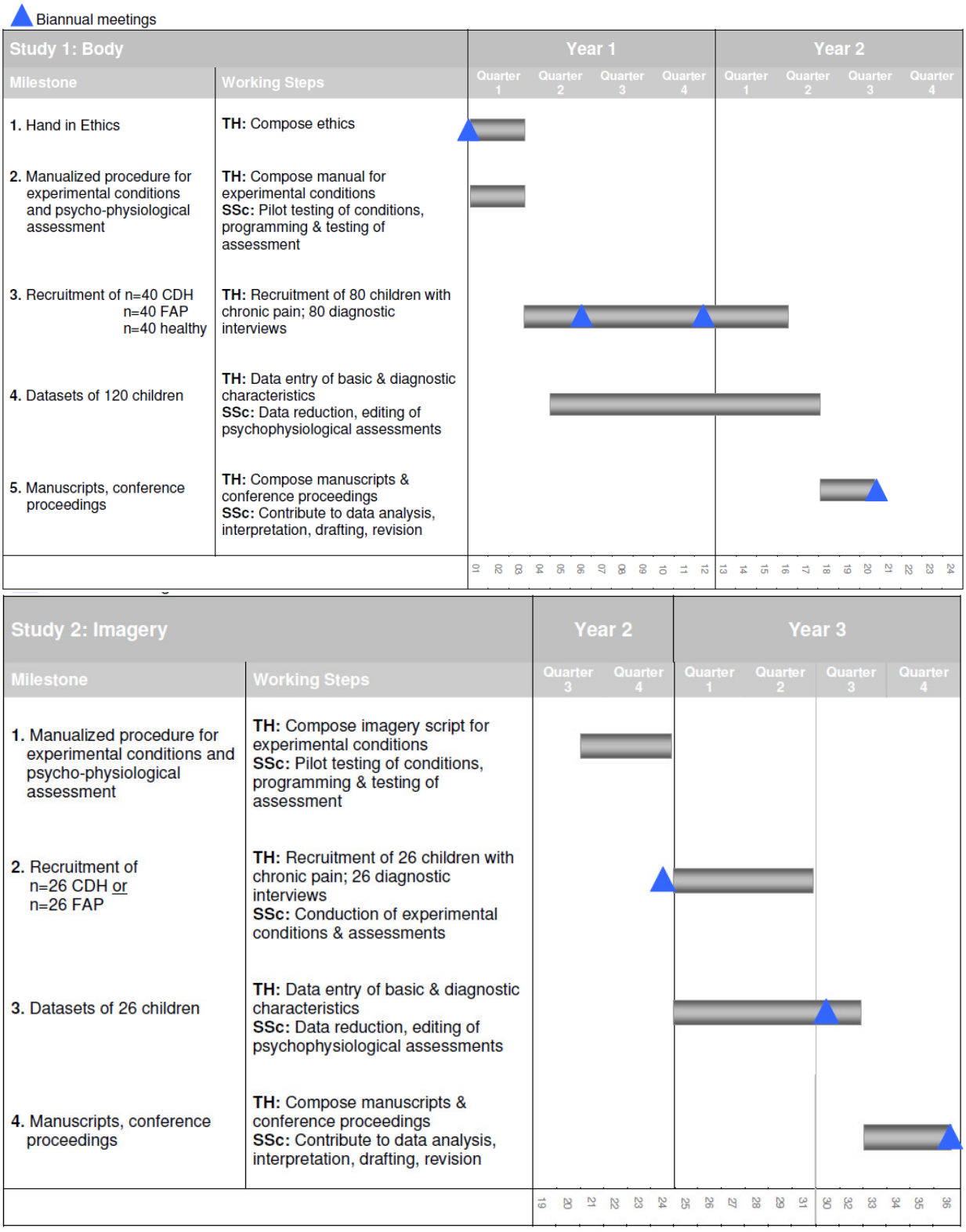

Figure 3: Schedule of the milestones, working steps, and tasks of the research groups.
TH: Tanja Hechler; SSc: Silvia Schneider

2.4 Data handling

Data management will be conducted according to Good Clinical Practice Guidelines. The quality of the data management will be ensured by applying published guidelines and conventions established for psychophysiological research (e.g. [5]) and by the use of a data management manual and the second-look procedure for the data entry of self-reports. In line with the statement of sharing data to improve public health, standards of data management will be developed, promoted and entrenched in the present project so that data can be shared routinely. Data will be examined by programmed range checks, validity checks, and consistency checks. Data management will be supported by Dipl. Stat. Xiao Chi Zhang, division of psychometrics and biostatistics at MHRTC. Sampling and data collection is continuously monitored for quality by existing experienced staff in Bochum. To ensure safety and minimize risk, only professionally trained staff members will conduct clinical interviews and psychophysiological assessments. All adverse events will be immediately reported to the principal investigators for consultation. Serious adverse events will be reported to the Ruhr-Universität Bochum Ethics Committee.

2.5 Other information

Please use this section for any additional information you feel is relevant which has not been provided elsewhere.
Not applicable.

2.6 Descriptions of proposed investigations involving experiments on humans, human materials or animals

The study will be conducted in full accordance with the Declaration of Helsinki, the German Data Protection Act, and the GCP-Guideline and will be sensitive to specific ethical considerations. The study protocol, amendments to the protocol (if applicable), patient recruitment procedures and the patients' information and informed consent form will be presented to the Ruhr-Universität Bochum Ethics Committee and handed in to the Ethics Committee of the Vestische Kinder- und Jugendklinik Datteln for approval. Informed consent will be obtained from the children and their caregivers. They will be provided with detailed information on the study procedure and assessment tools and can terminate the assessment at any time. The study procedures and assessments are not harmful to the participants and have been utilised widely in children [36,44]. Fear responses will be elicited by the experimentally controlled procedures by perception and imagination of interoceptive sensations, which frequently occur in daily life. According to previous studies which exposed children to fearful cues, such as hyperventilation tasks [44], we expect similar or lower fear responses than in natural settings. Even though the fear responses might be reduced, they provide valuable information for psychopathological processes in children with chronic pain.

2.7 Information on scientific and financial involvement of international cooperation partners

Not applicable.

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4 Requested modules/funds

Explain each item for each applicant (stating last name, first name).

4.1 Basic Module

4.1.1 Funding for Staff

Hechler: One doctoral researcher (65%, TVL 13/2) and two student assistants (10h/week) are required for the 36-month duration of the project.

Funding for doctoral researcher: The doctoral candidate should be qualified in clinical psychology (MSc. or Dipl.-Psych.) with experience in experimentally controlled studies in children. The candidate is expected to complete his/her Ph.D. during the project. The tasks comprise (see **Figure 3**): organisation of regular meetings with the project group, preparation of ethics applications and of standard procedures for the threat and safe conditions,

recruitment and accomplishment of diagnostic interviews with children with CDH and FAP, preparation of a manual for data management, help with the data management and data analyses, preparation of presentations and publications of the study results.

Funding for two student assistants: Two study assistants (10h/week, customary rate: 15,60 €, **Required funds: 44.928€)** will assist the doctoral candidate over the 36-month period. Their tasks include: support of the recruitment of the children, support of the assessments, driving the children back and forth to the laboratory in Bochum, copying questionnaires, data management, data entry, support with literature search.

Schneider: One doctoral researcher (65%, TVL 13/2) and one student assistant (10h/week) are required for the 36-month duration of the project.

Funding for doctoral researcher: The doctoral candidate should be qualified in clinical psychology (MSc. or Dipl.-Psych.) with experience in diagnostic assessments and in the conduction of psychophysiological assessments in children. The candidate is expected to complete his/her Ph.D. during the project. The tasks comprise (see **Figure 3**): recruitment and diagnostic assessment of HC, conduction of all psychophysiological assessments at the MHRTC, data entry, help with the data management and data analyses, preparation of presentations and publications of the study results.

Funding for student assistant: One study assistant (10h/week, customary rate: 15,60 €, **Required funds:** 22.464€) will assist the doctoral candidate over the 36-month period. His/her tasks include: support of the recruitment of the children, support of the assessments, copying questionnaires, support with study management.

4.1.2 Direct Project Costs

4.1.2.1 Equipment up to €10,000, Software and Consumables

The research group of Prof. **Schneider** will apply for the consumables, software and hardware. The presentation software is needed for stimulus delivery and assessment of participants' subjective responses. The workgroup has extensive experience with the software and is already equipped with one license. However, this license is permanently in use with ongoing research. The workgroup will provide the Anslab software to analyse the psychophysiological data. This software package is based on the Matlab environment. The workgroup is currently equipped with only one Matlab license and one laptop computer dedicated to data analysis. This workstation is also permanently in use with ongoing research. Thus, to assure timely data assessment and analysis, another presentation license, an additional Matlab license (including Statistics and Signal processing toolboxes) and another laptop computer are needed. The laptop computer will be purchased via the Ruhr-Universität Bochum's purchasing department framework contract.

Consumables:

Disposable ECG electrodes, EMG and SCL electrodes, electrode gel, skin preparation gel, abrasive pads, adhesive disks, towels to conduct the psychophysiological assessment with N=133 children 1000 €

Software:

1 License presentation Software for 36 months: 709,73 €

1 License Matlab Software basic package plus Signal Processing and Statistics Toolbox: 1178,10 €

Hardware:

1 laptop computer for data analysis purposes (Dell Latitude 15 6000 series, Core i7): 1272,16 €

Total Schneider 4.1.2.1: 4.159,99 €

4.1.2.2 Travel Expenses

Hechler: Travel expenses will arise due to driving the children from the Datteln to the Bochum site (35 km one way; 2.226 €) and due to regular meetings of the research group. To foster

collaboration with other scientists, participation in two national conferences (Fachgruppentagung Klinische Psychologie & Biologische Psychologie, à 700 €) and two international conferences (IASP, EABCT à 1.500 €) is planned for the doctoral candidate and the principal investigator with active contributions by both via oral and poster presentations.

Total for Hechler 4.1.2.2: 11.173 €

Schneider: The results of the study will be presented at international and national conferences to disseminate the study results and to foster national and international collaboration: both the doctoral candidate and the co-operating investigatorwill contribute oral and poster presentations at two national (DGP Congress, DGKJP Congress, á 700 €) and two international conferences (ABCT, EABCT, á 1500 €).

Total for Schneider 4.1.2.2: 8.800 €

4.1.2.3 Visiting Researchers (excluding Mercator Fellows)

Not applicable.

4.1.2.4 Expenses for Laboratory Animals

Not applicable.

4.1.2.5 Other Costs

Schneider: Reimbursement of 10 € for n=40 healthy children, because the experiment will last up to 1.5h (400€). Travel expenses of the 40 families will be compensated. The average travel distance was calculated with 30km based on previous research projects, compensated with 0,30 € per km (360 €).

Total for Schneider 4.1.2.5: 760 €

4.1.2.6 Project-related publication expenses

Hechler/ Schneider: Costs for proof-reading manuscripts or other publication expenses (e.g. colour fees) for the research project will sum up to 1.500 €.

Total: 1.500 €

4.1.3 Instrumentation

4.1.3.1 Equipment exceeding Euro 10,000

Not applicable.

4.1.3.2 Major Instrumentation exceeding Euro 50,000

Not applicable.

4.2 Module Temporary Position for Funding

Not applicable.

4.3 Module Replacement Funding

Not applicable.

4.4 Module Temporary Clinician Substitute

Not applicable.

4.5 Module Mercator Fellows

Not applicable.

4.6 Module Workshop Funding

Not applicable.

4.7 Module Public Relations Funding

Not applicable.

5 Project requirements

5.1 Employment status information

For each applicant, state the last name, first name, and employment status (including duration of contract and funding body, if on a fixed-term contract).

- Hechler, Tanja, Head of the Research Team at the German Paediatric Pain Center, Vestische Kinder- und Jugendklinik, Datteln, permanent position.
- Schneider, Silvia, Professor of Clinical Child and Adolescent Psychology at the Ruhr-Universität Bochum, Department of Clinical Child and Adolescent Psychology, permanent position.

5.2 First-time proposal data

Not applicable.

5.3 Composition of the project group

- Adolph, Dirk, PhD, clinical psychologist and psychophysiologist, permanent position at Ruhr-Universität Bochum
- Dobe, Michael, PhD, clinical psychologist, permanent position at the German Paediatric Pain Centre, Vestische Kinder- und Jugendklinik Datteln.
- Gerlach, Alexander, Professor of Clinical Psychology at the University of Cologne, Germany, permanent position.
- Hirschfeld, Gerrit, PhD, post doctoral researcher, temporary position at the German Paediatric Pain Centre, Vestische Kinder- und Jugendklinik Datteln.
- Pané-Farré, Christiane Anne, nee Melzig, PhD, post-doctoral researcher, temporary position at the Ernst-Moritz-Arndt-University, Greifswald.
- Zernikow, Boris, Professor at the Witten/Herdecke University and Head of the German Paediatric Pain Centre, Vestische Kinder- und Jugendklinik Datteln, permanent position

5.4 Cooperation with other researchers

5.4.1 Researchers with whom you have agreed to cooperate on this project

Not applicable.

5.4.2 Researchers with whom you have collaborated scientifically within the past three years

Hechler

- Prof. Dr. Silja, Vocks, Clinical Psychology and Psychotherapy, Universität Osnabrück
- Prof. Dr. Christiane Hermann, Clinical Psychology and Psychotherapy, Justus-Liebig-Universität Gießen
- Ass. Prof. Laura Simons, Boston Children's Hospital, Harvard Medical School, USA.

Schneider

- Prof. Dr. Eni Becker & Dr. Mike Rink, Clinical Psychology and Behavioural Science Institute, Radboud University Nijmegen, Netherlands
- Prof. Dr. Thalia Eley, Institute of Psychiatry, King's College, London UK
- Prof. Dr. Johannes Hebebrand, Child- and Adolescent Psychiatry, Universität Duisburg-Essen
- Dr. Jane Herbert, Department of Psychology, University of Sheffield, UK
- Prof. Dr. Tina In-Albon, Clinical Child- and Adolescent Psychology, Universität Landau
- Prof. Dr. Simone Munsch, Institute of Psychology, Clinical Child and Adolescent Psychology, University of Lausanne, Switzerland

- Prof. Dr. Matthew R. Sanders, Parenting and Family Support Centre, University of Queensland, Australia
- Prof. Dr. Silja Vocks, Clinical Psychology and Psychotherapy, Universität Osnabrück
- Prof. Dr. Frank Wilhelm, Clinical Psychology, Psychotherapy and Health Psychology, Universität Salzburg, Austria
- Prof. Dr. Ulrich Wittchen, Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden

5.5 Scientific equipment

List larger instruments that will be available to you for the project. These may include large computer facilities if computing capacity will be needed.

Hechler: Workplaces for the doctoral candidate and the research assistant will be made available.
Schneider: All laboratory equipment will be provided, including psychophysiological amplifier system, stimulus delivery computer, and the Anslab software package to analyse the psychophysiological data.

5.6 Project-relevant interests in commercial enterprises

Information on connections between the project and the production branch of the enterprise

Not applicable.

6 Additional information

If applicable, please list proposals requesting major instrumentation and/or those previously submitted to a third party here.

We hereby confirm that this project is currently not under consideration by another sponsor.